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How Scientists Produce Institutions: The Practice and Politics of Genome Editing

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How Scientists Produce Institutions: The Practice and Politics of Genome Editing

by

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in

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in the

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of the

University of California, Berkeley

Committee in Charge:

Professor Marion Fourcade, Chair

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Abstract

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Doctor of Philosophy in Sociology

and the Designated Emphasis in Science and Technology Studies

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The subject of the 2020 Nobel Prize in chemistry, the CRISPR-Cas9, has been heralded by researchers as a breakthrough biotechnology and has gained widespread use in biomedicine and the life sciences since the first publication that showed that the CRISPR-Cas9 system could be used as a tool for "editing" DNA sequences in 2012. With over 20 clinical trials for treating genetic diseases with genome-editing technologies underway, scientists, regulators, and patients continue to lag in addressing concerns over equity, racial justice, public health and ableism in biomedicine. This dissertation reframes concerns over the ethics of genome editing as a problem of institutionalization: How is the idea and discourse of genome editing rendered into a durable set of practices that become routine, legitimated and, ultimately, taken for granted?

Methodologically I draw from participant observation, in-depth interviews, and archival research. From 2015 to 2019, I've conducted participant observation following the extended case method at sites ranging from laboratories in the San Francisco Bay Area, to conference halls in Hong Kong. By observing scientists across these sites, I trace the winding trajectory of scientific practices as they move from the laboratory to the clinic. I have supplemented these observations with in-depth interviews with over 60 researchers and regulators. To gain purchase on the broader context of these observational data, I have collected over 880 archival documents ranging from Twitter threads, news articles, and clinical trial registries. From these sources I unpack the discursive struggles being waged over the moral and technical basis of genome editing and piece together which stakeholders are involved and when.

To describe processes of institutionalization, this project builds on past work in political sociology, science and technology studies (STS) and the sociology of organizations. Work at the intersection of these fields has analyzed the interplay between science and politics by tracing networks of actors and has identified mechanisms by which technologies are legitimated. I bridge these fields to develop a theory of institutionalization that centers the normative construction of technology. I describe how scientists produce new genome editing practices when managing technical, semantic, and regulatory uncertainty during the adoption of CRISPR technologies. These practices are then routinized and normalized in a way that affirms not only their epistemic contribution but also their moral value. For example, scientists used various metaphors, such as *gene surgery*, to bring these laboratory practices into the clinic. I further show how partnerships between academic laboratories and biopharmaceutical firms reify construction of genome editing as morally good.

Ultimately, I argue that scientists shape the direction of genome editing by resisting the encroachment of regulatory bodies, co-opting bioethicists, and carefully drawing the boundaries of self-governance. While this has allowed them to establish discursive and practical autonomy, it has also left patient communities, disability justice advocates and civil society groups on the sidelines.

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I had been told that writing a dissertation in sociology was a lonely exercise. I suppose this is partially true, especially for a project that was completed during the COVID-19 pandemic. I would certainly like to keep the follies and fumbles of this project to myself. However, the other part, where this dissertation succeeds and constitutes a creative contribution, is due to a community of intellectual and emotional support. I am in grate debt to this spectacular and loving community.

First and foremost, my intellectual partner and friend Vivi H. Nguyễn has been a beacon of reason, critique, and growth. In my view, to be committed to an ethnographer means to be participate wholly in the coproduction of the ethnography. From joining in lab holiday parties and lab picnics to an international conference in Hong Kong, through their own lens, Vivi helped ground this inquiry and unpack my own musings, and sometimes frustrations, with the field. Since my primary field site was local, this work was constant. I would bike home, down Shattuck Ave. in Oakland from campus or off the BART, having squeezed my bike through crowds of commuters, and show up stoked to talk through the observations of the day with them. I credit Vivi with cultivating in me the tools to think critically not just about the organizations I observed, but to think critically about my own complicity in the process of science and my participation in elitist institutions.

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Since I spend some time in this dissertation unpacking the politics of acknowledgement, it is worth explicitly stating that this project would not have been possible without the support of my informants. They not only put up with my presence and constant questioning but welcomed me in as a member of their community. While I cannot thank them by name, I hope this project contributes to the development of a reflexive and socially just science. This project was also supported through generous funding from the National Science Foundation (DDRIG#190432).

Ch.1. Introduction: Discovering Genome Editing Discourse

1.1. From Bench to Bedside.

> "There are a couple of the points that you can look back and say, "here's where things changed," and I think that this would be one of those times. Because it's always been hard to change genes. In biology there are these things called model organisms. They are ones where we found tools to do genetics: change genes, ask what do these genes do and things like that. […] And using this variety of genome[1] editing tools its now become clear that we can do this not only in human cells, but we can do it a huge number of other non-model organisms. […] And now not only do we have a way to make models of disease, we have ways of asking questions about the biological world around us that we had never been able to answer before." – Jacob Corn, genome editing scientist, during an interview with a journalist, in March 2016.

> "They go from cells that make sickle cells to super-cells — the cells that help me be better. […] That's what all of this is about — the edited cells. It's the super-cells that's what's going to make the difference between me having the sickle cell pain crises and not having them," - Victoria Gray, the first sickle cell patient to participate in a CRISPR-based genome editing clinical trial, July 2019 (Stein 2019)

In rare and welcome moments, science stubs its toe on something previously unseen. In even rarer moments, that same thing may be recognized as being itself capable of finding more things—and so science continues to stumble along. The CRISPR-Cas9 system is one of these rare things. CRISPR, pronounced 'cris-per', and the class of associated enzymes[2] (Cas, Cas9 being one of many) has been heralded by researchers as a revolutionary biotechnology. Since the first publication that showed that CRISPR-Cas9 could be used as a tool for modifying DNA sequences (Jinek et al. 2012), researchers have developed CRISPR-Cas9 into an entire laboratory toolbox for finding new things, answering old questions, and posing new ones. As the first quote above from molecular biologist Jacob Corn suggests, the revolutionary potential of CRISPR techniques at first lay in their power as experimental tools in the lab. The scientists who have rallied around this technology have propelled what they characterize as a new paradigm for how science approaches the biology of all living things: genome editing.

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[1] Throughout the dissertation I include brief footnotes defining biological terms. In some cases, these are borrowed by a technical glossary developed by the science communication team at my field site. The "genome" refers to the entire DNA sequence of an organism or virus. The genome is a huge set of instructions for making individual parts of a cell and directing cellular processes. It includes individual genes that code for proteins as well as non-coding regions of DNA.

[2] Enzymes are proteins that catalyze biochemical reactions in cells, fulfilling crucial metabolic and functional mechanism of cell life.

The second quote above captures the promise of genome-editing technologies for those who perhaps stand to gain the most from this scientific innovation: patients of rare genetic diseases. Among researchers who hoped to bring CRISPR-Cas9 to the clinic, sickle-cell disease arose as an early poster child for therapeutic genome editing because it was the first molecular disease to be fully characterized at the genetic level, and despite the significant need, there are few options for patients. Victoria Gray, a 35-year-old Black woman from Mississippi, has become that literal poster child after NPR aired exclusive interviews with her once she started treatment for the first ex-vivo[3] genome-editing clinical trial in the United States in 2019. With over 20 clinical trials for treating human diseases by "editing" the DNA of patients underway in 2020 (Henderson 2021; Li et al. 2020; Urnov 2020), scientists and regulators wait anxiously for early evidence of more patient outcomes like Victoria Gray's recovery to date.

This dissertation explores the winding and uncertain trajectory of genome editing as it travels from the laboratory to the clinic. I trace the discursive struggles between academic scientists, biotechnology firms, biohackers, disability justice advocates, pharmaceutical companies, regulatory bodies, research hospitals and patient communities involved circulating this biotechnology, using it, and legitimizing it to broader publics. This dissertation frames these struggles as a problem of institutionalization and asks: How is the idea and discourse of genome editing rendered into a durable set of practices that become routine, legitimated and, ultimately, taken for granted?

To answer this question, I draw from ethnographic, interview and archival data to interrogate the sites at which ethical guidelines and standards of practice are articulated around emerging genome-editing technologies: How are new experimental protocols developed? How do best practices and ethical agreements become institutionalized into formal policies, guidelines, and norms? How do democratic efforts at deliberation between scientists, patient groups, industry, bioethicists, and social scientists contribute to this process, if at all? What is at stake in adopting terminology and metaphors for modifying DNA? And what and whose interests are reflected in this process? Studying institutionalization ethnographically allows me to capture the progression of genome editing as it is being articulated, as one scientist put it at a conference, "we are building this car [genome editing] as we are driving it down the road […] everything is constantly changing," (Field Notes, May 2016). This dissertation takes this indeterminacy as an epistemic starting point and develops a methodological approach that flexibly, but systematically, responds to the field as it shifts (see Methodological Appendix).

Previous research in sociology and science and technology studies (STS) suggests that whether the technology underlying genome editing, the CRISPR-Cas9 system, is fated to be a flash in the pan or a durable fixture in biomedicine will not just depend on whether the clinical promise of the technology is realized or not. It also depends on whether robust and reproducible alignment can form between the multitude of actors involved in the practice and politics of genome editing and whether the practice of modifying human DNA can be normalized. In short, the production of knowledge and technology is coupled with the production and transformation of a corresponding social order, both internal to science (Bourdieu 1975; Frickel and Gross 2005; Hagstrom 1965; Kuhn 1962) and external to it (Jasanoff 2004; Latour 1993; Merton 1938; Mukerji 1990). The insights of philosopher of science Thomas Kuhn offer a useful heuristic to help explain how "The CRISPR

[3] *Ex-vivo* editing refers to an experimental process where a patient's cells are modified outside of their body and then re-implanted, as opposed to *in-vivo* which would be modifying the cells without taking them out of the tissue where they live.

Revolution" works. For Kuhn, science progresses through a circular dialectic of revolutionary science and normal science, where the observation of a new phenomenon or technological breakthrough that makes that observation possible challenges the received wisdom of the pre-existing paradigm (Kuhn 1962). That *revolutionary* observation then eventually stabilizes and becomes its own basis for the more sustained mode of knowledge production via puzzle solving that Kuhn calls *normal* science. Since Kuhn's writings, two things have changed: social scientists have empirically specified the social mechanisms by which this paradigm shift happens, for example, through the political contestation over authority and consensus in the field (Au 2021; Frickel and Gross 2005; Parker and Hackett 2012; Shwed and Bearman 2010); second, scientists themselves have adopted and internalized Kuhn's terminology (Restivo 1983).[4] The approach I take here factors in these developments and pushes past the binary of internal and external determinants of scientific change through an analysis of the affective and normative frameworks surrounding scientific work. As a postdoctoral researcher put it after I described my project's focus on institutionalization, "I get it. You are trying to explain what it will take for CRISPR to become boring."

As I describe in this introduction, this sociological approach to understanding genome editing through the lens of institutionalization departs from the story of CRISPR thus far as told by scientists and journalists. It differs not because I am interested in what makes CRISPR boring, but because it situates genome editing historically and develops an account of its social emergence, rather than its social impact. Here, I first begin to analyze how the discourse of genome editing itself is the subject and object of a social and historical process. I draw from work in the philosophy of science and the social construction of technology to unpack the layered ontology of the CRISPR-Cas9 system. I then clarify the theoretical bases of the dissertation, which is built on work in political sociology of science, the sociology of standards and technology, and the sociology of bureaucracy and organizations.

1.2. Metaphors of Mutagenesis

In addition to being described as a "revolution" CRISPR-Cas9 is referred to in many ways: as a system, an editing tool, an autoimmune strategy, a technique, a therapy, a technology, and a security risk. Scientists regularly refer to the activity of Cas9 as "cutting" and scissors regularly appear in conference slides and diagrams depicting the technology (See Fig. 1). This discursive heterogeneity has only multiplied alongside the spread of CRISPR and the media hype it has generated. Since 2015 every major U.S. news media outlet has produced an article on CRISPR-Cas9. The advent of CRISPR-Cas9 has been fodder for sensational news titles and has fueled provocative imaginaries about genetically engineered designer babies (Regalado 2015), a cancer free world (Khan et al. 2016; Shi et al. 2015), malaria resistant mosquitos (Ledford and Callaway 2015), biological terrorism (Acharya and Acharya 2017), bio-engineered artwork (Yetisen et al. 2015), and billions of dollars' worth of biotech and corporate investment (van Erp et al. 2015). The adoption of CRISPR-Cas9 in a wide variety of economic sectors suggests that it is a potential general-purpose-technology (GPT). GPTs are a class of innovations recognized by economists to restructure and reinvigorate of economic growth in multiple sectors of industry (Bresnahan and Trajtenberg 1995; Helpman 1998). Journalists mainly draw from interviews with high-profile lab Principal Investigators (PIs) and key review articles published in major journals like *Science* and *Nature*. Virtually all news articles aim to

[4] This is analogous to the co-optation of Marxist critiques by the capitalist and bourgeoisie and resulting accommodation of capitalism (Boltanski and Chiapello 2005)

answer two questions: What is CRISPR-Cas9? And why does it matter? Answering these questions depends on whom you ask.

Figure 1. Scientists regularly refer to the activity of Cas9 as "cutting" and scissors regularly appear in conference slides and diagrams depicting the technology. Image taken from presentation slides compiled by Integrated DNA Technologies, a large for-profit supplier of nucleic acids. The presentation, "Rewriting the Genome with gBlocks ® and Synthetic Fragments, Harnessing the Power of CRISRP and Synthetic Biology," aims to summarize CRISPR/Cas technology and highlights the company's products that support scientific work with CRISPR-Cas9. (Clore 2015)

The readymade account found across news articles, in introductory methods slides, or biology glossaries define CRISPR-Cas9 as a genetic engineering tool in molecular biology by which the DNA of living organisms can be modified. Definitions then typically refers to the origin of the technology, as an anti-viral immune system found in nature across species of bacteria. For a bacteriologist, CRISPR is neither new nor revolutionary. In 1987, or 26 B.C. (Before CRISPR) as one scientist put it (Urnov 2018), scientists in the field of bacteriology stumbled upon CRISPR in *Escherichia coli* (Ishino et al. 1987). CRISPR was later functionally characterized as a complex molecular immune "system" (Bolotin et al. 2005; Hsu, Lander, and Zhang 2014; Mojica et al. 2005; Pourcel, Salvignol, and Vergnaud 2005). The acronym stands for Clustered-Regularly-Interspaced-Short-Palindromic-Repeats (CRISPR), which is a region in the bacterial genome where the genetic signatures of viruses that the bacterial cell has fought off are recorded. This "CRISPR region" gives the bacterial cell the information needed for the Cas enzyme to recognize viral DNA and "cleave" the virus DNA, thus protecting the bacterial cell from future attacks. Cas enzymes are part of a class of enzymes called nucleases; they attach themselves to strands of DNA and break apart the DNA molecule at a specific site.

In 2012 researchers in biochemist Jennifer Dounda's lab at UC Berkeley and their collaborators were able to modify one of these Cas enzymes, Cas9, and show that it could be used to "edit" DNA *in vitro* (Jinek et al. 2012). CRISPR-Cas9 had been instrumentalized; in a profound sense it had been decontextualized from its place as a bacterial immune system and repurposed. It had

been "domesticated" and conceived of as a modular and programmable technology (Urnov 2016). As a technology, there are essentially two parts to the mechanism of CRISPR-Cas9: the Cas9 enzyme and a guide RNA (gRNA). The gRNA is a synthetic molecule that matches to the "target" sequence where you want to make a modification. It is basically the instructions you give to the Cas9 enzyme to go do its thing. It is in this sense that researchers refer to Cas9 as "programmable"; it can be instructed to go to any specific "target" region of the genome. At a fundamental level, Cas9 does not itself change DNA sequences, it merely cuts DNA, increases the chances that a mutation will occur at the site where it cut. In this sense, it most accurately defined as a tool for *directed mutagenesis*.[5]

What this means is that no laboratory has a tube with the label "CRISPR." You will however find tubes for Cas9 and guide RNAs. To the humor of some scientists, BBC news coverage in 2017 of the use of the genome editing in human embryos showed a video of a micro syringe piercing a human embryo and the letters "CRISPR" flowing through the syringe into the embryo (Figure 2.). This use of the term, while technically inaccurate, makes some sense since "CRISPR" is the discursive shorthand for the technology.

Figure 2. BBC News clip describing an experiment performed by British scientists where "CRISPR" is injected into human embryos.

Along with scientists and journalists a host of other actors would similarly ask and answer the question, "what is CRISPR-Cas9?" Ethicists, industry representatives, high school students, patients, and I shaped our understanding of CRISPR-Cas9 in relation to commitments and interests that are implicitly or explicitly held both specifically towards CRISPR-Cas9 and more broadly in daily life. Explaining and analyzing the commitments that underlie answers to the question "what is

[5] Mutagenesis is an umbrella terms that describes the creation of a mutation anywhere on the genome. Mutations can be a single nucleotide change (A to C), insertion of longer sequences, deletions, or translocations.

CRISPR-Cas?" however, are complicated by fundamental discursive ambiguity that is pervasive throughout the discourse of genetic engineering: the referent of the acronym "CRISPR-Cas9" shifts between the phenomenon and the technology.

Work in the history and philosophy of science and in sociology of knowledge has laid useful groundwork for unpacking this ambiguity. For Kuhn, what this complex history underscores is that "any attempt to date the discovery must inevitably be arbitrary because discovering a new sort of phenomenon is necessarily a complex event, one which involves recognizing both *that* something is and *what* it is." (Kuhn 1962:55). CRISPR-Cas9 is a case of what historian and philosopher of science Gaston Bachelard referred to as "phenomeno-technology." That is, a method of objectification whose purpose is to "amplify that which is beyond appearance," (Bachelard 1984:13). Objectification, as I use it here, refers to the process by which nature is instrumentalized and treated as "standing-reserve" (Heidegger 1954), or as something ready-made or open to use. As part of theory of technology, this in Marxist-Heideggerian approach conceptualizes technologies as instruments of production that are only temporarily taken out of their natural context. Because biotechnology is in this sense an ontological hybrid, shifting between a natural phenomenon and an instrument, it is analytically problematic to take for granted scientists' straightforward account that CRISPR-Cas9 is a tool, akin to a "pair of scissors for DNA," (see Figure 1). Historian of science Hans-Jörg Rheinberger builds on Bachelard's philosophy to introduce the distinction between *epistemic things* and *technical objects*. On the one hand *epistemic things* are the objects of scientific inquiry, and on the other, *technical objects* are the experimental conditions that produce or reveal. In practice, the two are in a dynamic interplay; "the technical conditions determine the realm of possible representations of an epistemic thing: and sufficiently stabilized epistemic things turn into the technical repertoire of experimental arrangement," (Rheinberger 1997:29). Rheinberger focuses on the practices of experimentation of scientists in a specific laboratory. In this way, he localizes this stabilization to the experiences of scientists in their workspaces, interacting with natural phenomenon alongside instruments in an organized arrangement he called an *experimental system*. Because of this dynamic, new biotechnologies, like the CRISPR-Cas9 system, can be used without knowing everything about how they work.

As Bachelard, and later other analyses of technology, recognized, this process of stabilization, or elsewhere "translation" (Gerson 2015), is conditioned on the ability of scientists to de-situate phenomenon conceptually through the explanations and representations that identify the object (Bijker, Hughes, and Pinch 2012; Nersessian 2005). Existing models of this process suggest that once sufficiently stabilized, the complexity of the phenomenon is reduced and black boxed, enabling its mobility across social worlds (Howlett and Morgan 2011; Latour 1987). For example, in his own study of the emergence of the polymerase-chain reaction technique[6] (PCR), anthropologist Paul Rabinow has suggested that when a biotechnology is put into a new context, the ontological status of the object itself is shaped by the new interests and commitments that scientific actors in the new experimental setting bring to bear on the technology and its underlying phenomenon (Rabinow 1996).

[6] PCR is a technique that allows scientists take a small amount of DNA and make millions or billions of copies of it, allowing scientists to study it in greater detail via sequencing. It has become a fundamental technique of modern biology and biomedicine that is highly routinized since its invention in the 1980s.

The notion that things found in nature, such as the CRISPR-Cas9 system, can be neatly thought of as discrete tools is further unsettled when we look at the early discourse surrounding genome editing. Scientists who aimed to use the CRISPR-Cas9 system developed metaphorical representations of what the biological phenomenon *is* to articulate the CRISPR-Cas9 system to their experimental work and manage the epistemic uncertainty that is endogenous to biological complexity. It is not a novel insight that scientists use metaphors to instrumentalize things in nature in an effort to stabilize them or use them to communicate. Historian of modern biology Evelyn Fox Keller has argued that, "scientists working in a specific field of research form a restricted linguistic community whose members recognize and share the use of key metaphors in their domain," (Keller 2002:135) and in this sense are constitutive of the cultural boundaries of subfields. Modern biology, for example is organized around the metaphor of DNA as information or text, for example the Human Genome Project "de-coded" human DNA, genomes are the "blueprints" of life (Lewontin 2002:3).

Beyond their use for understanding processes or phenomena that cannot be directly observed, metaphors can embody political and economic value. In the 1970s, the metaphor of the cell as a factory helped genetic engineering scientists develop practices and regulatory policy for advancing the biotech industry (Colyvas 2007). An analogous case, outside of biology, is the metaphor of "algorithms" and its corresponding family of metaphors (e.g. "run" and "cloud") which shape the "public-facing identity and new promotional discourses that depicts [computational processes] as efficient, valuable, powerful, and objective," (Sandvig 2014). Even at a greater scale, metaphors do meaningful moral work. Take for example, sociologist Marion Fourcade's analysis of the clustering of different nations in international financial discourse as 'BRICS' (Brazil-Russia-India-China) versus 'PIGS' (Portugal-Italy-Greece-Spain) based on a symbolic representation of their economic trustworthiness (Fourcade 2013). How then do the metaphors surrounding genome editing shape the development of the frameworks of morality and value that institutionalize directed mutagenesis?

Many of the metaphors surrounding the CRISPR-Cas9 system are incommensurate and have divergent moral and practical implications. A non-exhaustive list of the metaphors surrounding CRISPR would include editing, a find and replace function for DNA, molecular scissors, a gene scalpel, a sledgehammer, Swiss Army knife, guided missile, programmable nuclease, etc. In Fall 2015 at the first "CRISPR Revolution Meeting" at Cold Spring Harbor Laboratories on Long Island, New York, I sat in the audience as researcher after researcher shared their own slides that attempted to represent a linear history of genetic engineering tools. For example, one started by characterizing early genetic engineering technologies as stone tools, then knives and spears, and then CRISPR as Swiss Army knife. Another presenter used a history of transportation: the wheel, then a horse drawn buggy, then the Ford Model-T, then CRISPR as Optimus Prime, the fictional sentient semi-truck in Transformers. Bioethicists and researchers in the humanities have recently scrutinized these metaphors in hopes of improving how scientists communicate their work. For example, bioethicist Megan O'Keefe and colleagues argue that the metaphor of "editing" obscures the ethical and safety risks of making changes to the genome, connoting a benign change or correction (O'Keefe et al. 2015). Additional work in disability studies has challenged the metaphor of DNA as text in the Human Genome Project, suggesting that this metaphor implies normative connotations for what is "the standard" human (Wilson 2002).

As the concept of genome editing circulated more widely, the discourse and basic grammar surrounding the technology also developed. For example, during a talk given by a prominent genome-editing researcher, a physician asked whether brain cells could be 'CRISPRed'. This use of

the term as verb departed from the standard use in the field and the presenter chuckled, "Yes there are some groups working on editing neurons." Within the field of gene editing, some researchers try to avoid using 'CRISPR' all together, preferring instead to the use the actual molecule "Cas9" or its derivatives when talking about the technology. Similarly, researchers at the forefront of the technology debated whether to use a hyphen (CRISPR-Cas9) or a dash (CRISPR/Cas9) arguing over the implications of suggesting the system was composed of both CRISPR *and* Cas9 versus CRISPR *or* Cas9. These discussions would sometimes then become the basis for the development of more stable classificatory standards, such as those found in textbooks, glossaries, and formal guidelines of experimental practice.

The multi-valence of CRISPR-Cas9 is additionally complicated by its wide variety of applications as an experimental tool. To briefly summarize its applications so far, CRISPR technologies are used to conduct: a) "knock-out" experiments, which are tests of function where a gene is deleted or its expression is regulated: *negative manipulation*; b) editing experiments where a specific mutation is induced, or "knocked-in": *positive manipulation*; c) genome-wide screens for identifying genes or loci[7] associated with a particular phenotype (Gilbert et al. 2014): *identification*; and d) fluorescent tagging of genes and proteins for studying protein-protein interactions and for visualizing the genome (for more detailed reviews see (Addgene 2016; Ran et al. 2013): *visualization*. This diverse set of methodological uses illustrates the degree to which the initial CRISPR-Cas9 technology has been tinkered with and is being adapted for different experimental needs. Moreover, many of the underlying molecular mechanisms underlying the biological activity of the technology itself are still being characterized (Doudna and Charpentier 2014). In this sense, the objectification of CRISPR-Cas9 as a tool is pluralistic and the boundaries of genome editing are fluid.

Given the distinction and these complications, where then, could we look for a definition of CRISPR-Cas9? Common sources that anthropologists, historians, philosophers, and sociologists of science draw from to find such explanations and representations of biotechnology include peer-reviewed publications, grant proposals and other inscriptions found in laboratory settings, such as lab manuals and experimental protocols (Latour and Woolgar 1979). Furthermore, the full array of visual media in scientific work, such as graphs, models, diagrams, and photographs, has been sourced for explaining how scientific objects are constructed (Daston and Galison 2010; Griesemer 1990; Hacking 1983; Vertesi 2015). In addition, traces of the stabilization of scientific objects *as* tools are found throughout the bureaucratic infrastructure, "the files" (Weber 1922) surrounding scientific work (Star 1999). These include technology patents, technology-transfer forms, sponsored research agreements, institutional review board protocols, biohazard and work safety compliance documentation, and official policy reports that describe what CRISPR-Cas9 is being used for and to what end. They further provide a documentary record that scientists, administrators, policy makers and ethicists can draw from in subsequent performances of scientific work, during public engagements, when filing forms for local oversight, or during interviews with journalists to legitimize the science of genome editing. What the discursive heterogeneity surrounding genome editing suggests from a sociological standpoint, however, is that exactly what the CRISPR-Cas9 system is and what it is for not just open but was actively contested.

[7] A specific region on the genome; locus.

1.3. Editing Human DNA in Modern Societies

Calling genome editing a contested topic is putting it mildly. At the news of the ability to modify human DNA, popular discourse quickly turned to sci-fi narratives about designer babies and a new class of enhanced super-humans. Among experts, concerns over the equity, safety, and morality of modifying human DNA are widespread. The few surveys of the public in the United States conducted to date show wide support for the clinical use of genome editing to treat genetic diseases that are incurable or fatal such as Huntington's disease, and about two thirds of Americans also favor using gene editing to prevent the inheritance of non-fatal conditions such as blindness or reducing risk of disease (Scheufele et. al. 2017; AP-NORC 2018).

However, different patient communities have divergent views regarding the desirability of genome editing (Beckman et al. 2019). Disability rights activists contend that many of the diseases that have been identified as potentially treatable with genome editing, such as congenital forms of blindness and hearing loss, are not diseases at all (Beitiks 2016; Benjamin 2016a; Boardman 2020; Garland-Thomson 2020; Obasogie and Darnovsky 2018). Sickle-cell patients and their families are optimistic that clinical genome editing might work but are cautious because of the history of harm to Black communities at the hands of biomedical researchers. They also know it is unlikely that any resulting treatment will be affordable (Hollister et al. 2019; Persaud et al. 2019). In the absence of baseline shared moral discourse, it is likely that efforts to legitimize genome editing will be regularly unsettled.

To attend to these concerns, scientists, bioethicists, and a handful of social scientists have rushed to develop democratic forums to discuss the social and ethical implications of altering human DNA (Baltimore et al. 2015; Bosley et al. 2015; Guttinger 2018; Hurlbut 2015; Jasanoff, Hurlbut, and Saha 2015; Parthasarathy 2015). These discussions have largely centered on the possibility of making modifications to human DNA that can be passed down to children, modifying embryos for research and toying with human enhancement. While these democratic forums have helped draw more public insight to the topic of genome editing, it unclear whether or how they shape the practice of CRISPR-Cas9 at the lab bench. Additionally, few of these forums meaningfully engage with the history of biomedicine and eugenics.

Without an account of the ideological origins of the practice of manipulating human DNA and heredity, especially in the United States, it is likely that any effort to take CRISPR into the clinic will reproduce or exacerbate racial health inequities. The ideology underlying the increased penetration of genetic technologies and genetic explanations in the fabric of society was best articulated by sociologist Troy Duster. In his research, Duster traced the rise of attempts to explain human behavior and deviance in genetic terms starting in the mid-1970's. For Duster, this rise was due to the proliferation of the "prism of heritability," a lens through which the causal arrow of nature favors genetic determinism (Duster 1996). The advent of genome editing, however, suggests that Duster's estimation that "we are a long way from the kind of genetic manipulation that would permit a dash of blond hair or Olympic gymnastic potential here, a gene splice for some genius there," (Duster 2003:4) may have been premature.

This dissertation continues this line of sociological inquiry and offers a history of the present and look at possible future paths that for what genome editing is and will be in society. Will genome editing become part of the under-regulated reproductive industry? Will it receive the snake oil fate of unverified stem cell therapies? Will it be relegated to a laboratory instrument or standard experimental technique like PCR? Will it receive a regulatory freeze as a response to public outcry or become marked with distrust like GMOs? Will it become a popular commodity to be gifted on the holidays like direct-to-consumer ancestry tests? Or a celebrated reproductive ritual like over-the-top

gender reveal parties? Will it become a routine public health measure as part of a national health campaign to reduce the incidence of rare genetic diseases, improving the population for future generations? Or will CRISPR be replaced by a still undiscovered, more powerful technology and forgotten?

1.4. Disentangling Institutionalization and Normalization

Exactly what paths and what outcome the technology takes will depend on the scope of genome editing as an institution. Despite its utility and ubiquity in sociology, the concept of institution has many faces. Ambiguity in the operation of the concept has allowed for wide variety of social phenomena to be described as institutions: norms, categories, practices, and organizations can all be institutionalized. Institutions are typically seen as having one common property: permanence, which sets it apart from a fad. Some sociologists argue that the moral acceptability or legal legitimacy of a practice is an additional criterion, though this rarely seen as being both necessary and sufficient for something to treated as an institution. Take, for instance, the observation that a dowry was paid in 95% of marriages in India from 1960-2008, despite being illegal since 1961 (Anukriti, Prakash, and Kwon 2021).

Here, I define an institution as a practice or set of practices that can be reliably performed in different situations and reproduced over time (Berger and Luckmann 1967; Colyvas and Maroulis 2015; Jepperson 1991; Zucker 1977). An institution is enacted or performed by an actor, either an individual or an organization. Note that my use is different than that in common use, which sometimes treats institutions as synonymous with organizations. Instead, an institution can be thought of as a fixture of a society. Institutions can vary in scale, from something very micro- like shaking hands when you meet someone, to something broader historically and situationally, like racism. And yet they must endure the contingent fate of history; like shaking hands in the midst of the COVID-19 pandemic; or ignoring the state-sanctioned murder of Black and Brown folks in the wake of the George Floyd protests and the Black Lives Matter Movement.

Following Lynn Zucker (1977) and others, institutionalization is both a process and a property variable. It describes how a practice, typically a new one, comes to be seen as normal. As I explore in the chapters that follow, new institutions are constructed and reproduced at the site of interaction between different kinds of actors. In this case, between different kinds of scientists, between scientists and bioethicists, journalists, patients, regulators, and, on occasion, social scientists.

Throughout the dissertation I elaborate on the closely related concept of *normalization*: the fundamental process is one in which the moral becomes factual (Zucker 1977). By approaching institutionalization in relation to normalization, I can explore the discursive production of normative frameworks and the way they motivate or justify the enactment of specific practices when they are internalized. To avoid the pitfalls of functionalist conceptualizations of institutionalization (Robert King Merton 1957; Parsons 1951), normalization homes in on the interactionist (Blumer 1986) and phenomenological (Berger and Luckmann 1967) dimensions of institutionalization and centers on the work that actors engage in to stabilize practices (May et al. 2007; May and Finch 2009). In other terms, this approach to normalization has been described as the microfoundations of institutions (Harmon 2020; Harmon, Haack, and Roulet 2019; Meyer 2019). By combining this approach with an analysis of discourse, this conceptualization brings institutions closer to Foucault's concept of *dispotif* or apparatus, "a thoroughly heterogeneous ensemble consisting of discourses, institutions, architectural forms, regulatory decisions, laws, administrative measures, scientific statements,

philosophical, moral and philanthropic propositions -in short, the said as much as the unsaid. Such are the elements of the apparatus." (Foucault 1980:194).

Under this broad motivating framework, this project details the social mechanisms underlying the process by which genome editing is becoming *normative*. This aim is guided by and connects the insights from the literature in political sociology, the sociology of science and technology, and the sociology of organizations. While each subfield offers a rich theoretical body in their own right, this dissertation draws components of each to frame the process by which practices, norms, ethics, and regulatory policy develop as a process of institutionalization. The focus of each of the three literatures drawn from suggests three interlocking social mechanisms– whereby certain actors have varying degrees of influence over the process institutionalization and the fate of CRISPR-Cas9 technology.

Political Sociology: Standards and moral guidelines are heavily influenced by civil action and public responses to genome editing through the reconfiguring of networks and changes to policy discourse.

Past scholarship on the relationship between politics and science has identified two routes by which networks of organizations and individuals shape the direction, form, and content of scientific research. The first is through resistance and accommodation (Frickel and Moore 2006). Drawing from work in the sociology of law and social movements, these studies highlight cases where mobilized civil society groups can affect, for example, funding directives for biomedical research (Epstein 2009), the enactment of local environmental health policies (Frickel 2004; Kroll-Smith, Brown, and Gunter 2000), and the development of protocols for human subjects research (Moore 2006). In these studies, when organized social actors resist they are able to reconfigure the networks where decision-making power is held, leading to co-constructed consensus and in the process legitimating new arrangements of knowledge production and technology use.

The second route through which civil society groups can shape research governance is through policy discourse. Seen through this lens, the policy discourse surrounding genome editing represents "an organized assemblage of concepts, categories, narratives, metaphors, and frames that gives structure to an arena of policymaking" and if successful it can "become embodied in institutional structures, legal doctrine, analytical techniques, and standard operating procedures" (Hilgartner 2009:201). This can occur, for example, when journalism and other forms of media shape public opinion and, by extension, shape the frames and narratives adopted by policy makers (Campbell 2002; Gamson and Modigliani 1989). Overall, this political science framework suggests that interested non-scientific publics (patient advocacy groups, disability rights activists, religious communities, etc.) have the capacity to direct the course of genome editing research and influence the standards by which clinical applications will be evaluated as desirable, safe, and ethical.

Sociology of Laboratory Science: Standards and moral guidelines are the product of local practical compromises made by scientific stakeholders from academic and industry organizations.

Work in the field of sociology of science and technology offers additional theoretical grounding for the proposed project. Work in this field has emphasized the increasing ability of standards to impose order on modern social life (Star and Lampland 2009; Timmermans and Epstein 2010). Here, *standardization* refers to "a process of constructing uniformities across time and space, through the generation of agreed-upon rules," (Timmermans and Epstein 2010:71). In much of this literature, standards emerge as solutions to practical problems that arise from the complex

interplay of the actors, materials, and tools of the laboratory (Fujimura 1992; Jordan and Lynch 1998; Timmermans and Berg 2003). The social mechanism underlying the process of standardization highlighted in this literature is one where local actors identify "what works" for the specific epistemic challenges they are faced with.

This view is theoretically grounded in constructivist theories of knowledge production from laboratory ethnographies (Latour and Woolgar 1979). These ethnographic accounts theorize networks of human and non-human actors (ANT) where the outcomes of research are largely determined by which actors control the flow of information (Callon 1999; Latour 2005). More contemporary research in this vein has detailed the effects brought about by the increasing commercialization of academic science on laboratory work (Hoffman 2017). In part because of their empirical focus on the production of facts and the shaping of technologies, these scholars examine how technical standards are simultaneously the result of local political struggles over the control of resources and knowledge. As I describe in Chapter 2, participant observation in two biomedical laboratories actively using CRISPR-Cas9 suggests well-positioned scientists can rapidly disseminate the best practices and experimental protocols they develop, setting standards not just for their immediate projects but extending these to other scientists at conferences and through collaborations.

Sociology of Bureaucratic Organizations: Standards and moral guidelines are predominantly set by governing agencies based on prior agency decisions and bureaucratic procedure.

A key insight from prior research on standards is that they rarely exist independently of other standards (Star and Lampland 2009). In fact, this is the point emphasized by many studies of bureaucratic practice and the challenges to enacting policy changes (Clemens and Cook 1999). Instead, the existing regulatory models of the larger institutions that researchers work in can shape how organizations establish and maintain legitimacy (Suchman 1995). This work provides useful analytics and a rich body of work for representing the processes by which practices become institutionalized (Kimberly 1979; Levitt and March 1988; Zucker 1987). Additionally, the insight that formal rules and roles are often decoupled from how they operate in practice, in a way that does not hamper the workings and stability of an organization (Meyer and Rowan 1977) motivates the research questions of this dissertation. When applied to science, these theories have illustrated how scientific work processes are shaped by their local organizational contexts (Shwed and Bearman 2010; Vertesi 2015).

Research on the role of routines in governance has extended Weber's theory of bureaucracy (Weber 1922) to study the academic and governmental organizations that govern and fund science. These studies have, for example, shown that institutional review boards (IRBs) reviewing biomedical research rely heavily on the spirit of past decisions made by the IRB during the review of novel protocols (Stark 2011). Research on the organizational innovation that led to the institutionalization of biotechnology patenting has also shown that decision-making practices that were originally conceived to be special-one-off cases can become archetypes for future decisions (Berman 2012b; Colyvas 2007). More specific to the aims of this project, studies of the FDA, following Weber's theoretical insight, have highlighted how individuals in the agency can garner reputation and become gatekeepers, precluding the possibility of new policies and guidelines being instituted (Carpenter

2010). Overall, research in this subfield in the sociology of organizations suggest that regulatory organizations themselves are likely to more autonomously set technical standards and ethical guidelines based on previously established routine.

1.5. Methodology[8]

Guided by these frameworks, in order to study the process by which standards of practice and ethical guidelines for therapeutic genome editing are institutionalized, since 2015 I conducted multi-sited participant observation, in-depth interviews, and archival research. Methodologically, this approach was rooted in the *extended case method* of participant observation, a model of participant observation that emphasizes the extra-local and historical conditions of the object of study (Burawoy 1988; Tavory and Timmermans 2009). By relying on comparative data from multiple sites, the extended case method can trace decentralized social processes that would otherwise be difficult to reliably observe. The extended case method is additionally well suited for examining the hypothesis outlined by the literature because of the method's emphasis on a more deductive interplay between theory and data. In this way, I innovate methodologically on the tradition of laboratory studies which has primarily focused on observing and detailing scientific work inductively in specific situations and discreet sites (Clarke, Friese, and Washburn 2015).

By following proponents of genome editing into their social networks and capturing their engagements in particular sites of discursive contestation, technical standard setting and ethical guideline articulation, my dissertation develops a thickly-described, empirical account of how and in what ways genome editing is getting instituted by its adherents. The project draws from data collected at two kinds of sites from 2015 to 2019: 1) research laboratories and their parent organizations; and 2) public and private meetings of professional associations of scientists and regulatory bodies. I purposively selected formative moments— or "field-configuring events" (Hardy and Maguire 2010)—where I could directly observe stakeholders in social context as they attempt to define, assert, and contest genome-editing discourse with each other and their professional communities. Over the course of this fieldwork, 50 semi-structured and ethnographic interviews were conducted with scientists at all career stages, regulators, staff members, citizen scientists, and bioethicists.

Drawing from observational data gathered at laboratory meetings, the lab bench, conferences, poster sessions, and online forums, a core piece of this research extends from being embedded as the "house sociologist" or "resident ethnographer" in two labs: One is focused on studying a form of congenital blindness and is based out of the Gladstone Institutes of UCSF. The other, based out the Department of Molecular Biology at UC Berkeley is focused on developing novel applications for the CRISPR-Cas9 system and clinical genome editing for sickle-cell anemia. Data gleaned from this research has given me purchase on the production of local technical standards by research assistants and graduate students who are tasked with figuring out optimal conditions for experiments.

To observe how and whether civil society groups and non-scientific publics can shape the genome editing, I have analyzed the international summits convened by the National Academies of

[8] This research has been approved by the Committee of Human Subjects at UC Berkeley, Protocol ID 2016-08-9036.

Science, Engineering and Medicine (NASEM) in Washington DC, in 2015 and in Hong Kong, in November 2018. These summits offer an opportune site at which to study the discourse surrounding genome editing. To further exhaust possible data sources that may evince changes in the policy discourse around genome editing in the ethical guidelines reported by NASEM (2017), I have obtained comments submitted to the NASEM Genome Editing Consensus Study committee by external sources from the Public Access Records Office (PARO) of the NASEM.

To gain purchase on the broader context of these observational data, I have collected over 880 archival documents ranging from Twitter discussions, peer-reviewed journal articles, blogs, Reddit AMAs with leading scientists, policy reports, news articles, film clips, handbooks, and clinical trial registries. From these sources I unpack the discursive struggles being waged over the moral and technical basis genome editing and piece together which stakeholders are involved and when. Analyzing the discourse across these various forms of media, has helped me better understand how scientists and bioethicists produce and frame genome editing and how genome editing discourse spreads and is reframed by a swath of publics (venture capitalists, patients, disability rights activists, journalists and biohackers).

I expand on my methodology, its assumptions, strengths, and limitations in the Methodological Appendix. I elaborate how I used these data to triangulate the unfolding of events and the paths of institutionalization that were not taken by genome editing scientists. Of crucial importance to understanding these data, I detail my own reflexive position and, in some cases, complicity in the institutionalization of genome editing.

1.6. Summary of Argument

The narrative arc of my argument is structured by my descriptive account of the process of institutionalization. Here the narrative essentially travels from the daily frustrations of graduate students trying to make experiments work at lab benches outwards to large live-streamed public conferences that make international headlines and the cafeteria tables outside of closed-door committee meetings for setting measurement standards in a secure government facility. The data are presented in roughly chronological order. At the heart of the dissertation, I advance the claim that scientists can produce new institutions autonomously through the construction of novel technologies and control over the terms of discourse, discourse that entrenches the moral frameworks that normalize these technologies. The scope of the institution (what it applies to and who reproduces it) in part depends on the mobilization of different actors and the establishment of durable collaborations between them. As I explore, the political positioning of scientists in academia, biotechnology firms, media outlets, patient groups and regulatory bodies in relation to CRISPR determines the scope of genome editing as a social institution.

In **Ch. 2 The Construction of CRISPR-Cas9 Technology and the Circulation of Practice** I describe how scientists use the technology and get it to work for the purposes of their research programs. I sketch out a model of how scientific research programs advance and draw from my ethnographic data in two laboratories to illustrate the progression of research projects in light of the experimental opportunities afforded by genome-editing technologies. This chapter describes the technical details of new experiments and the biological phenomenon being studied to illustrate how the construction of genome editing stands in a dynamic relation to the content of scientific research. I show how scientists at the lab bench navigate multiple forms of uncertainty when they adopt genome editing practices. I argue that through the management of this uncertainty at the time of adoption, new practices are produced and refined that then continue to institutionalize genome

editing at the level of laboratory. In effect, this chapter describes how genome editing must be brought into step with pre-existing routines, local repertoires of practice, and standards of measurement in the laboratory to be operationalized. I further show how and why genome-editing practices were able to spread rapidly across laboratories in a way that outpaced previous genetic engineering techniques. I describe the crucial role of the creation of social and material infrastructures that enable the circulation of genome-editing practices throughout academic laboratories and between the various subfields of the life sciences.

Ch.3 The Production of Organizational Structures and the Moral Economy of Genome Editing turns to account for how interactions and partnerships between academic laboratories and the biotech and pharma industries shapes the institutionalization of genome editing. To do this, this chapter illustrates the ways in which academic capitalism is both a determinant of the organizational structures within which CRISPR is used and is also a cultural way of producing and attributing epistemic and moral value to its use. By drawing on the tensions that are endemic to public-private partnerships in science, I show how scientists come to internalize a moral order that serves to normalize genome editing as a social good. I also show how genome editing discourse reflects a tension between fervent optimism about the utility and feasibility of CRISPR and a deep anxiety and fear over its technical failures and eventual obsolescence.

Ch.4 Governance, Crisis, and the Normalization of Genome Editing takes a step back to understand the origins of the political basis that has allowed the governance genome editing to be led by scientists. I examine social and cultural conditions behind the highly publicized case of He Jiankui, the scientist who claimed to "create" the first genetically modified babies at outset of the Second International Summit on Genome Editing in 2018. From this analysis of the crisis of legitimacy that ensued and the repair mechanisms that followed, I show how a pattern of positive deviance is reproduced at the edge of science and how scientists' moral ambivalence towards the ethics of genome editing is co-constructed and maintained through bureaucratic governing structures.

Finally, in **Ch.5 Conclusion: Towards a Biopolitics of Genome Editing** I examine the implications of theory of institutions for sociological work on scientific change. I additionally describe the impact of my findings for civil society, which has, to this point, not been given a seat at the table in the governance of CRISPR. I argue here for the development of an account of the biopolitics of scientific and technological institutions to better understand how sociology can contribute to a more egalitarian and equitable basis for addressing health disparities.

Ch. 2. The Construction of CRISPR-Cas9 Technology and the Circulation of Practice

> Emmanuel Charpentier and Jennifer Doudna: "Their technique, CRISPR-Cas9, gives scientists the power to remove or add genetic material at will." – *TIME Magazine*, 100 Most Influential People. (King 2015)

> "Developing any technology as complex and widely used as CRISPR invariably involves contributions from many scientists. Patent fights over claims of discovery and licensing rights are common. Zhang, the Broad Institute, and M.I.T. are now embroiled in such a dispute with Jennifer Doudna and the University of California; she is a professor of chemistry and of molecular biology at Berkeley."**–** *The New Yorker* (Specter 2015)

> "You can't stop science from progressing," Jinek says. "Science is what it is." He's right. Science gives people power. And power is unpredictable. – *Wired* (Maxmen 2017)

Existing narratives of the origins of the CRISPR-Cas9 genome editing system will typically attempt to pinpoint a moment of creative ingenuity and become embroiled in the historical details of CRISPR's mythology (Doudna and Sternberg 2017a). Such as the events surrounding Jennifer Doudna and Emmanuel Charpentier on the streets of San Juan, Puerto Rico where they met at a microbiology conference and began the collaboration that would lead to the first study to suggest that the system could be instrumentalized (Jinek et al. 2012). Other authors venture into the depths of bacteriology and virology, or the vats of a Danish yogurt factory, where the molecular functions of CRISPR in nature were characterized. Both accounts, however, fall prey to the romantic idea that scientific innovations are attributable to individuals, an idea that is upheld by merit systems in science but exists in tension with scientists' own understandings of the collective work of their communities. A linear understanding of institutionalization would place the first step of the process in the hands of the individual or community responsible for the production of a practice. Indeed, the questions of how new practices are developed and how they spread are typically treated as analytically separate by sociologists and economists who study innovation and emergence (Padgett and Powell 2012). For example, one prevalent model of how new technologies and the practices associated with them spread draws from an epidemiological metaphor to describe the diffusion of innovation through networks of actors following lines of communication. This model typically treats the innovation as a stable entity, making it easy enough to pinpoint an inventor or site of first diffusion. The issue with this model is that it obscures the dynamic process by which the object, in this case an epistemologically and ontologically unstable biotechnology, interacts with and is shaped by its application. Instead, a Foucauldian approach to the spread of genome editing offers the spatial metaphor of circulation, whereby the unruly nature of discourse and practice is embraced.

Rather than delving into the work of the Doudna or Charpentier, both of whom received the Nobel prize for the invention, I trace the work of the construction of genome-editing practices to those laboratories who would be "early adopters" in a diffusion of innovation model. In this

chapter, I first draw from my observations of scientists at two biomedical laboratories in the San Francisco Bay Area to argue that new genome-editing practices are produced as they are adopted and adapted. Then, I travel to Cambridge, MA to better understand the social and material infrastructures that facilitate the sharing of genome-editing practices and rapidly accelerated the spread of CRISPR. I argue that scientists construct genome-editing technologies when they adopt them and attempt new experiments in the context of their research programs. But why focus on adoption as a way of explaining the production of novel practices? Doesn't something need to be invented first for it to spread?

Previous sociological research has shown that the edge of scientific change is characterized by a lack of consensus over standards of validity and the absence of agreed upon terminology (Peterson 2015; Star 1985). Additionally, scientists must confront ambiguity over the utility and moral value of the new horizons they work on (Hoffman 2017; Shapin 2008). I make the case here that the construction of practices ultimately arises through scientists' management of epistemic, semantic, and regulatory uncertainty at the edge of science. This chapter examines the relationship between these uncertainties and the production and adoption of genome-editing practices. To make this case, I link individual scientists' strategic decision-making under conditions of uncertainty and the complex arrangement of research instruments, biological materials and practices that are constitutive of biomedical research. This shows how the production of new institutions in science is a function of how arrangements between scientists, their materials and their organizations change over time. While the strategic leadership decisions of principal investigators (PIs) were strong drivers of how CRISPR was constructed, the differences between how laboratories use and develop the CRISPR-Cas9 system are also shaped by the collection of practical repertoires held by personnel within laboratory and the partnerships held with industry funders and academic collaborators. As a function of institutionalization, situations of uncertainty serve as sites at which different actors' understandings of what genome editing is and how to talk about it can converge or diverge. As CRISPR-Cas9 is adopted into new research contexts, its meaning changes and its institutional scope widens.

The magnitude and speed of the adoption of CRISPR-Cas9 is an indicator of how genome editing, as an institution, has spread. This can be roughly measured by using the scientometrics of CRISPR as a proxy. A quick query through the Web of Science, shows that the number of papers per year reporting the use of a CRISPR-based technique grew from 1,716 in 2012, to 13,311 in 2019, a growth in magnitude that dwarfs prior technical breakthroughs in genetic engineering. However, during periods of rapid advancement such as this, scientific work is surrounded by a great deal of uncertainty. With each adoption, scientists like the ones I observed must ask themselves various questions as they navigate the hype around CRISPR: Will new, faster, or more accurate developments replace current technologies? Will new regulations curb investment in the technology and its products? Is the technology as precise as its proponents claim it to be? Will I be able to apply it to the organisms or cell lines I work with? And for biomedical researchers, will it be safe when the science of the lab bench is translated into the science of the bedside?

2.1. Technology and Uncertainty at the Edge of Science

When scientists are figuring out whether and how to adopt new experimental technology, previous studies of scientific change suggest that two things are key: whether they can make the technology work on what they want it to, and the organization of expertise connected to the lab. On the one hand, work in the sociology of science and technology tends to emphasize that the local

assemblages of materials and resources lead actors to construct and use technology in context-specific ways (Fujimura 1987, 1988; Knorr-Cetina 1983; Peterson 2015; Pickering 1993; Shinn 1998). On the other hand, studies of organizational change suggest that how firms and individuals respond to new technologies can be explained by their networks of communication and organizations' capacity to incorporate risky or novel ways of doing things (Cohen and Levinthal 1990). Some models of scientific change are roughly analogous to this, suggesting for example, that theory replacement and advancement are the product of social rearrangements of the field or the struggles between opposing groups of scientists (Bourdieu 1975; Fleck 1935; Frickel and Gross 2005; Kuhn 1962; Robert K. Merton 1957; Shwed and Bearman 2010). Rather than treating these streams of work as having divergent explanations for how scientists produce new practices, after briefly highlighting their contributions to the problem at hand, I outline a model of scientific research programs that draws out their complementarity. By focusing on how research programs contribute to the development of practices, rather than individuals, I sidestep the problem of tracing the genesis of technology to individual inventors.

Laboratory Studies and the Social Construction of Technology

Research in the sociology of science and knowledge has taken strides towards understanding the relationship between technological innovation and scientific change. Some have argued that the introduction of a new technique with a great deal of generative potential, like the CRISPR-Cas system, can lead to competition between scientific groups and that this competition can drive advancement (Bourdieu 1975; Ravetz 1971). Others have focused on the analysis of the day-to-day activity of science (Collins 1985; Knorr-Cetina 1981; Latour and Woolgar 1979; Star 1989). Extensions of this work have shown that scientists working in rapidly advancing fields are constantly surrounded by uncertainty. Put simply, when science is revolutionary, experiments push the researcher into a space of discovery.

For example, Star (1985) identified multiple forms of uncertainty that arise as a result scientific change in biomedicine: *taxonomic uncertainty* over how things are talked about, *diagnostic uncertainty* over the medical outcomes of therapeutic interventions, *political uncertainty* over the division of labor, and *technical uncertainty* over how to evaluate practices and standardize measurements. Hoffman's analysis of the field of artificial intelligence similarly describes multiple forms of ambiguity: *ontological ambiguity* about the nature object of study, *epistemological ambiguity* from the absence of clear, consistent, and accepted methodological standards, and *application ambiguity* about how a technology will be evaluated or used outside of the local settings of the laboratory bench (Hoffman 2017).

Prevalent theories of the social construction of technology pay close attention to how technologies emerge through a multidirectional process that is highly context specific (Pinch and Bijker 1984). For example, in their exposition of the importance of material tools as objects of analysis in science and technology studies, Clarke and Fujimura (1992) argue that how research instruments are used in scientific work is situationally determined. More recent elaborations stress the close relationship between the perception of advancement or change in the sciences and the specific conditions of experimental work. Peterson (2015) argues that what distinguishes advancement in life sciences from the social sciences is a back-and-forth process of *bench-building*, where scientists "at the unstable and ambiguous research frontier concentrate their efforts on the production of reliable effects through an iterative process whereby they incorporate new techniques and technologies," (Peterson 2015). *Bench-building* comes down to the re-arrangement of practices

and experimental technologies to find out what works to produce the data that will allow projects to be pushed forward.

Organizational Approaches to Technology Adoption in Science

In a separate vein, studies of how social change occurs in relation to the adoption of new technologies and practices suggests that actors strategically manage uncertainty in ways that are shaped by the networks they are a part of and the internal hierarchies of the organization (Koppenjan and Klijn 2004). Studies of the emergence of the biotechnology industry have shown that the risks that scientists are willing to take are contingent on the interactions between biotechnology firms, academic scientists, and pharmaceutical companies (Casper 2007; Ebers and Powell 2007; Powell et al. 2005; Saxenian 1994; Stuart, Ozdemir, and Ding 2007). In these models, new technologies and practices spread through networks of expertise, with key firms arising as movers of the field. Additional research in this area has shown the importance of the organizational environment of academic scientists for explaining how technology spreads and changes. For example, university patenting and technology-transfer practices shape whether scientists or groups of scientists adopt and develop new technologies (Berman 2008; Colyvas 2007; Jones 2009; Owen-Smith 2011; Owen-Smith and Powell 2001).[9]

Research Programs as the Drivers of Practice in Science

The model of scientific change I describe bridges these two areas conceptually: what scientists work on shapes the way their experimental work is organized and who they work with. To capture the relationship between the content of science and its form, I conceptualize the scientific research program as a representation of an organized set of practices that are oriented towards both the production of knowledge and the self-perpetuation of the laboratory as an organization. In this sense, it differs considerably from the theory of research programs developed by the philosopher of science Imre Lakatos.[10] Research programs are organized around a set of core projects devoted to not only the resolution of research questions or problems and their derivatives but also to their postulation. Scientific work, in this sense, is committed to its own reproduction (Laudan 1978). This focus on the advancement of projects supports a dynamic model where the absorptive capacity of the lab shifts over time.

In the model I propose, the research program is not empirically limited to a readily identifiable group of researchers in the lab, nor is limited to the analysis of discreet situations. In this sense, a research program differs from the concepts of *epistemic culture* or *epistemic community* (Haas

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[9] In genome editing as an area of research, intense patent disputes between the University of California Berkeley and the Broad Institute of Harvard and MIT over the licensing of the CRISPR-Cas9 system and its applications have structured the network of biotechnology and pharmaceutical firms surrounding the CRISPR-Cas9 system and other gene-modification technologies (Cloney 2016; Contreras and Sherkow 2017).

[10] For Lakatos a research programme represented a core set of theories and claims that were dogmatically held to be true. In order to preserve this core, the researchers who were committed to the research program would develop, recycle and modify auxiliary hypotheses, which would be strategically replaced in light of anomalies and controversial claims (Lakatos 1980).

1992; Knorr-Cetina 1991, 1999) in that it does not principally serve to identify a group of actors. The aims of my conceptualization are also distinct from that of *scientific and intellectual movements*, which focus on the mobilization of actors to support the development of consensus in a scientific community (Au 2021; Frickel and Gross 2005). Instead, I build on Gieryn's (1978) theory of scientific problem choice to draw attention to the project structure of a research program. The projects that constitute a particular research program can branch out, diversify, be replaced, or dropped altogether. Projects are executed by a coordinated arrangement of actors and various material and non-material resources.

To make sense of the coordinated interplay of personnel, equipment and objects of research, the concept of research programs builds on a family of concepts in philosophy of science: *experimental system* (Rheinberger 1997), *laboratory system* (Griesemer 1992; Griesemer and Wade 1988); *ensembles of research technologies* (Hackett et al. 2004); *research system* (Gerson 1983, 2015; Wimsatt 2001), and *repertoire* (Ankeny and Leonelli 2016). In these models of scientific change, the relationships between instruments, actors and materials are the outcome of pragmatic compromises about what works and what does not for specific projects. This idea that scientific practice arises through the research program doesn't erase the contributions of individual scientists. As the genome-editing labs I describe in this chapter evince, laboratory turnover of personnel and individual mobility stand in an unstable relation of mutual dependence to the structure of scientific research programs. Researchers in leadership imbue the research program with a personal touch by setting the agenda for research projects and designing experimental paths that build on and reflect the outcomes of prior work. At the other end, research assistants and technicians operationalize the research aspirations of leadership and figure out how to make proposed experiments work. When researchers in training transition out of the laboratory they leave gaps in practice at the level of the research program. In this sense, research programs are loosely biographical, bearing similarity to what historian of science Frederick Holmes describes as an *investigative pathway* (Holmes 2004). That is, the research program reflects the commitments and interests of those scientists who have control over the direction of research such as PIs and post-doctoral researchers and depend on the labor of researchers in earlier career stages. This theory of research programs helps unpack actors' decision-making under conditions of uncertainty by drawing attention to how actors make projections of their future work in relation to the life cycle of their projects.

In what follows, I describe how scientists develop genome editing practices in reference to a flexible commitment to a particular view of the future, such as the "direction" of the field, an expected decrease in the cost of a technology or an increase in its efficiency. Moreover, in order for a new technology to become absorbed into the research program, actors must articulate a series of commitments to the relevance and epistemic value of the technology and the practices associated with it. The epistemic value of a material resource or technology refers to its applicability or usefulness in answering or generating research questions. In other words, the epistemic value of a new experimental technology depends on whether it can help scientists work through a condition of uncertainty, engaging in what sociologist David Peterson describes as *bench-building* (Peterson 2015). This process ultimately contributes to construction of practices and the development of value frameworks that support their institutionalization at the level of the laboratory.

2.2. The Sledgehammer and the Scalpel: Navigating Uncertainty Through Metaphor

> "Scientists use the Cas9 protein *like a molecular scalpel* to slice a DNA site in two."
> (Innovative Genomics Institute n.d., emphasis added)

> "Like the early stone carvers, we are just beginning to learn how to properly use these new tools. […] Perhaps *CRISPR nucleases can be used as sledgehammers* […]." (Conklin 2013, emphasis added)

Scientists used metaphors as heuristics for explaining how the molecular components of the CRISPR-Cas system could be thought of as tools. In doing so, they constructed frameworks of meaning that become embedded in the applications for genome editing tool. These metaphors also help scientists process the multiple forms of uncertainty that come with adopting new practices. For the two biomedical labs I was a part of, the Nielsen Lab, and the Oak Lab,[11] this occurred in divergent ways that were specific to the research programs of each lab. While both research programs advocated for the use of the CRISPR-Cas9 system in biomedical research and eventually for clinical use, the way the technology was used to advance each research program differed.

The Nielsen Lab was based out of the Gladstone Institute at the University of California San Francisco (UCSF), an independent nonprofit biomedical research organization located at UCSF's Mission Bay Campus. Andrew Nielsen, M.D. a Senior Investigator and Professor in the Department of Medicine headed the lab. For the Nielsen Lab, the CRISPR-Cas9 system was a means to resolve past technical challenges and as a way of modeling diseases. Early in the development of CRISPR-Cas9 technology, Andrew Nielsen, perceived these new techniques to be still too unreliable for widespread use in biomedical research: he believed the innovation needed further proof of concept. In one weekly email he circulated a paper that characterized CRISPR as a "sledgehammer," where scientists were attempting to "sculpt genomes in the dark."

In contrast, the Oak Lab rallied around the characterizations of CRISPR-Cas9 as a "scalpel" or "molecular scissors" (Himeda, Jones, and Jones 2016). The Oak Lab was formally a part of the Cell and Molecular Biology Department at the University of California Berkeley. Samuel Oak, its PI, was an Assistant Adjunct Professor of Biochemistry, Biophysics and Structural Biology. For the Oak Lab, the technology was both a means *and* an end.

The source of this contrast is not one of "applied" vs. "basic" biology, as both labs have elements of each, nor is it attributable solely to the dispositions of each PI. Instead, it is a reflection of the different ways in which uncertainty can drive scientists to construct experimental technologies and develop stably reproducing practices to support their use. The differences between them serve to illustrate how what you choose to use CRISPR on and the pre-existing arrangement of expertise and projects fundamentally shapes the construction of genome editing as an institutional fixture in the lab.

2.3. The Nielsen Lab: An Established Research Program with Low Project Heterogeneity

During the first half of my fieldwork, the Nielsen lab's research program was highly specialized; the lab was exclusively interested in modeling heart diseases and detailing the function of

[11] To protect the confidentiality of PIs and lab's members I have used pseudonyms. These pseudonyms do not reflect the ethnic background of my informants and any resemblance is coincidental. The gender of my informants is reflected in their pseudonyms. Because the reputation and status of graduate students, post-docs, undergraduates and other mid-level employees is at a greater threat than that of the PIs, I have been particularly attentive to minimizing any risks they might incur and have consulted them about their involvement of the project. I have opted to keep the names of their surrounding organizations because contextual features of the data would be lost.

genes that have been previously shown to cause these diseases. Early in the spread of CRISPR-based techniques, Nielsen largely saw CRISPR as a technology that could be incorporated to further pursue the lab's already successful and established research program. Nielsen's early hesitation to endorse the therapeutic application of CRISPR-Cas9 technologies stemmed from *political* and *clinical uncertainty* over the regulation of genome editing techniques, and *technical uncertainty* over the ability to overcome limitations of early genome editing protocols.12 The lab particularly struggled with uncertainty that was specific to the complexity of research on congenital heart diseases and tried to manage this uncertainty according to what had worked with previous projects.

The Nielsen Lab was a well-established biomedical research program with a history. Since 2005 the Nielsen Lab's research program has focused on using induced pluripotent stem cells (iPSCs)13 to study heart diseases. The past success of his lab's highly regarded work with stem cells had already produced an extensive list of publications and had afforded the lab many collaborators that conduct stem cell research and cardiovascular disease research. While advantageous in terms of the lab's reputation, the accumulated and routinized practical experience made it challenging for the lab to productively integrate a new technology into their workflow. When the integration was successful, the CRISPR-Cas9 system was deployed to resolve pragmatic limitations to past experiments.

a) Narrow Project Structure: modeling cardiomyopathy.

The Nielsen Lab used genome-engineering techniques, including CRISPR-Cas9 and its predecessors, to create mutations in iPSCs. This allows them to study various cardiac genetic diseases at the cellular level. To put it crudely, they produced many different strains of sick muscle cells by giving them specific mutations, a set of experiments described as "knock-ins" and "knock-outs." Nielsen and his team produced cell-lines[14] of these sick cells so that the lab could conduct experiments on them. These sick cells work as models of disease, both as material representations and de-situated 'instances of' the disease (Landecker 2007, Lock 2001). They also shared the cell-lines with other labs around the world. In this respect, the lab was a leader in using stem cells for medical discovery. Prior to the development of CRISPR, the lab had ventured into using some of genetic engineering tools that preceded it, developing protocols for using Zinc Finger nucleases,

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12 For example, the rate of "off-targets" was of widespread concern. "Off-targets" are mistakes that the Cas9 enzyme makes–instances where the molecular machinery makes a modification in the genome where it isn't intended. This can be particularly problematic, for example, if a mutation is induced in a region of the genome that controls the growth and reproduction of the cell, which could turn it into a cancer cell. For bioethicists and policy makers, the threat of potential off-targets effects was central to how they shaped their regulatory standpoint. They strongly advocate further research into the extent to which these off targets could be predicted and minimized (National Academies of Sciences, Engineering, and Medicine, 2017).

13 Induced pluripotent stem cells are a type of stem cell that is generated from matured somatic cells. Because they can propagate indefinitely and can be transformed into every other cell type (neurons, skin, muscle, etc.) they are commonly used in biomedical research and regenerative medicine.

[14] A *cell line* is a population of cells descended from a single cell and containing the same genetic makeup. When these cells are gown under controlled conditions they are referred to as a *cell culture*.

expensive custom designed enzymes that could also make modifications to the genome. This focus on disease modeling through iPS cells had the potential to then be facilitated by the genetic manipulation permitted by the much more programmable, modular and cost-effective CRISPR-Cas9 system.

Operating in clinical settings shaped how the lab garnered funding, which in turn shaped the desired outcomes for projects. These material conditions and the orientations around the outcomes of projects that go with them can shape how a new experimental technique is valued. The bulk of the Nielsen Lab's funds derived from large federally funded research grants. While the lab enjoyed funding specifically due to its expertise in using stem cells from the California Institute for Regenerative Medicine (CIRM) and the National Institutes of Health (NIH), these multi-year grants are also designed to hone the work of the lab towards specific research goals. In this way, these grants are structured so as to keep the lab from venturing into uncertain or risky terrain via reliance on well-defined metrics and milestones. Over the course of my observations, the Nielsen Lab developed an NIH grant proposal that would re-orient the lab's research questions in a way that would make more use of the techniques derived from the CRISPR-Cas9 system. In this case, the lab's research program was subject to external pressures that recognize the potential of genetic engineering for the medical field.

At the beginning of my observations the lab was reaching the tail end of a seven-year multi-million-dollar grant, on behalf of the NIH Progenitor Cell Biology Consortium. At the NIH meeting he went to, Nielsen learned that the funding program was being "rebranded" and now emphasizes the translation of "basic science" about cellular processes into actionable medical tools. Nielsen explained that this meant that the lab would have to put together a new grant proposal to continue this funding line for another seven years. However, this required that the lab produce an 'IND' a, 'investigational new drug,' or as Nielsen put it, "something going into people at the end of the 7 years," (Field Note, November 2015).

The seven-year NIH funding schedule put constraints on the lab's ability to innovate rapidly, since a departure from their expected budgets and the re-purposing of resources would require additional bureaucratic work. While Nielsen was the PI on multiple NIH research grants and served on multiple advisory boards, younger lab members characterized the overall funding environment as a threat to the conduct of their research because funding wasn't always available for the experiments or projects they wanted to work on, and it was unclear where funding would come from in the future. Additionally, because these grants were targeted and specialized, the lab was competing with a small selection of other well-recognized labs with established research programs. Funding pressures and the external conditions of the lab constrain the relative autonomy of the lab and its members to pursue risky projects they deem worthwhile.

The second constraint on the lab's adoption of CRISPR-Cas is that iPSCs are not particularly "easy" cells to work with. As the substantive biological materials of most of the lab's experimental work, the cells had to be cultured, grown and maintained. For example, research assistants must track the growth of the stem cells to make sure they don't mature into other kinds of cells you don't want to work with. In this sense, stem cells are more unstable than other cell lines, for example cancer cells, that can more easily reproduce. When recounting the lab's history in an orientation meeting for two new research assistants, Nielsen explained how the lab had come to focus on iPS cells as their primary model organism and technical challenges faced prior to the development of CRISPR-Cas technology.

> "So, I should say that [when] we started the human IPS stuff, you know we took the iPS stuff opportunistically. Because conceptually it was the right thing to do and also because of the kind of aura of iPS cells and stuff like that, they were just raining money on top of us to do iPS stuff. We didn't actually need any preliminary data or anything, you would just apply for grants and [our collaborator] was really good at that. And NIH was just desperate to actually get more people doing this stuff. But conceptually it was there, but in reality, there was this period from human iPS, when we started using human iPS [with] TALENs, there were like four years where it was pretty ugly actually. Because we didn't know how to differentiate the cells, we had cells that were developing from people, but we didn't have the ability to make isogenic controls. It was very… One could not have imagined that genome engineering would have happened. So if that had been pushed out here, it would be pretty grim actually. In some sense, we got into it too early it was foolhardy in the sense that you couldn't predict that CRISPR would happen, but it did. And I am very grateful for that." (Field Notes November 2016)

In the absence of the CRISPR-Cas gene-editing system, Nielsen's lab had undergone a period of stagnation as a result of technical uncertainty surrounding early stem cell protocols. Most significantly, the ability to manipulate the genetic makeup of their model organisms was simply not there. As the PI put it emphatically, "it was really grim when you think about the possibilities of doing an experiment. In 2008, there was a paper that reviewed all the knock-outs in human iPS cells and there were only eight of them!" During this period, the Nielsen Lab invested in refining protocols for the cultivation of stem cells and developed a rich *repertoire of practice* (Ankeny and Leonelli 2016) for maintaining cell lines. This would set them up well to take advantage of the technical opportunities offered by CRISPR later on. As Nielsen recounted in a presentation of the lab's history, "I have to say, going back it was the right time to do [work on iPSCs], just because of what happened afterwards. Not because we knew what would happen." While the timing of their speculative orientation was slightly off, ultimately, Nielsen's research program was set up with the expectation that there would be technical breakthroughs for working in human iPSCs in the near future, and it paid off.

The ebb and flow of expectations informed how Nielsen and his team decided which direction the research program should take. In Nielsen's early view, CRISPR-Cas9 genome-editing therapies still had a long way to go, and the pressure of the NIH to put CRISPR in the clinic was a bit premature. Instead, he proposed that the lab focus on the production of assays, screens, and tools for disease diagnosis. By 2016, however, Nielsen decidedly shifted both his personal views and the direction of his research program –reorienting his framing of the innovation as a "sledgehammer" and adopting the metaphor of the "scalpel". Nielsen and the clinician in his lab, Marvin, pivoted and identified research problems that more fully embraced the therapeutic potential of genome editing. This shift also coincided with an almost complete turnover in the personnel of the laboratory. As a result, the research program diversified, and new projects emerged around completely new tissues and diseases where the CRISPR-Cas system showed greater promise of being turned into a potential therapy than cardiomyopathies. Ultimately, Nielsen reordered his lab's research program around the idea of "genome surgery." The diversification and overall re-branding of the Nielsen lab's research program occurred in the context of refinements to CRISPR techniques by other nearby labs, and new funding opportunities that allowed the lab to invest time and resources into adapting genome editing technology for the lab's program.

In part, this was because expectations about the clinical utility for CRISPR were affected by

the availability of funding for research with CRISPR. That year, the Chan-Zuckerberg Initiative (CZI), Facebook mogul's philanthropic venture, spawned the Chan-Zuckerberg BioHub and pledged $600 million to fund research that took innovative approaches to studying and treating diseases. In consultation with the BioHub's scientific advisors, Nielsen put together an application for a piece of these funds. Additionally, the Nielsen Lab received seed funding from the Innovative Genomics Institute (IGI), founded by Jennifer Doudna, to hire research associates to work on new CRISPR-related projects. Nielsen's eventual appointment to the leadership team of IGI also propelled him into a position where he had a greater stake in the advancement of the CRISPR-Cas9 system. These local opportunities loosened the lab's commitments and facilitated the change in direction. I further examine the economic conditions that enabled this shift if Ch. 3, which further details the relationship between Nielsen's research program and the broader context of biomedical research in the SF Bay Area.

With increased involvement in IGI affairs, Samuel Oak and Andrew Nielsen began to work more closely. To familiarize his lab with Nielsen's work and to explore collaborative opportunities, Oak invited Nielsen to give a presentation at their weekly lab meeting. Here, Nielsen brainstormed with Oak and his group of post-docs about possible directions for his lab. Nielsen humorously recounted some of the challenges his lab had faced and how they had overcome them,

> "One of my disappointments with the cardiac stuff was that cardiac is not really on this list of potential therapeutic targets [for genome editing]. And that's because if you actually edit the heart, you could cure some diseases, okay, but there's a lot of bad things that could happen if you edit in an uneven way. So if you edit fifty-percent of the cells and another fifty-percent of the cells [you don't] and then that causes a bad electrical circuit. Your heart stops… for even ten minutes, it ruins your whole day. [Laughter from lab] Really bad. So it's not a place that you want to be doing that kind of experiment on, right? So what you want to do is you want to be thinking of other types of tissues for which you could essentially you know do radical things to, but keep the person alive. So the heart is useful for therapy because it is so important for keeping people alive. But it isn't actually a good place for doing therapeutic editing. So I've been looking for other places, and to some extent because I primarily work on the heart and I am pluripotent to where else I go." (Field Notes, July 2016)

Nielsen's humor here condenses the dimensions of uncertainty that biomedical scientists encounter at the edge of knowledge. He juxtaposes the uncertainty that therapeutic editing in the heart may yield uneven modifications across muscle cells, and the certainty that if your heart short circuits and the organ fails, you'll die. In doing so he uses the mounting medical risk of using CRISPR as a therapeutic approach for cardiovascular diseases as a justification for a shift in the direction of his research program. Nielsen's re-orientation also exemplifies the impact that adopting genome editing can have on the direction of science, not just as a set of practices, but as a way of thinking about biomedical research more generally. Also in his explanation is a sense of excitement from moving into his work into new directions, even if what those new directions are is at first unclear.

By early 2017 Nielsen began to wander toward working in two new tissues: first, the eye and later, motor neurons. Understanding this shift helps shed light on how the strategies that scientific actors can deploy to take advantage of an innovation are contingent on the history and structure of their research programs. In this case, the Nielsen's research program was established and worked in a focused problem area. Starting to work on congenital diseases of the eye and neurological genetic

diseases meant entering new problem spaces (Newell and Simon 1972) that Nielsen's research team was inexperienced in.

The choice of diseases is indicative of the broader transformation of genetics as a field that genome editing can bring about. The rationale behind working on these tissues was the potential of treating a class of genetic disorders that occur when one copy of a gene, an allele, is dysfunctional. Working alongside the clinician in his lab and through discussions with other PIs at UCSF, Nielsen identified two of these diseases that would serve as "proof of concept" for a form of therapeutic editing that Nielsen described as *excision*, or more technically "allele-specific editing."

This new orientation was fueled by new conceptual goal: Rather than thinking of the clinical use of the CRISPR-Cas9 system as a therapy using a biological drug, Nielsen began to advocate for the idea of "genome surgery." This conceptual re-orientation helped the lab manage the downstream clinical uncertainty of using CRISPR-based tools. The two new projects would revolve around modeling two rare genetic diseases: Best disease, a kind of macular degeneration that leads to blindness, and Charcot-Marie-Tooth or CMT a hereditary neuropathy that causes progressive loss of muscle function and sensation. For Nielsen and his team, the shift away from their specialization in cardiomyopathies, however, had profound implications for how work in the lab was organized. The shift further required the production of new experimental protocols that would bridge Nielsen's prior research using stem cells with new genome editing techniques in new types of cells.

b) Established Program: trained personnel and practical bottlenecks

In addition to the clinical uncertainty surrounding genome editing that the lab faced because of its previous focus on heart diseases, the established character of the research program shapes how technical challenges and practical uncertainties for using new technologies are dealt with. In the Nielsen Lab, post-docs worked on a set of closely related research problems and specialized primarily in one of two areas: congenital heart diseases and stem cell biology. Due to the external recognition received in its area of concentration, the Nielsen Lab attracted a relatively focused group of investigators. At the beginning of my research, the Nielsen Lab was staffed by three post-doctoral fellows and two graduate students: a stem cell biologist, a bioengineer, a clinician with expertise in genetics and cell biology, and two cell biologists. The post-docs I spoke to were drawn to Nielsen's lab in hopes of acquiring skills for doing experiments with stem cells and understanding the molecular basis of cardiomyopathies. At Gladstone, research associates (RAs)—paid researchers with technical specializations–supported post-doc's work. Research associates held technical expertise in specific aspects of the experimental workflow, such as cell culture maintenance and care or biostatistical and computational work. In short, they had a really good sense of what worked and didn't work in their experiments.

Members of the lab engaged in bench building (Peterson 2015) to articulate CRISPR-Cas9 editing techniques to the ongoing experimental work of the lab. While the division of labor between members of the lab was not purely based on position or on methodological expertise, during group meetings research associates responded to clarifying questions about technique and strategy more defensively than their post-doctoral counterparts. In order to defend their technical decisions, research associates referenced two things: their repetitive trial-and-error work and their use of protocols developed by other labs.

The Nielsen Lab was less interested in adding projects aimed at developing and refining CRISPR-Cas9 technology for its own sake. In order to adopt the innovation into their workflow, the

lab's researchers had to adapt available techniques to fit their problem areas. As another PI put it, the Nielsen Lab was interested in using CRISPR-Cas9 "off-the-shelf." While Nielsen and his team were among the first to conduct CRISPR experiments in stem cells, CRISPR techniques developed for use in other model organisms, were not as easily deployed in iPS cells. To carry out their work, post-docs and grad students in the Nielsen lab relied heavily on input and aid from specialized labs in the Bay Area that produced and shared protocols and reagents. For example, researchers in the Nielsen Lab corresponded regularly with the Weissman Lab, one of the leading CRISPR labs in the Bay Area. When describing his workflow during lab meeting, Marvin, one of the post-docs, acknowledged the work of the Weissman Lab and described his unfamiliarity with the techniques,

> "So the next step after doing the sorting[15] and fixing[16] the cells, just for the growth screen is to do the genomic amplification[17] of wherever the guide RNA is treated with. I was a little overwhelmed when I came to this point because the Weissman Lab… they have this giant protocol with all these steps but they've kind of designed their methods based on doing very large-scale screens with hundreds and millions of cells and our samples, you know we are only thirteen million. They are tackling a much bigger problem than we are. So, um, I was talking a lot with the technician at the Weissman Lab, talking to Ryan, talking to Max, seeing, you know, what we can change about that protocol to kind of suit our needs and suit our screen." (Lab Meeting, March 2017)

Whether or not the CRISPR-Cas9 system is useful depended not only on the specific needs of each project and the availability of materials and instruments, but also the tacit knowledge required to execute formalized protocols. In the absence of this tacit knowledge, the practical uncertainty entailed by the adoption of a new technology became a challenge that was not always met with enthusiasm by research associates. As was mentioned in multiple lab meetings, protocol adaptation often involved a great deal of tedious troubleshooting. During this meeting, Nielsen and Manuel, the research associate working under Marvin, argued over the differences in parameters and standards that their collaborators at the Weissman Lab had set. Where Manuel urged that the parameters did not match what had worked in his experience. Dealing with this was the reason researchers across UCSF had organized a "CRISPR-Users" workshop in the first place. While learning and successfully implementing CRISPR-Cas9 techniques gave the Nielsen Lab a new avenue for recognition and allowed post-docs to market themselves as being on the forefront, doing so entailed a risk of both time and effort in the eyes of research associates who were unsure what to expect from the new techniques or even how to evaluate their results.

At the end of 2016, however, three post-doctoral fellows in the lab transitioned out into new positions and two research associates were happily sent off to graduate school. For Andrew Nielsen, this meant that research projects would have to be re-coordinated,

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[15] Cell sorting is a method of isolating cells from a larger population of cells according to some characteristic of interest such as the cells' morphology.

[16] Fixation refers to the preservation of biological tissues from decay. In the process of doing so, the cells die and become 'fixed' in place, which allows them to be better visualized.

[17] Increasing the number of copies of a particular region in genome so that the DNA can be analyzed.

> "We are going through a big turnover. We have a number of post-docs who are naturally going to move forward and the way I hire new RAs and things like that is also going to [change], the people will move on. So it's going to be a new lab. So you have to think about hiring wisely but also, you know just the disruptive nature of that. Because we have been relatively stable in the last few years in terms of senior staff, actually. But you know, you don't plan on having everyone turn over at once, but that is the cliff I am facing." (Field Notes, November 2016)

The turnover was "disruptive" because of the loss of tacit knowledge the lab had gained throughout the history of its research program. The loss, however, was approached strategically by the lab's leadership as it provided the internal conditions that would facilitate the shift towards new problem areas. To get the BEST1 project going Nielsen invited experts in the field to help train a new research assistant who had just completed her undergraduate degree. For the remainder of 2017, this research assistant, Allison, was the only person working on the project while Nielsen attempted to recruit a post-doctoral fellow to lead the project. The practical challenges she met, even though the lab had already acquired the tools and know-how for using the CRISPR-Cas9 system in iPSCs reflect the bench building needed to manage the practical uncertainty involved in shifting the research program. In an interview, Allison described one central challenge: the ability to produce retinal pigment epithelial cells (RPE), the specific type of eye cell that deteriorates in the new disease the lab was studying, Best disease.

> "A: Basically, when I first started it was really obvious that there were a couple bottlenecks to the project moving forward, and it was really frustrating. Because we wanted to make allele-specific editing, we also wanted to test these [CRISPR] systems. So, I tested all these systems in iPS, and they are fine, but that's not the point. But at this time, it's no longer the point. We know that we can do it, but it's more relevant to test it in the cell type that you are working in. And a year ago it was pretty impossible to differentiate the cell type that we were working in.
>
> SM: The RPE?
>
> A: Yeah. It would just take forever, and it was really expensive, and we didn't really get a good yield and it was just a lot of work and time for not a lot of results. So then this is why I started working on this cell line that you could pretty much induce into RPE and I thought it was really cool that we could use this for my project," (Interview transcript, December 2017)

In order to produce a cell line that she could programmatically differentiate into RPE, over the course of nine months, Allison attempted to execute several protocols to try to figure out what works. Doing so entailed corresponding with experts studying macular degeneration and the molecular biology of RPE. After doing more digging in the literature, Allison was able to identify a set of proteins that when produced by the stem cells, would lead them to differentiate into RPE. Allison then used the CRISPR-Cas9 system to engineer an iPS cell line that would express a set of these proteins. This tedious work was fundamental to the set-up of the project because Allison's preliminary data became the basis for grants and funding applications to move the project forward.

This groundwork, figuring out what works to produce RPE, began to establish the research program in a new problem area. Moreover, the protocols for using the CRISPR-Cas9 system in this way then became the groundwork for methodological publications, in their own right. In this way, they served not only as a cornerstone for the project but further

establishing the laboratory as a genome editing lab. This production of a genome editing protocol for RPE cells further extended the reach of CRISPR-Cas9 into the subfields of ophthalmology and medical genetics.

To summarize the case thus far, early in my fieldwork at the Nielsen Lab, CRISPR-Cas9 technologies were brought into the workflow to support the lab's pre-existing cardiomyopathy projects. In order to adopt and put CRISPR-Cas9 technology to work, the lab relied on an extensive collaboration network for external validation of methods. Nielsen's suggestion, to "choose the tool that best fits the job," situated the technology and the articulation of its function both prior and external to the work of lab members. For their work on cardiomyopathies and stem cells, the CRISPR-Cas9 system was a means to address technical issues and limitations of scalability. The clinical uncertainty of doing therapeutic genome editing in the heart, however, pushed the lab to start new projects in new problem spaces. This reverses the mantra advanced by other sociologists of science, that scientists construct technologies in finding the right tools for the job (Clarke and Fujimura 1992). In this case, scientists found the best job for the tool. In the new projects, the idea was to use CRISPR-Cas9 system as a way of *excising* the bad copy of a gene in genetic diseases of the eye and nervous system. Towards the end of my fieldwork these new projects already showed early success, since Nielsen was able to secure seed funding from both the NIH and philanthropic donors to pursue these new lines of research. The Nielsen Lab's early orientation towards the CRISPR-Cas9 system stands in contrast to the adoptive strategy of the Oak Lab, where the tinkering with CRISPR-Cas9 technologies to better understand the mechanisms underlying the technology and improving upon the technology itself was a central goal of the lab's work.

2.4. The Oak Lab: A New Research Program with High Project Heterogeneity

The Oak Lab was a younger research program, having only started in 2013. The PI's experience and connections in industry, however, made him sensitive to the rapidly changing commercial field. With an already reputable background as a Project Leader at biotechnology giant Genentech (a position analogous to that of principal investigator) Samuel Oak brought a distinctive repertoire of problem-solving techniques into the operation of his lab's research and the management of uncertainty. Over the course of my fieldwork this burgeoning research program built itself by acquiring new equipment and personnel. Under entrepreneurial leadership, a coordinated group of teams conducted fast-paced work. With this, the research program gained external recognition for its use of CRISPR-Cas9 genome-editing techniques and by 2017 the lab laid an impressive track record of publications in top tier journals. Despite this success, the Oak Lab did not acquire a narrow set of skills for working in a discreet problem area in the same sense as in the Nielsen Lab, or specialized recognition for work on a specific disease. The Oak Lab's research program was distinct from the Nielsen Lab's in the heterogeneity of its research projects: Samuel Oak and the post-docs who worked in his lab sought to answer different sorts of questions, at different scales, about different diseases, in different cells and with different goals. What tied projects together was a shared interest in not just using the CRISPR-Cas9 system, but actively searching for ways to improve its use by better understanding its mechanism and potential new functions. In contrast to the Nielsen Lab, the uncertainty that came with a new technology was embraced as the foundation for the lab's work and became generative of protocols that refined and improved CRISPR techniques that could then be applied in different experimental systems.

a) Broad Project Structure: "feeling our way in the dark"

In the Oak Lab, CRISPR itself generated a new, incompletely specified, and relatively immature research program. Unlike the Nielsen Lab, The Oak Lab was relatively unspecialized. It aimed to "[use] genome editing to bridge reductionist principles and complex cellular phenotypes for fundamental understanding and human health," (Lab Website 2016). This "bridging" referred to the identification of specific molecular mechanisms between a DNA mutation and a trait, or disease. The lab further branded itself as taking a "multidisciplinary approach, starting from next-generation genome-editing technologies such as CRISPR-Cas9." The last of the lab's areas of interest was "to investigate the fundamental bases of cellular signaling[18]." For the Oak Lab's research program, in its early stages, CRISPR-Cas9 technologies were opening up exciting new areas and the perceived value of the new tool was high, even though the lab might have to work through technical uncertainty on regular basis. The payoff of trying new, but uncertain techniques was perceived to be high, in part because the lab had yet to publish extensively or gain recognition for work in one specific problem space. The Oak Lab hoped to continue to refine and improve CRISPR-Cas9 technologies, approaching the technical uncertainty surrounding the technology as an opportunity to create "precise and efficient" techniques.

The Oak Lab's research program tackled the diverse goals listed above through three problem areas, each entailing multiple projects. Together these three problem spaces structured their nascent research program. This structure allowed the lab to uncouple and organize the technical and clinical uncertainty surrounding CRISPR. In an interview, Oak listed the relevant research projects the lab tackled in terms of those problem spaces:

> "[The work] falls into three major categories: the first one is 'what is the mechanism of genome editing? And how can we use that mechanism to improve the process?' That's where the DNA damage[19] part comes in. The basic question is: gene-editing tools go in; gene editing goes out: what happened in between? So, we want to understand that process.
>
> Then there's, 'okay, let's pretend we don't care what is in the box, let's just use the tool,' for that, that's where some of the ubiquitin stuff comes in. How do we use genome editing and transcription regulation20 to gain new biological insight into processes where we could not have done any of the stuff before? So, we're, Elizabeth is tagging[21] multiple genes in cells and following these gene products in response to stress. Erica and Arthur are

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[18] 'Cellular signaling' is an umbrella term for the complex system that regulates everything a cell does. It is often modeled as network of interacting enzymes and other molecules.

[19] DNA repair is the process by which proteins inside of cells routinely fix breaks and irregularities in the genome. This damage occurs constantly when cells divide or are exposed to mutagens, such as UV rays from sunlight.

[20] 'Transcription' is part of the process of gene expression, where various enzymes read the information coded in DNA to produce gene products like proteins.

[21] 'Tagging' refers to a technique were a biochemical marker (which is often fluorescent) is attached to a gene and consequently to its product. This usually makes the protein in the cell visible under the microscope. For example, if you were to tag a gene that codes for a protein that localizes to the mitochondria with green-fluorescent protein (GFP) you would be able to see the mitochondria under a fluorescent microscope.

> using those big CRISPRi libraries[22] to find out what genes are involved in these complicated processes like autophagy[23]. So, this is using tools that we didn't have before to ask questions that we had but had no way to answer.
>
> And then the therapeutic stuff, sickle and stuff like that is similar. We didn't have tools, but let's put it in a more translational24 bent. Rather than basic discovery mode, okay, rather than saying basic discovery, we don't know what goes on in this process. Or how do we follow these gene products through cells. Translational [means] we know exactly what we want to do. Sickle cell: we know exactly what genes are involved; we've known about the mutation for a long time, but we don't have the tools to be able to do anything about before. So, let's do something about it." (Interview Transcript, May 2016)

These research problems and the sub-problems that arose shaped and organized the activity of the lab. The lab was organized into research subgroups, corresponding to the three areas of investigation outlined above. The list of specific topics Oak mentioned was ample: DNA damage and repair, ubiquitin biology (ubiquitins area special class of small proteins that are found in every cell), cell autophagy (when cells eat themselves), and sickle cell disease. In addition, other members of the lab were given a fair amount of autonomy and were studying multiple types of cancer, metabolic disorders, the formation of blood cells and the regulation of the immune system. This diversity and the broad problem space it entailed, contrasts with that of the narrow research program in the Nielsen Lab.

To complement the heterogeneity of its projects the lab relied heavily on an interdisciplinary team. This fitting of the structure of the research program to the laboratory's membership was deliberate, as Oak described in an interview, "My style of running the lab is I want as many people with as many diverse backgrounds as possible thinking about similar problems. Because I think you get the most creative ideas from having people, who come from very different ways of thinking, all thinking about the same problem." (Interview Transcript, May 2016). As the lab increasingly gained external recognition and its research program continued to diversify, more research fellows and post-docs joined the lab. By 2018 the lab hosted eight post-doctoral students: a biophysicist, a chemist, a mathematician, a cellular and molecular physiologist, two cancer biologists, and two molecular biologists. Two or more post-docs lead each subgroup and guided the work of graduate students, a small group of paid research associates and what was referred to as "an army of undergraduates."

The availability of undergraduate volunteers at UC Berkeley supported the bench building demanded by the projects at the Oak Lab. From this tedious and iterative bench building, new protocols were tested, tweaked and re-tested. This extra tier of lab members added to the complexity of the social organization of the Oak Lab, in comparison with the Nielsen Lab. Additionally, the pedagogical ties formed tight bonds between post-docs, graduate students, and undergraduates in

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[22] 'Libraries' are collections of fragments DNA sequences that correspond to known regions of the genome (Qi et al. 2013).

[23] 'Autophagy' is the process by which cells digest their own organelles, often before they die.

[24] 'Translation' in this context refers to turning biomedical research into a clinical outcome, "translating" the science into medicine.

each subgroup. Oak himself routinely remarked that current undergraduate researchers who are learning genome-editing techniques as commonplace and standard practices would be the ones to take the new technology into interesting directions. To them, the power of the techniques they were learning was something they could take for granted. Allowing them greater aspiration to work off of them in creative ways. To keep track of this work, the Oak Lab maintained a repository of versions of protocols; a record that became increasingly important to keep current as their work came out in pre-print publications and top tier journals.

The heterogeneous project structure of the research program also shaped the financial resources available to the Oak Lab in a way that yielded a different funding base as compared to the Nielsen Lab. This broad focus allowed the lab to market itself in multiple ways and made it eligible for multiple sources of funding: those related to medical discovery, biotechnology invention and development, and basic biological research. The Nielsen Lab primarily drew its funding from traditional sources such as federal NIH Grants and donations funneled through the Gladstone Institutes. In contrast, the early in my fieldwork, the Oak Lab received funding from pharmaceutical collaborators, small biotech firms, and private philanthropic funds through its immediate organization, the IGI, only to start receiving federal and state funding once the lab had a publishing record.

As the Scientific Director of the IGI, Oak was responsible for the development of the organization, setting its strategic scientific goals, attracting funders, and identifying partners that shared the IGI's vision for genome editing. In this sense, Samuel Oak had individually established himself as prominent voice in articulating the techniques, applications, and promises of the innovation. Additionally, because of Oak's network in the biotechnology industry, representatives from both start-up biotech companies and larger firms frequently visited the lab and gave presentations of their own during lab meeting. Often, these visits were geared towards identifying ways in which technical challenges faced by the lab could be addressed by firms that developed instruments, software and reagents that support lab work. These external indicators of Oak's individual position as a newcomer to the area of genome editing were also reflected internally in how his research program was structured around the CRISPR-Cas9 system.

In one lab meeting Oak attempted to give clarity towards the direction of the lab and his vision for gene-editing more broadly. He echoed a concern that was common in the workshops I attended, "as I think most of the people in the lab have recognized, [CRISPR-Cas9] technology doesn't always work the way it's supposed to on paper. So, we're still feeling our way in the dark, what does this do and what does it not do," (Lab meeting February 2017). Because the CRISPR-Cas9 system had a wide functional scope and the molecular mechanisms that constitute it where unclear, it was surrounded by a general sense of uncertainty and a pragmatic vacuum.

In contrast to the Nielsen Lab, however, this technical uncertainty was seen as an opportunity for further invention in the Oak Lab, as the researchers further stepped into problem spaces that did not have clear outcomes. In one lab meeting, one of the first graduate students to join the lab, Kyle, presented a project that exemplified of how CRISPR-Cas9 was not only adopted by the Oak Lab's research program but was being creatively tinkered with. In this project, the CRISPR-Cas9 system was both part of the experimental toolkit and the object of investigation. During the meeting, Kyle nervously introduced his topic in the first slides of his presentation: the repurposing of CRISPR-Cas9 technology to study the proteins that lead to removal of active component of the technology, the Cas9 (**C**RISPR **a**ssociated protein **9**), from DNA. To do this he used a modified version of the biotechnology: Cas-BirA*. Kyle explained to his lab-mates that the protein he had biochemically attached to Cas, BirA* could be used to visualize enzymes inside of

cells by "tagging" the enzymes it comes into contact within the cell. When it is in the right kind of solution, called an eluate, BirA* could be used to biochemically pick out those enzymes from others in the cell. Kyle walked us through the experimental workflow he used to identify the different enzymes that were uniquely associated with the activity of Cas9. If an enzyme came into contact with his Cas-BirA* plasmid construct, it would be tagged and could then be identified.

He showed us his main results, which represented over five months of work. The unveiling of results was a dramatic moment where a vacuum of knowledge could be filled, or at the very least offer an opportunity to better understand the contours of uncertainty in a specific problem space. Kyle skillfully paused for about a minute to give the lab time to interpret the gel image he projected on the screen that showed his results, along with the list of enzymes he had identified. He then gave us a brief interpretation. Drawing from the mounting excitement in the room, Oak leaned back in his chair, arms raised, and enthusiastically urged Kyle to take the remaining eluate and his construct and "treat them like gold" to use in further experiments.

Kyle was applauded by the lab for his successful development of a method for identifying other enzymes associated with Cas9 activity. By stepping into a space of uncertainty with methods that were shrouded in technical uncertainty, Kyle pushed the boundary of research in his own way. Because Kyle's findings were applicable to the challenges faced by other subgroups, the rest of the lab immediately wanted to incorporate his construct into their own experiments. Other lab members were themselves intrigued and asked Kyle to make more of the construct and the eluate for them to use. The trial-and-error required for preparing the materials that supported CRISPR-Cas9 uses was itself an object of praise and recognition. As the rest of the lab put his construct to the test, it became further refined and allowed him to improve its scalability for larger experiments.

Since then, Kyle's Cas9-BirA* construct has been shared with other labs interested in trying out the experiment on their work. In 2017, Kyle and Oak filed to patent the construct through UC Berkeley. Repurposing CRISPR-Cas9 construct variants across different problem spaces within the lab provided an internal validation of techniques that departed from the Nielsen's research program. Moreover, the external recognition gained from sharing techniques and reagents helped build the lab's research program and establish its reputation among other labs that were using and developing the CRISPR-Cas9 system.

To better get a handle on the heterogeneity of strategies that scientists at the forefront of research can deploy, it is necessary to show the similarities across labs that aim to apply the technology; in the sense described by Nielsen as, "off the shelf" and by Oak as, "let's pretend we don't care what is in the box." Another subgroup of the lab worked on a project that treated the CRISPR-Cas9 system as a means to solve past limitations in a discreet problem area, similar to what I observed in the Nielsen Lab. This project built on Samuel Oak's prior research when he was a graduate student and then at Genentech. As such the project reflected his individual investigative pathway. Erica, a graduate student, Arthur, a post-doctoral fellow, and Elizabeth, a research associate, formed this subgroup. Their project aimed to study the role of ubiqutins, a special class of small and modular proteins, in the process by which cells "eat" or "digest" their own organelles, autophagy. As a postdoctoral fellow, Arthur was a stage of his career where he was laying the groundwork for his own investigative pathway. This gave him a personal investment in the project's development. As he explained during one lab meeting, because ubiquitins are, to wit, ubiquitous throughout the cell and their role in cellular processes involves many other molecules, studying them at the genetic level had been particularly difficult. This was because older techniques for genetic manipulation were constrained to study the effect of only a small selection of genes at a time and efforts to localize the activity of ubiquitin throughout the cell routinely returned contradictory

results. With the advent of CRISPR-based technologies, the Oak Lab was able to work through the prior technical limitations in a new way and had consequently been successful with finding new targets for investigation. This generative application of the new technology was similar to that of the Nielsen Lab's cardiomyopathy project, where CRISPR-Cas9 served a supplementary role in facilitating or speeding up their previous research program.

Over the course of two weeks, I shadowed Arthur and Erica as they worked through a set of experiments called a CRISPRi screen where they used genome editing to sort out cells with specific characteristics (Qi et al. 2013; Hsu et al. 2014). This example, when compared to the experiments conducted by Marvin at the Nielsen Lab with iPSCs, illustrates how the biological materials that scientists work with, can affect how they manage the uncertainty that comes with adopting new technologies. In CRISPRi screens a deactivated form of Cas9 (dCas9) is used to block thousands of specific genes from being transcribed into proteins. In this case, the screen was performed on a strain of human embryonic kidney cells, HEK293s, that Arthur had engineered to produce the dCas9 enzyme. Unlike the unstable iPSCs that the Nielsen Lab works with, HEK293s grow rapidly and are more easily maintained. Having a robust cell type was instrumental to the experiments they set up because they aimed to study the process by which cells digest their own organelles.

A lot of Arthur and Erica's work consisted of taking care of the cells as they grew in petri-dishes and adding different reagents to their gel-like environment. Because of the cell type they were using, they were able to put the cells in stressful, nutrient-poor conditions. Under these conditions, the cells would start digesting their own organelles. The experimental protocols of the CRISPRi screen were tweaked and adapted to studying this complex molecular process. To get the screen started, Erica took the HEK293 cells that Arthur had produced and transfected[25] them with a pooled plasmid library26 of gRNAs at a low multiplicity of infection (MOI) so that, on average, one cell gets one gRNA. Over the course of months, the experiments were repeated, which each medication of the protocol being diligently recorded. The output of the data was a list of genes that were thought to have an influence in how ubiquitins facilitate this process. Elizabeth, a research associate with experience in biostatistics, then analyzed the data to further refine the list of genes. The "top hits" appearing in this list of genes would then become the target of more directed research. The refinement of these protocols further validated the use of CRISPRi techniques for the subfields of molecular and cell biology that Arthur wanted to work in: autophagy and cell signaling. As his work progressed, he went on to present the findings of his research in highly specialized international conferences devoted to the study of these processes. Increasing the visibility and applicability of genome editing in smaller corners of biology.

These two extended examples only begin to capture the diversity of projects in the Oak Lab. The third problem space, which was devoted to the translational potential of the CRISPR-Cas9 system, included projects on a wide variety of diseases and cell types, with each project requiring an extensive network of collaboration between academia and industry and separate streams of funding. Over the course of my research, the Oak Lab grew in terms of access to both physical space and

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[25] Transfection is the process of deliberately introducing purified nucleic acids (DNA or RNA) into eukaryotic cells without using a virus.

[26] A pooled library is a collection of plasmids (circular bits of DNA or RNA) all built with the same sequence backbone and only differing in a small region. "Pooled" libraries are normally supplied as a single tube with all the different plasmids mixed together. (Addgene: https://www.addgene.org/pooled-library/)

personnel by more than fifty percent, reaching over twenty-two lab members. The lab also relocated to a different building where it took over the vacated space of multiple other labs. This growth reflects ongoing increases to the lab's funding base and its progressive establishment as, what one biotech company sales representative referred to as a "CRISPR lab, full of CRISPR people."

b) A Young Research Program: "light everything on fire"

For the PI, the broad project structure was both a deliberate strategy and also reflected the research program's age. In Oak's terms, "Our lab is much younger than [Andrew Nielsen's] so we are still in this phase of let's light everything on fire and see what catches." (Interview Transcript, May 2016). Because the research program was still growing, Oak moved his laboratory's work in multiple directions that had been conceptually opened up by the experimental potential of the CRISPR-Cas9 system. Even though the likelihood of success of new projects in emerging areas was only speculative, in my interviews several lab members described how the excitement and hype surrounding the CRISPR-Cas9 system had attracted them Oak Lab. As the research program's projects continued to develop and yield data, Oak increasingly pushed researchers to publish.

In light of exciting data, in 2016 and 2017 Oak increased his conference travel. These trips were also geared towards establishing the lab externally. As a result of his travel schedule the subgroups were then left to manage the different aspects of the research program. This organization of the research program offered its members the opportunity to pursue their curiosity with relative autonomy and decide what experiments should be conducted. The emergent character of the research program was also perceived as a risk by post-docs and graduate students who were competing for recognition, funding and jobs with other researchers. For example, I interviewed Sherry, a post-doc in the lab who was funded by an international pharmaceutical company. During our interview, Sherry discussed the risks involved in working at a new organization,

> "…When you are applying for jobs, you know, especially academic jobs, where you are coming from is going to get you in the door a lot of times. Of course, not always. Not always and so the IGI, being relatively new and not having that kind of reputation to show what kind of work it does, the kind of scientific thought or integrity it had behind its work, will make it harder for people to judge what kind of lab environment or institution it is." (Interview Transcript, February 2016)

Carl, another post-doc, shared similar sentiments about the risks of joining the younger Oak Lab. The risks, for Carl additionally reflected the risks to his work and the pursuit of his own investigative pathway. He described that because the IGI is so young it does not yet have "institutional knowledge to fall back on." When I probed further, Carl described "institutional knowledge" as being about, for example, what assays take longer, faster and which kind of results will have greater impact on the field, "knowing what is the low hanging fruit, a sort of cost-benefit analysis (sic.)." This is the sort of know-how that Andrew Nielsen's research program possessed in cardiomyopathy disease modeling and stem cell culture.

In order to fill the practical vacuum entailed by the CRISPR-Cas9 system and the lack of a historical accumulation of tacit knowledge, a significant part of the Oak Lab's work was devoted to figuring out what assays were faster, what techniques were more efficient, what concentrations were optimal and developing protocols that captured this know-how. The ability to testing the same experimental conditions in a wide variety of cell types and projects helped the teams move forward through technical challenges. Addressing this uncertainty did not immediately result in clear

publishable outcomes. Instead, sharing protocols and reagents, with the Nielsen Lab for example, was itself a valued outcome for the research program and helped build the program's collaborative network.

In sum, the high project heterogeneity and lack of working history of the Oak Lab's research program shaped the lab's organization and its aims. These structural features of the research program help explain the lab's orientation towards the CRISPR-Cas9 system as both a means and an end. Graduate students and post-docs successfully adopted the system and continued to develop it through the multidisciplinary configuration of the laboratory's subgroups and the availability of undergraduate volunteers to conduct experiments geared at optimizing protocols. These organizational dynamics of the research program changed as projects progressed and the lab became recognized for its work in more specific areas. Additionally, as the IGI continued to formalize into an institute, the Oak Lab's position relative to other nearby labs that use genetic engineering techniques, like the Nielsen Lab, also shifted.

2.5. Producing Practice Through Adoption

As a popular meme circulated among the Oak Lab put it, "*Theory* is when you know everything, but nothing works. *Practice* is when everything works, but no one knows why. *In our lab* theory and practice are combined: Nothing works, and no one knows why," (emphasis in original). The cases examined here illustrate how genome editing scientists manage the uncertainty surrounding the adoption of a promissory new technology in relation to the structure of their scientific research program. I have compared two research programs along two major axes: the project structure of the research program and whether or not the program has established itself both internally and externally. Coupled with the changes to the surrounding organizational landscape of the labs, these two axes help explain differences in the strategies deployed by scientists to manage the uncertainty at the edge of science.

While the Oak and Nielsen labs use genome editing for distinct research goals and their unique organizational work strategies influence these uses, by articulating the innovation with their existing research program, they are both involved in producing CRISPR-Cas9 as a revolutionary and valuable tool in the life sciences more broadly. The dynamics of these two research programs begin to illustrate four broader dynamics at play in the spread of new technologies: a) in principle, familiarity with other instruments, techniques, methods, and protocols shapes what individuals will prioritize or consider to be a challenge to the adoption of new technology; b) the stage of the career of an individual lab member and the history of a research program can influence their likelihood of adopting techniques that have yet to be proven effective; c) the content of the research program heavily determines how a new technology will be used; d) large scale organizational re-configurations can give rise to a robust collaborative network around the new technology. In case of genome editing, the dynamic relationship between the form and content of scientific work suggests a process of fitting, wherein what you use CRISPR *on* shapes the technology itself through the inscription of practice into protocols which accompany the technology. Over time, the production and accumulation of protocols for using a technology reduce the epistemological and ontological uncertainty and provide stability to the research program, allowing practices to be replicated.

As the research program acquires grants, moves its projects forward, develops more collaborations, publishes results, and gains recognition it becomes more established and develops a sense of its own history. This history is re-told, for example, during lab retreats and when new members join. Importantly, an older and established research program has faced and overcome

pragmatic challenges. This affords some members of the laboratory a reflective capacity that can mediate their adoption of new technologies. With this, the research program's personnel have developed a sense of 'what works.' These technical commitments can be inscribed in standard operating procedures and experimental protocols, over time acquiring the status of what one informant referred to as "voodoo." In short, an established research program has gone through a process of institutional drift (Becker 1982:303–4; Dekker 2011). This sense of 'what works', or the laboratory's *signature* (Mukerji 1990), mediates how scientists work with instruments, interpret data and choose research problems (Mok and Westerdiep 1974).

In the above analysis I have re-specified the scale of the object of analysis when attempting to pinpoint the origins of new scientific practices and propose a model of scientific research programs where the research history and the temporality of personnel, materials and equipment sets the pace for advancement. My aim in this analysis has been to offer an account of processes of technology adoption, adaptation, and re-tooling in relation to the subject matter of the research itself and to the epistemological decisions made by lab members. Instead of focusing on either the laboratory or individuals as the vehicles of circulation, I have traced the impacts of technological adoption and adaptation into scientific research programs. Additionally, as I return to in the Methodological Appendix, the shifts in the research programs described above draws attention to the limits of treating units of analysis as static entities and emphasizes the value of process-based accounts of individual and organizational phenomena. In terms of the microfoundations of institutions, what these two cases suggest is that the practical situations of scientists at the lab bench shape the contours of the institution of genome editing as they push the technology into new spaces of application and reify the routines that support the technologies use.

2.6. Tracing the Circulation of Practice: Social and Material Infrastructures

To understand how the new practices that lab members like Arthur, Kyle, Allison and Marvin developed can then themselves spread, producing an institution at scale, I travelled to Cambridge, MA to the headquarters of the organization that Oak and others attributed to exponential uptake of the CRISPR-Cas9 system: Addgene. Addgene is a non-profit organization that operates as a mediator between the exchange of practices and biological materials between research programs by managing the depositing of plasmids to the repository and fulfilling the request of plasmids from the repository. Because plasmids are central to many biological experiments and are key for CRISPR-based techniques, scientists rely of the availability of these circular pieces of DNA as a key reagent. For example, one method for getting the Cas9 enzyme to cut the piece of DNA you want is to create pores in the membrane of the cell and add a plasmid, which will go through the membrane into the cell: transfecting the cells. This plasmid encodes the information necessary for the cell to transcribe and assemble Cas9 inside the cell. Designing plasmid constructs and trying them out is a basic step in most of the experiment work I've observed so far, as exemplified by Kyle's Cas-BirA* construct and plasmid library used by Arthur and Erica's subgroups. Since receiving its first CRISPR plasmid in 2012, Addgene now has over 8,000 different CRISPR plasmids in the repository, sharing them over 140,000 times with laboratories across 75 different countries (Tsang 2019). In this section I draw from the interviews and a focus group I conducted with representatives from Addgene to begin to understand the development of the social and material infrastructures that facilitate the sharing of CRISPR-based practices across academic organizations.

Addgene was well positioned to handle the hype surrounding CRISPR because of the infrastructure they had built prior to the "craze." In 2004 its founders addressed a glaring issue they

saw as slowing down collaborations and scientific advancement: researchers had to package and ship their own plasmids, sharing them with other researchers who had requested them after publishing their work. In addition to being time consuming, this process was also wasteful, as similar plasmid constructs would have to be created in different laboratories and older plasmids would be lost as graduate students and postdocs would move onto different organizations, as Addgene put it: "the waste of the vast resources stuck in lab freezers is what drives us every day," (Joung, Voytas, and Kamens 2015).

Beyond this, the sharing of materials is bureaucratically managed by the technology transfer offices of universities, which pay close attention to the potential for profit stemming from the intellectual property associated with biological materials like plasmids (Berman 2008; Owen and Powell 2001). This is largely managed through contracts, called Material Transfer Agreements (MTAs), which govern the transfer of research materials. At a gene editing conference, one vocal scientist characterized these contracts as "the end of scientific freedom." To get around this, the founders of the organization capitalized on the social position and hierarchies of science. As their one of their heads of outreach put it: "when it started it was literally Addgene founders knocking on the doors and saying, 'hey you have great tools, if you want to share them we can handle the distribution and storage,'" (Focus Group, August 2017). Another scientist in leadership specified, "they were a little bit strategic about that, because they chose famous scientists." In this way, Addgene ensured that people associated depositing their plasmids the repository as a legitimate and desirable thing for a published scientist to do. As one Addgene representative recounted alongside a CRISPR pioneer, "In a fast-moving field in which intellectual property is a commercialization impediment and freedom to operate is a business nightmare academics can request these plasmids at cost ($65 per plasmid) and have them shipped to their lab within days," (Focus Group, August 2017).

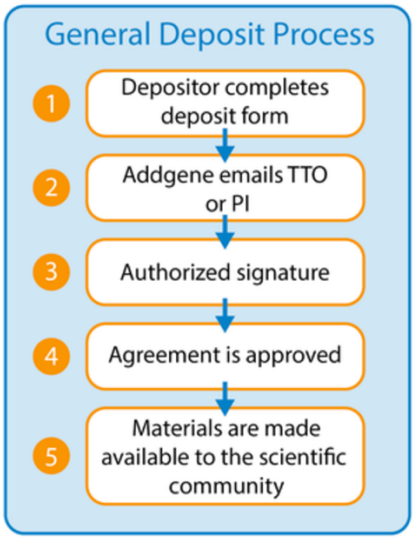

Fig. 3. Addgene general deposit process workflow. (Accessed Online 6/4/2020: https://www.addgene.org/techtransfer/)

Addgene has facilitated the spread and institutionalization of genome editing in five ways:

1. First, it performs quality control on the plasmids submitted materials, sequencing deposited plasmids and doing validation experiments.
2. Second, by taking over the logistics of CRISPR distribution, moving biological materials from place to place. As Joanne Kamens, then executive director of Addgene, showed me during a tour, everyday UPS comes through to collect around 300 boxes of plasmids neatly

stacked and organized across a long table. In managing this, they allow researchers from smaller universities and universities outside the United States to adopt the practices developed at higher resourced laboratories. This effectively contributed to what scientists described as the "democratization" of genome editing.

3. Third by keeping a detailed records of every innovative plasmid deposited and every request they created a system for easily tracing what plasmid is needed for what experiment. As Kamens explained to me on the tour in a mech-filled room adjacent to the packing room, "We have this very complicated inventory management system. Let's say there a CRISPR plasmid that is popular, and it gets requested ten times in one day, not uncommon, [the Addgene scientists] don't have to keep going in and out, it tells them they need to pick that one out ten times. So, they take the one tube out, they pick it ten times and the barcoding system, and the computer organizes it by shipping and then it goes into the right orders. So, to get it more fruitful we've had to do more automation." The operation as a whole has been likened to Amazon (Regalado 2016).
4. Fourth, Addgene contributes to the institutionalization of CRISPR-Cas9 by producing guidelines and protocols that support the use of some of the plasmids. For example, Addgene was the first to develop a textbook for CRISPR. Their CRISPR 101 eBook has been downloaded more than 30,000 times and their informative CRISPR blog posts have been visited over 500,000 as of 2019. In it, detailed definitions of new genome editing techniques and terms of art are spelled out for curious adopters. Additionally, the scientific team at Addgene works with the scientists who are depositing plasmids to coproduce useful documentation to accompany the plasmids. Acting as an up-to-date clearing house and tracker of CRISPR innovations in academic and non-profit laboratories (Addgene does not share plasmids with for-profit organizations.).
5. Finally, they kept lawyers happy with detailed record keeping and by electronically managing MTAs through a Universal Biological Material Transfer Agreement (UBMTA) that relaxed the institutional constraints on the transfer of biological materials. The head of Addgene's legal team further explained the benefits of imposing a universal contract, "the terms under which universities deposit with us gives us the right to distribute under that MTA. So when a requesting institution wants to add some terms to it, we just say, "Nope! We can't do that." And its take it or leave it, and because their scientist wants it, they are going to take it. So that's really simplified the process," (Focus Group, August 2017).

Fig. 4 "The Packing Room" (courtesy of Addgene).

The amelioration of the constraints for technology transfer facilitated the ease with which CRISPR-based practices spread in connection to the plasmids. This arrangement of tech-transfer offices, the non-profit sector and university researchers provided a reliable practical rubric for managing the excitement over the technology and appeasing the IP concerns. What this amounted to in practice was a subversion of the bureaucratic control over the sharing of biological materials. As the CEO of Addgene put it: "frankly the MTA is meaningless."

The MTA contract itself is meaningless (at least to the scientists) in at least three ways: the "material", the "transfer" and the "agreement." The "material" is meaningless, because as my respondents repeatedly confirmed, if you wanted to, you could synthesize the plasmid yourself. Producing the material on your own, as had been done historically. This is expensive and time consuming, however. From one of my respondent's views, this was essentially her experience in the biotech and pharma industries. At a non-profit research organization, the ease of ordering was more desirable due to resource availability. So, scientists will email each other and request plasmids if they think they'll be useful. This is where the "transfer" bit is meaningless too. The sharing of materials is ubiquitous and can occur between individual scientists on a one-on-one basis. All one needs is a way of distributing the materials. Moreover, transferring the materials doesn't tell you much about how to make it work, or what is exactly can be used for or its own. In many cases the plasmids may serve as a reference for building a different construct. The tacit knowledge doesn't as easily transfer through the FedEx package. Lastly, the "agreement" is meaningless in the case of Addgene because they impose the terms of the Universal Biological MTA (UBMTA). Rather than agreement between the technology transfer offices of two universities, Addgene strictly imposes its terms. In other situations, where this isn't the case, the agreement can lead to protracted legal negotiations over the specifics of the contract that can delay research for months.

This amelioration helped speed the circulation of genome editing practices, which Addgene quickly learned would be highly requested. For some scientists, the value of Addgene was obvious. For example, the Addgene executives I interviewed discussed a high-profile publication in *Nature* by MIT biologist Feng Zhang. In anticipation of a huge wave of requests for the Cas9 variant plasmid his team had developed for the paper, Zhang contacted Addgene to make the deposit ahead of the release of the pre-preprint of his paper. Zhang, who was the main inventor behind the MIT/Broad

side of the patent dispute with UC Berkeley, is responsible for four of the top 10 most requested plasmids, and as of June 2018 had shared CRISPR related plasmids more than 4200 times (Zhang 2018). Building partnerships with "famous scientists", like Zhang, was one of the strategies that Addgene's founders used when starting the organization.

However, to further develop a culture of regularly depositing plasmids and adopting the terms of the MTA, Addgene incentivized scientists in a variety of ways. For example, it created a points system where if your lab's plasmids are requested 15 times, you are afforded one free plasmid. As Kamens explained to me, "So if their plasmid is popular, then that helps the repository stay afloat and they get a free one. It doesn't really affect our bottom line too much because many of the labs that have a lot of points, they just go on and request normally. But sometimes they do and its very useful for smaller labs and labs that have less funding," (Focus Group, August 2017). Additionally, Addgene developed a tiered award hierarchy for depositors depending on the popularity of their plasmids, going from a Yellow Flame, Red Flame, to Blue Flame (Hannon 2016). For every plasmid that reaches over 100 requests, they send a plaque to the depositing scientist that can be sported in Tweet.

James Gagnon from Alex Schier's lab at Harvard tweets about the Blue Flame Award.

Fig. 5 A scientist shows off their "Blue Flame" award on social media (courtesy of Addgene).

The last, and perhaps most important incentive for sharing the experimental materials of CRISPR is visibility. Kamens put it plainly, "…if you have the CRISPR plasmid that is not on the website, you are not going to get cited." When coupled with the scientometric measure of CRISPR's growth in popularity from the begging of this chapter, Addgene's facilitation of the sharing of CRISPR tools highlights the importance of adoption and collaboration as a mechanism of institutionalization in academia. One analysis, showed that published papers whose corresponding plasmids were deposited with Addgene amassed four times as many citations as papers that did not,

and still got two to three times more even when controlling for journal and publication year (Thompson and Zoyntz 2020; Zoyntz and Thompson 2017).

Addgene is just one of the organizations that are key to the institutionalization of genome editing because the provide a social infrastructure to the spread of materials, practices, standards, and guidelines. This infrastructure scaffolds the work of scientists at the lab bench like those in the Nielsen and Oak labs, helping them manage the uncertainty they confront at the edge of science and facilitating the adoption of CRISPR-Cas9 technology. As I explore in greater depth in the next chapter, this social infrastructure is supported by affective norms and value frameworks. In this case, motivators aligned with the Mertonian norm of *communalism* and helped actors in academia and non-profit laboratories reproduce their work, share tacit knowledge, and establish records of best practices. Additionally, by minimizing the bureaucratic lag of technology transfer practices that govern the sharing of practices and materials Addgene fueled the proliferation of genome editing practices across sub-specialties of biomedicine and the life sciences in academia.

But that's just it. Addgene only partially explain the institutionalization of genome editing in academic laboratories like Nielsen and Oak's. Certainly, scientists at the bench are driven to solve complex problems and follow the mantra of the deductive nomological model: "fuck around and find out," as one grad student had posted at their desk in the lab (Fig. 6). However, this pursuit cannot be understood independently of the economic and political conditions that make bench building possible and make genome editing normative in terms of the societal or biomedical impacts of science. In effect, even though a set of practices spreads widely does not by itself ensure it will endure and successfully be reproduced over time.

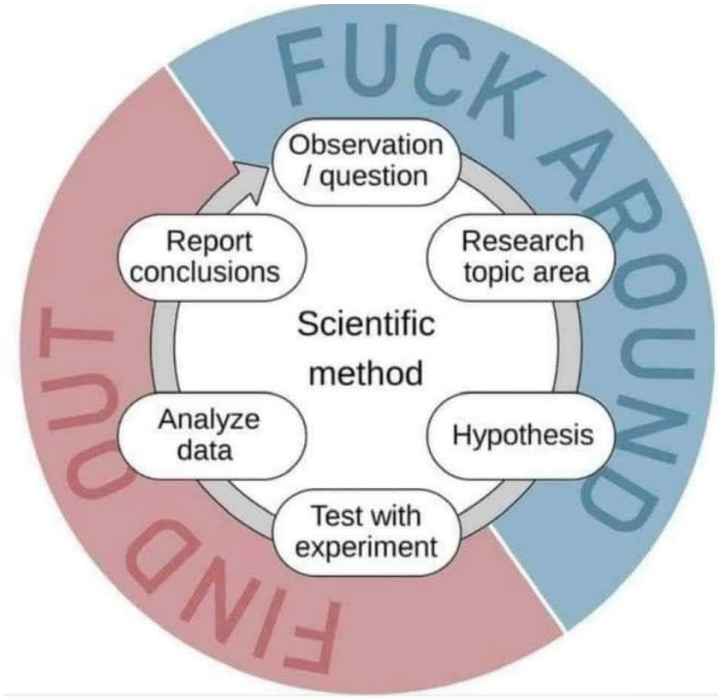

Fig. 6 Representation of the scientific method from a lab members' desk.

Ch. 3. The Production of Organizational Structures and the Moral Economy of Genome Editing

> "I skate to where the puck is going to be, not where it has been." - Wayne Gretzky – quoted in Nielsen Lab research grant for Chan-Zuckerberg BioHub, October 2016.
>
> "I will admit my sort of deep anxiety for CRISPR is sort of the story... and don't laugh, I'm dead serious... is sort of the story of the Segway. If you've ever ridden a Segway, it's amazing. I mean, it takes five seconds to learn, it's super-fast, it's super safe, it's amazing! It's just… nobody uses it. I mean, police do use it and tourists in San Francisco. So once upon a time, there was a world where people thought that everybody would be riding Segways everywhere, and it has become a niche thing. *So my raison d'etre is to try to make sure that pretty much CRISPR everything*, at least that is impactful to the real world, is not niche, and is in fact quite widespread." – IGI Scientist, formerly scientific lead in early genome editing company.

Previous sociological research suggests that whether the technology underlying genome editing, the CRISPR-Cas9 system, is fated to be a flash in the pan or a durable institution in biomedicine will not just depend on whether scientists at the lab bench can get the technology to work or not. It also depends on whether robust and reproducible alignment can form between the multitude of actors involved in the practice and politics of genome editing. Academic scientists, research hospitals, biotechnology firms, pharmaceutical companies, regulatory bodies, and patient communities all have a stake in the development of genome editing.

Partnerships between academic laboratories and the biotech and pharma industries, in particular, have become the norm in 21st century biomedicine. The routinization of academic-industry relations is central to the broad array of practices that universities and their faculty engage in to produce revenue from research. Under the analytic umbrella of *academic capitalism*,[27] research has described how this way of organizing science has become an imperative for both universities and the state (Hackett 1990, 2014). Economic and organizational research has shown that ecosystems made up of research universities and small technology startups, like Boston-Cambridge, Massachusetts and the San Francisco Bay Area in California are hubs of production for new biotechnologies. This work illustrates how these arrangements of different kinds of organizations shapes the structure of scientific work and how well-positioned actors are able to concentrate both knowledge and capital to set the terms of exchange and production for new technologies (Oliver 2004; Powell, Koput, and Smith-Doerr 1996; Shwed and Bearman 2010).

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[27] A family of closely related concepts likewise describe the long-term institutional shift in how universities operate: "entrepreneurial university" (Clark 1998), "neoliberal science" (Lave, Mirowski, and Randalls 2010; Moore et al. 2011) and in research policy, the "triple helix" describes the coordination between organizations of the state, industry and academia (Etzkowitz 2008).

In a separate vein, research has shown how science can shape the production of values and value that can then spread across domains of society and vice-versa, how markets can shape the moral order(s) underlying science and medicine (Fourcade and Healy 2007; Healy 2006; Livne 2019; Quinn 2008; Zelizer 2005, 2017). Work in the sociology of science and biomedicine suggests that the success of organizations that are developing, testing, and marketing novel technologies will also depend on whether a corresponding social order and value framework can be co-produced and normalized (Frickel and Moore 2006; Jasanoff 2004; May 2006).

This chapter extends the sociological research on the emergence of the field of biotechnology and biotechnology clusters, to interrogate the conditions from which new organizational forms and moral discourse surrounding genome editing are emerging. Do partnerships between academic labs and for-profit biotech and pharma industries shape the moral order of genome editing? If so, how and to what effect? Departing methodologically from previous research on biotechnology clusters which focuses on networks and patent analysis, I draw from participant observation and interview data to further describe the micropolitics of CRISPR research. This chapter continues to extend the ethnographic reach of the project and sifts through a thicket of relationships and interactions between academic scientists, industry researchers, venture capitalists, bioethicists, and clinicians to identify the development of discursive positions and frameworks of meaning that advance human genome editing. This chapter lays groundwork for future research on the politics of knowledge sketching out a conceptual framework for studying how structural changes in the relationships between academic and industry science shape the production of values and value of genome editing. Ultimately, I argue in this chapter that academic capitalism has shaped the institutionalization of genome editing in two mutually enforcing ways: structurally, when the for-profit and academic actors attempting to control the fate of genome editing become aligned; and affectively, when moral commitments become embedded in market ideologies about what clinical genome editing will look like. Understanding the interplay of the structural and affective conditions from which new technology is constructed contributes to contemporary theories of the affinity between science and capitalism.

3.1. The Moral Economies of Academic Capitalism

Previous work has documented and analyzed the institutional shifts where academic organizations are increasingly adopting the practices and bureaucratic frameworks of for-profit organizations in industry. Building on the theoretical grounds laid by Max Weber and Karl Mannheim, this work argues that beyond the corporatization of higher education (Slaughter and Rhoades 2004) and the establishment of academic entrepreneurs (Jones 2009), academic institutions have shifted ideologically to align with neoliberal economic and social policies. Under the analytic lens of *academic capitalism* this body of scholarship has opened up a line of inquiry into the ways in which these shifts have re-shaped scientific work (Hackett 1990). One key insight has been that it is not that economic incentives are somehow contaminating otherwise "pure" science, but that capitalism is a cultural way of producing, attributing and accumulating multiple forms of value (Fochler 2016). Like other modes of production, academic-industry relations are ameliorated by a *moral economy*. Building on Fourcade (2016), I here use the concept of moral economy to examine the circulation and exchange of intuitions, feelings, opinions, and discourses. This understanding of moral is not normative in the sense of: is CRISPR good or bad? But is instead sociological, what do scientists categorize as moral and what are the justifications that scaffold their own debates about what is meaningful and good. Historian of science Lorraine Daston describes it as, "a web of affect-saturated values that stand and function in well-defined relationship to one another (…) a balanced

system of emotional forces, with equilibrium points and constraints," (Daston 1995; see also Thompson 1971). These affective and value commitments shape how actors justify their work and the emerging discourse surrounding new technologies. For example, as I described in Ch.2, Addgene created incentives that would establish the value of depositing plasmids and sharing CRISPR-based techniques between academic labs. In this chapter, I pivot to unpack the ubiquity of the economization and capitalization of academic science and identify the effects of these shifts on how genome-editing technologies are constructed.

Understanding the Capitalist Conditions of Contemporary Science

Within universities, organizational units manage the potential for profitability of scientific discoveries and for managing claims to intellectual property rights (Berman 2012b). Technology transfer offices, now ubiquitous, bureaucratically regulate the sharing of research materials and instruments (Colyvas 2007). These changes have put pressure on scientists to patent the products of their work (Fabrizio and Di Minin 2008) and add bureaucratic barriers to the open exchange of research materials between labs. Precisely the barriers that Addgene helps scientists circumvent.

Interactions between universities and industry can take a variety of forms. These include (by no means comprehensively): a) informal interactions where ideas and know-how are shared, such as shared lab meetings, discussions at conferences and correspondence between scientists in academia and those in industry; b) Labs in academia share research materials and reagents with industry labs and vice-versa; c) Likewise, companies that manufacture equipment for laboratories may beta-test their instruments in academic facilities to learn how their products can be integrated with the workflow of scientists in different specialties. These can later include formal purchase or exchange of these materials as mediated by technology transfer offices of the university; d) Formal partnerships can be established where capital from companies helps fund the work of academic labs, either via paid salaries of individual personnel, unrestricted funds for general research expenses, or contracted work. Paralleling the increased reliance on for-profit industry investment in academic science, philanthropic funding for biomedical research has also increased since the end of the 20th century (Murray 2013).

In biomedicine, structural changes within universities and interactions with organizations in biotechnology and pharma have re-aligned values and norms in molecular biology and biochemistry. These changes put the values academic scientists receive through their training, such as openness and disinterestedness, in conflict with the values embodied endemic to work with for-profit entities, such as caution when sharing tacit knowledge and corporate ownership over intellectual products. Previous research suggests that this conflict creates ambivalence, alienation and anomie in academic scientists via competitive and financial incentives and can drive scientists to engage in misconduct or deviant behavior (Croissant and Restivo 2001; Hackett 1990). This process has been characterized by social scientists as an asymmetrical convergence of scientific work and norms in industry and academia, wherein the norms of industry take increasing precedence in universities, rather than academic norms spreading and reproducing in industry (Kleinman and Vallas 2001; Mirowski 2011). In the fields of genetics and plant biology this leads scientists to become more insular and secretive (Campbell et al. 2002; Evans 2010). In others it can shape entire research trends, for example, research on the influence of the pharmaceutical industry on biomedicine has suggested that biased clinical results and regulatory circumvention increase with for-profit partnerships (Dumit 2012; Sismondo 2007, 2008). Moreover, financial conflicts of interest can shape regulation and policy

surrounding the uses and ownership of emerging technology (Krimsky and Schwab 2017; Sleeboom-Faulkner 2019).

These modes of organizing science shape and can fortify the epistemic conditions from which technology and knowledge are produced and, in that sense, carry important normative dimensions. For example, academic capitalism shapes the valuation of technology and biological materials. It affects local economies of the sale, donation, exchange and travel of bodies, tissue, blood, and individual's biological data (Abadie 2010; Almeling 2011; Cooper and Waldby 2014; Franklin 2006; Healy 2006; Rajan 2006). Anthropological work in this vein has shown that the effects of academic capitalism vary from country to country in ways that are shaped by global economic and political forces (Deomampo 2016; Greenhalgh 2016; Ocal and Kavak 2018; Rajan 2005). To offer an example outside of biomedicine, in the field of artificial intelligence, whether research is funded through industry partnerships or through national grants can shape which areas of research are valued by scientists and can determine the aims of their work (Hoffman 2017).

Moral Order and Technological Change

What is less understood is the effect that academic capitalism can have on the construction of an emergent technology and the values that justify and legitimate its use. How are value frameworks produced or adapted to create moral economies for emerging technologies? How does the alignment of financial and moral interests between academic scientists, physicians, investors, industry researchers, patients and users shape this production? In addressing these questions, this paper empirically grounds Fourcade's (2018) observations on the moral philosophy underlying the "will to progress" in late-stage capitalism: namely, that economic and scientific development is fueled by the belief that technology is inherently egalitarian and democratic, and always aligned with what is seen as morally good. To do this, I draw out the structural and affective dimensions of genome editing discourse.

3.2. Histories of Genetic Engineering

A brief contextualization of CRISPR-Cas9 in the history of genetic engineering helps account for the origins of the organizational relations and affective commitments that characterize the interface between the biotechnology industry and academic science today. As I explore in greater depth in Ch. 4, the life sciences have been undergoing this cultural transformation since the 1970's with the commercialization of recombinant DNA, a technology that allowed scientists to introduce new genes into living organisms (Berman 2008). When rDNA was invented, efforts to use these technologies on humans were largely tabled because they were generally seen morally problematic by the public and were technically unfeasible. Because human genetic engineering couldn't be done, debating its morality was seen by scientists as fear mongering. Genetic engineering instead had its glory in the manufacturing of chemicals and proteins: propelling the creation of the biotechnology industry (Colyvas 2007; Powell et al. 1996; Saxenian 2006; Yi 2015) and flourished at the intersection of the agricultural industry and plant biology.

Since then, biomedicine has seen genetic technologies and molecular modes of explanation become central (Clarke et al. 2003; Rose 2001, 2007). By the 1990s, the idea of using rDNA techniques to treat genetic diseases began to take root. This approach would come to form the field of gene therapy, where strands of DNA are inserted into patients' cells using viral vectors. After the completion of The Human Genome Project at the turn of the century, the development and

proliferation of other biomedical technologies, such as induced pluripotent stem cells, has led to the refinement of the administrative and legal structures that support public-private partnerships between universities and industry (Parthasarathy 2017; Thompson 2013).

These approaches form the experimental background onto which CRISPR-Cas9 genome editing arrived to in 2012. Because of its broad biomedical use as technique for altering DNA, the CRISPR-Cas9 system can find a home across multiple areas of biomedicine: as a supplement to in-vitro fertilization in the reproductive industry; as therapy for treating rare genetic diseases; as a preventive public health measure for reducing the risk of common diseases; as a tool for investigating the progressions and molecular mechanisms underlying genetic diseases tissue; as an instrument for small-molecule drug development; or as a platform for diagnosing disease and detecting health anomalies. In this sense, CRISPR has broad institutional scope within biomedicine.[28]

In addition to shaping a complex competitive environment between biomedical research labs, each of these applications is laden with its own set of ethical and moral dilemmas and entails a different set of organizational and individual actors. This heterogeneity has left the meaning of genome editing open and has continuously unsettled efforts to produce a coherent value framework. For example, while human *germline* genome editing–modifications to eggs, sperm, and embryos–has been a central focus of debates in public conferences and in the media, scientists often assume that *somatic*–non-germline cells–genome editing therapeutics are uncontroversial (Polcz and Lewis 2016). Because this latter work occupies the vast bulk of genome-editing research, this paper tables the high-profile debates about the recent controversy surrounding the birth of genome-edited twins in China (Li et al. 2019) for the next Chapter, and instead centers the discourse of genome-editing researchers in their everyday experience. The CRISPR-Cas9 system, poses an additional analytic challenge to social scientific work at the intersection of sociology of technology and medicine because of its broad scope of application. The multidimensionality, indeterminacy and high heterogeneity of applications makes genome editing an *exceptional case* for studying the rapid rearrangement of a moral economy. That is, treated heuristically as an *exceptional case* that "[magnifies] sets of relations that in extreme instances tend to remain invisible," (Ermakoff 2014:224).

I have organized findings from this analysis into two broad themes: those pertaining to the organizational dimensions of genome editing and those pertaining to the affective experiences of genome editing science. In the sections that follow, I dissect the relationship between these two to assess how academic capitalism has shaped the construction of genome-editing technologies and the discourse surrounding them.

3.3. Building CRISPR Organizations

The distribution of resources and expertise of academic capitalism in the San Francisco Bay Area is shaping the creation of organizational structures in which genome editing is practiced. To

[28] Application of the technology in agriculture are likewise widespread and no less disruptive. Researchers in plant and microbial biology have likewise adopted genome-editing technologies. In these fields, the industrial applications of CRISPR-Cas9 are vast: from the engineering of disease resistant crops (Tyagi et al. 2021) to the breeding of low-fat pigs (Zheng et al. 2017). Such research is likewise shaped deeply by the intersections of big agriculture and university research (Montenegro de Wit 2020)

build these organizations, academic scientists partnered with philanthropic and industry firms to create reproducible funding streams for developing CRISPR-Cas9 and public events that would legitimize this technology. Alignment with commercial entities was advantageous for early-stage genome-editing scientists as it opened avenues for the spread and refinement of the technology. Building on the momentum of public hype surrounding genome editing and a surge in publications as a result of CRISPR-based techniques, academic actors sought to develop bridges between their university and both biotechnology startups they had helped found and more established pharmaceutical companies who were curious about the commercial and R&D prospects of genome-editing technology. Public conferences further helped frame CRISPR-Cas9 as a public good to be developed at the intersection of industry and academia. At research sites, key academic actors operated entrepreneurially (Jones 2009) to shape how the organizations producing CRISPR-Cas9 were constructed financially and ideologically.

Innovative Genomics from Initiative to Institute: The Interstitial Organization

The creation of a center of organizational pull in the SF Bay Area re-ordered social ties between individual academic and commercial laboratories specifically around the practice of CRISPR-Cas9 technology. This center of gravity, the Innovative Genomics Institute (IGI), started as an initiative in 2014 led by Jennifer Doudna, one of the co-inventors of the CRISPR-Cas9 System and Jonathan Weissman, another lead developer. IGI was conceived with the goal of validating, refining, and improving the visibility of genome editing techniques. It was "dedicated to the enhancement and proliferation of genome editing research and technology in both the academic and commercial research communities" (IGI website Dec. 2014). In this capacity, IGI is an *interstitial organization,* connecting faculty and students at universities with market actors (Ocal and Kavak 2018; Slaughter and Rhoades 2004).

In part because of its interstitial goals, the identity and management of the organization was ambiguous to student researchers, employees, and principal investigators. At times the organization operated as collaborative space, encouraging different labs to share resources and tacit knowledge. At others, it acted in the spirit of a company, fighting alongside the UC system for control of the intellectual property of CRISPR-Cas9 technology. Still in other situations, it aimed to act as educational site, offering both practical workshops and training programs for undergraduates, graduate students, and senior researchers, as well as educational outreach efforts in nearby high schools.

At its conception, the initiative was comprised of a small collective of around 10 labs at UC Berkley, UC San Francisco and at Stanford. It received initial funding from a Hong Kong business magnate's philanthropic organization, the Li Ka-Shing Foundation–the second largest private philanthropic foundation in the world. With its name on life sciences and medical buildings at UC Berkeley and Stanford, the Li "Ka-ching!" foundation, as one senior scientist put it, had earned a reputation for founding large research organizations from scratch. As an initiative, the IGI awarded early-stage project funding to labs interested in developing CRISPR-Cas9-based techniques. In addition to funding, the IGI also began to offer key scaffolding for the practice of genome editing in the form of reagents, protocols, and workshops. Overall, the IGI included work in molecular biology, biochemistry, plant biology, microbial biology, and biomedicine with CRISPR-Cas9 as its keystone, ambitiously attempting to align multiple disciplines and the markets they are connected to. This broad organizational scope reflected both the novelty of CRISPR-Cas9, wherein new actors

had to learn the practices associated with CRISPR-Cas9 in order to adopt it, and its wide applicability across the life sciences.

In January 2016, these ambitious goals paid off. The initiative matured into an institute, after receiving further consecration from the University of California Office of the President and $43 million dollars in funding from gifts, grants, and industry sponsorship, combined with commitments of $30 million and matching contributions of $50 million dollars from the University. Throughout its growth, IGI leadership maintained close ties with emerging biotechnology startups focused on developing CRISPR therapeutics, several of which they themselves had founded. Excluding funds received for the conduct of research from private firms, survey and self-reported conflicted of interest data available through state funding bodies shows that scientists involved in developing genome editing tools individually held from $40-$150 thousand dollars in equity in biotech and pharmaceutical companies in any given year (Wei, Waldman, and Armstrong 2019). With the growth of the IGI as an institute, the directors restructured the leadership of the organization, in part to bring together UC Berkeley and UCSF in a co-venture. Throughout this process of maturation, faculty and administrators coordinated across a variety of private and governmental organizations to legitimize and establish the IGI. Access to stably reproducing funding streams also allowed the creation of permanent positions for research scientists, technicians, a biostatistician, a patent specialist, and fundraising personnel directly under IGI management in addition to the lab personnel that made up the labs affiliated with the organization,

The IGI further matured once it moved to take over a state-of-the-art multi-story building on the UC Berkeley campus, the Energy Biosciences Building (EBB). EBB had been built in 2007 as a result of the largest ever corporate sponsorship of university research: a pledge of $500M over 10 years from BP Energy, formerly British Petroleum, to UC Berkeley, Lawrence Berkeley National Laboratory and the University of Illinois at Urbana Champaign. After the BP oil spill in 2010, the Energy Biosciences Institute became so enwrapped in controversy and pressure from environmental activists that it was forced to dramatically downsize (Neuman 2015). With now four out of five floors vacant, the labs of principal investigators in IGI leadership moved to occupy the glass-clad building. With now a physical hub, came additional coordination opportunities such as regularly occurring events and greater investment in laboratory infrastructure that could advance CRISPR-Cas9.

The IGI's *interstitial* characteristics are exemplified by its Entrepreneurial Fellows Program, which professionalizes scientists at the postdoctoral stage of their careers. This program was "designed to catalyze the translation and commercialization of innovative research discoveries for practical benefit, this new program builds strong support networks in which accomplished, entrepreneurial-minded researchers are enabled to make substantial contributions to the biotech economy, and ultimately introduce breakthrough discoveries to the market," (IGI Website, September 2016). The IGI afforded one selected applicant a year up to $250K/year for research for a maximum of two years so that they may "contribute directly to the biotechnology investment space," (*ibid.*). In this way IGI leadership aimed to develop the organization into a biotech incubator, linking young researchers with lawyers who can help individuals start their own companies and protect the intellectual property of their inventions.

The *interstitial* character of the IGI is also manifested in the multi-valence of organizations' mission. The public-facing goals of the IGI were framed with a wide set of moral imperatives: 1) to cure genetic diseases by pioneering what they would call "genome surgery"; 2) to ensure healthy food for the world's growing population by addressing food safety and security; 3) to discover new antibiotics to solve the drug resistance crisis; and 4) to lead policy and bioethics debates surrounding

the technology. Bruno Latour's two-faced Janus offers a heuristic for explaining this ideologically (Figure 7.), wherein the IGI promised a CRISPR-panacea to funders and reporters with one face, and with the other, aimed to establish and refine experimental practices with CRISPR-Cas9 in the lab by studying the fundamental molecular mechanisms of the technology.

One of the final drafts of a public handout for dissemination to funders describes the overarching goals of the IGI in relation to CRISPR-Cas9. In it, CRISPR-Cas9 was defined as "a molecular scalpel with the capacity to correct errors in the genetic alphabet of plants, animals, or people, [it] can be programmed to reach into a genome with unprecedented ease and precision." (Public Handout v.10, May 2017). For the scientists at IGI, the metaphor of the scalpel helped communicate what the technology could be used for.

However, in practice, it was still uncertain whether the technology would be scalable. The metaphor obfuscated the molecular mechanisms underlaying the technology which were still being characterized. While "ease" and "precision" were hallmarks of the technology for designing and conducting experiments, researchers recognized a wide variety of basic technical challenges that required significant investment to be addressed (Cox, Platt, and Zhang 2015; Doudna 2020; Kempton and Qi 2019; Zhang, Wen, and Guo 2014). Scientists outside of leadership generally felt that the internal goals of research programs in the IGI differed in scope from the broader goals of the organization.

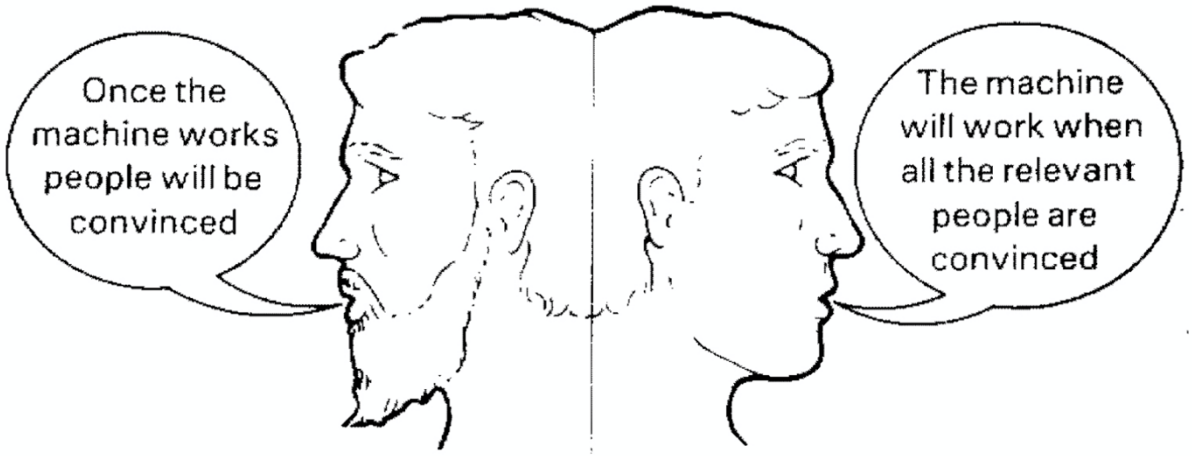

Figure 7. The Third Dictum of science's Janus (Latour 1987)

This disconnect between the imagined potential of genome-editing technology and the banality of the technical limitations of the technology in practice was characteristic of the discourse around CRISPR-Cas9 and was undergirded by a split in the moral economy. On the one hand, the technology may address issues where the ethical imperative was clear, such as relieving suffering from severe genetic diseases and developing disease-resistant crops to combat global food scarcity. On the other, this imperative justified the funding for fundamental and exploratory research to help develop technical laboratory protocols that would, in principle, contribute to these broader impacts. As I describe below, this dynamic triggered broader affective expectations about what genome editing was and when its applications would reach those in need. As the IGI continued to mature organizationally by establishing reproducible funding streams and positions for technicians, the

scientists in the IGI developed and refined technical protocols that would help push CRISPR-Cas9 out of the laboratory and into the market.

Shaping the direction of research: CRISPR-ventures

When scientists worked to translate CRISPR from an experimental tool used in academic labs to a productive tool in industry, the direction of their research also changed. In this sense, academic capitalism influences research priorities (Hoffman 2011). Here I examine a case where the creation of a biotechnology startup coincided with a shift in direction of work in the lab to highlight two ways this can occur: indirectly by determining which applications of CRISPR are likely to yield more medically relevant outcomes and which applications are viable in the market; and directly by shaping the organization of projects in a research program. This doesn't mean that research being directed by which areas are more profitable or that scientist's choices are driven by a financial incentive, but that scientists' understanding and projections of how market actors will do research and on what diseases informs how they assign value to different areas of application for CRISPR-Cas9 in academia.

As explored in Ch. 2, over the course of my fieldwork one of the laboratories affiliated with the IGI pivoted their research program dramatically. Since 2005 the Nielsen Lab's research program had focused on using induced pluripotent stem cells (iPSC) to study cardiovascular diseases by engineering cardiomyocytes–heart cells. Early in the development of CRISPR, the principal investigator of the lab, Andrew Nielsen, perceived these new techniques to be still too unreliable for widespread use in biomedical research: he believed the innovation needed further proof of concept. This early hesitation to endorse the therapeutic application of CRISPR technologies stemmed from general uncertainty over the regulation of genome editing techniques and uncertainty over the ability to overcome technical limitations.

During one lab meeting Nielsen discussed the emerging landscape of the field of genome editing with Samuel Oak. The senior scientists at the meeting projected, "therapeutic editing is going to remain a boutique area. But using editing to uncover more about disease etiology [...] every, single, pharma company is doing that." Under the competitive environment of both academic and for-profit genome editing, researchers estimated that sticking with boutique research projects would be more scientifically productive in the long run. This was because industry research was becoming heavily invested in using CRISPR-Cas9 to characterize diseases in order to find "druggable targets," molecular sites where small molecules could be used to intervene in biochemical pathways. Each of these small molecules could then be tested in the clinic and turned into a drug. The saturation of this problem space meant unnecessary competition with well-funded industry research.

In 2016, Nielsen and the clinician in his lab, followed this line of reasoning and pivoted away from doing research on heart diseases. They instead identified research areas that more fully embraced the therapeutic potential of genome editing, despite their early hesitation. By early 2017 Nielsen started projects on two rare genetic diseases: Best disease, a kind of macular degeneration that leads to blindness, and Charcot-Marie-Tooth or CMT a hereditary neuropathy that causes progressive loss of muscle function and sensation. Working alongside the clinician in his lab and through discussions with other PIs at UCSF, Nielsen chose these two diseases because in his estimation these would serve as a "proof of concept" for therapeutic editing and would keep the lab in a relatively boutique problem area. Because the patient population was small relative to other diseases–prevalence for Best disease is approximately 1 per 15,000 and CMT is 15.7 per 100,000 (Anon 2021)–Nielsen felt they were unlikely targets for pharmaceutical companies because they

represented such a small market. Unpacking the conditions and motivations behind the shift illustrates how academic capitalism, as a system of allocation of resources and relations between actors, shapes the organization of inquiry in science.

At one level, this transition was shaped by the specific arrangements of capital in the SF Bay Area. That year, CZI's BioHub had pledged $600 million for biomedical research that broke the mold of academic innovation. Zuckerberg and Dr. Pricilla Chan said they would invest at least $3 billion over the next decade toward disease cure and prevention. CZI, as an L.L.C., would also be positioned to spend on for-profit companies (Benner 2016). In consultation with the BioHub's scientific advisors, Nielsen put together an application, "Genome Surgery, a Disruptive Approach to Human Genetic Disease" that directly appealed to the CZI's interest in non-traditional science innovation. CZI additionally made a commitment to only enabling "open science," which Nielsen saw as in direct alignment with his work, as he described in his grant,

> "I am delighted by the mission of the Biohub and believe it is completely in sync with my own scientific goals. […] I have active collaborations in the Bay Area (Berkeley, Stanford, and UCSF) and have seen how these synergies strengthen and benefit all groups. I am an active believer in the power of open science […]. Collaboration is baked into all my research projects, since it helps to achieve our high impact goals faster and more effectively. I thrive on building communities to collaborate on innovative, empowering projects. I look forward to working with the Biohub to help bend the arc of science and discover novel therapies."

In addition to changes in the organizational environment, at another level, Nielsen's individual entrepreneurial goals were aligned with the shift in his research program. During this period, Andrew Nielsen and his colleagues at his institute founded a for-profit biopharmaceutical company, Almanor Therapeutics after receiving funding from high-profile biotech venture capitalists. The advertised aim of the company was to develop drugs for heart disease by targeting molecular pathologies in heart muscle cells and use cutting-edge research using induced pluripotent cells and CRISPR technologies. The inception and unfolding of this new company, Almanor, offers an example of how alignment is achieved between academic researchers and venture capitalism.

For the new company and the laboratory to align, there had to be a clear articulation of the projects the lab would be working on, who would be working on them and how data and results would be shared with the company. During an interview with a senior member of the lab, I asked whether a shift to working on Best diseases and CMT with CRISPR would prove challenging for the lab and whether it would force Nielsen to find new collaborative opportunities, since most of his work had been aligned with others in the field of cardiovascular disease research.

> "That, sorry? Um no, because the cardiomyocyte stuff is transitioning to Almanor. Which might be a good thing, because there's issues with conflict of interest and ethics, so it makes it cleaner and with interactions. [Andrew Nielsen's] thing is not specific to one cell type, he is about the tools like genome engineering and editing so it doesn't really affect the fact that he is transitioning to other cell types […]. So I would say it hasn't. I mean maybe it sort of, maybe he has had to look more outwards to collaborate, […] But he is collaborating on the floor, because of Almanor, they are all founders apart from a couple of PIs, they are still invested in getting [the CRISPR and cardiomyocyte research] to work through Almanor."

The lab member described how because of the emergent partnership with the startup company, the transition made sense, since continuing to work on cardiomyopathies could lead the

lab into professionally problematic territory. During other meetings, Nielsen also described how Almanor would offer a separate intellectual space where the research on heart diseases could continue. Nielsen and his colleagues conceived Almanor as a collaborative opportunity to share intellectual and material resources in a way that aligned their academic research goals and their commercial aspirations. By building out the products of their research into a company, they hoped their work would be more readily translated into clinical applications.

However, "collaborations" like this one required extensive legal coordination between organizations to establish terms for assigning intellectual property and allocating any potential profit. Much of this coordination centers on the establishment of a Sponsored Research Agreement (SRA) that delineated boundaries between projects, establishes restrictions on data dissemination and details ownership of the products of research. Substantively, the Nielsen lab was allotted $1.2 million a year (for 4 years) from the venture funding of Almanor for well-defined projects. Delineating exactly what the deliverables for this project were, i.e., what the lab could spend these funds on, was the meat of the SRA. Early ambiguity in the terms and aims of the company raised tension between the PIs who had founded the company and the members of their labs. For some of the individual graduate students and research assistants who had been working on the projects that would be carried on at Alamanor, the "transition" felt more like capture.

These feelings became exacerbated over the course of a few months where the first few employees of the company leased out space in the Nielsen Lab to do early research. The first employees from Almanor worked alongside the Nielsen Lab in a leased section of the lab, called a bay, and would be using their instruments for a period of time. To the chagrin of some of the lab personnel, Nielsen delivered some frustrating news in an email,

> "On Wed we will have a lab re-organization to make some more room for Almanor. Although, they have not asked for this space, Almanor is expanding so fast that it is getting too crowded in the shared bay. Since we have room elsewhere in the lab, I am very grateful that we can move, so that Nancy and Nick can work in space that is not shared with the ever-growing Almanor. I think it will be much better for them to have the bench providing a clear boundary. In addition, the Almanor scientists appreciate the space. I apologize for any inconvenience, but none of us anticipated Almanor growing so quickly."

The initial hope, that the lab and Almanor would share the space and exchange know-how in a collegial fashion was quickly replaced by a sense of encroachment and the need to set clear working boundaries.

In one meeting, lab members met with the founding PIs and a representative from Almanor and voiced some concerns. Throughout their exchange, the scientists articulate the some of the tensions that make up the moral economy of not just CRISPR research but academic and industry partnerships more generally,

> **Graduate Student:** I guess, you mentioned the relationship with Gladstone and Almanor being very transparent. I was wondering what the implications are when it comes to who gets credit for the intellectual property over discovery, […] I was wondering what for example, UCSF's role would be there, because some of us are 100% covered by the SRA, which makes it such that whatever they do goes to the company. But some of us are, because of our role here, we are 100% UCSF. So, anything that we discover or have credit, is something that we won't claim as intellectual property, but UCSF will definitely try to license that or whatever. And

that seems to be a big problem, *which is why people but barriers between industry and academia is to prevent these sorts of situations.* So as much it feels good [to have a collaborative environment], I am worried that will be a thing.

PI1: It's less of a worry for the individuals, it's more of a worry for the institutions. It's a grey area, so for any students or physician scientists who maybe from UCSF but training here, it's a grey area that actually hasn't been developed by either institution. […]

Lab Manager 2: I still get the impression that the sharing of equipment and the sharing of space makes everything substantially more complicated. So presumably once there is a separation–

PI1: -(interrupting) Yeah that's a good point. In their lease agreement, they are paying for the space and we also have a surcharge, knowing that when they are here they are going to be using the equipment here so there is an upcharge for that. And they can use our [facility services], so we charge them an outside rate. So its double what we pay. So you absolutely right though, a non-for profit institution should not be doing anything that would unfairly benefit one commercial entity versus another. That's definitely an issue.

The PI's deferral to the institutional offices of the two organizations is ultimately meant to remove responsibility from the individual scientists, effectively attempting organizationally silo ethical concerns. Still, the PI's idea of having a collaborative environment came into conflict with graduate student's ethics trainings, as one of the lab managers pointed out, "the case scenarios [in the NIH ethics course] are exactly like this one." As I return to in Ch. 4, ethics trainings sometimes fail to account for the conflicts of obligation that scientists might find themselves in. The competitive environment of commercialization and patenting in genome editing further fueled lab members' paranoia over the legal terms of the SRA. One of the ways senior researchers attempted to quell the concerns of lab members was by reifying a division between the goals of a for-profit biotechnology company and the goals academic laboratory.

The division one PI drew aimed to establish a division of labor between the laboratory with the company. With this division, he carved an epistemic and organizational boundary between the two entities. As this PI explained to group,

PI2: I think from a goal standpoint there is a clear separation. That is another issue, *I think we don't necessarily want there to be overlap on goals.* And so, it's easy to monitor right now and I think by the time that, over time that will evolve but *I think their focus is to develop a drug*, they are going to be solely focused on [that]. They have to get it as quickly as they can, not just figure out gene networks. They've got a time limit. Within three years they need to reach some inflection point, were they have to go to people and say, "this is something that could got to the next stage and we therefore need to get more money, or a higher valuation to bring this to a therapeutic," *not to knowledge*. So, to the extent that they are trying to develop knowledge, to get to a future pipeline, that will be valuable. They will be, form our sponsored research agreement, relying on us to provide knowledge that will feed into that product development. That's where the symmetry lies.

The specifics of how genome editing technologies were used makes concrete how this abstract alignment played out. In one lab meeting, one of the postdocs from the Nielsen Lab who was hired on as one of the first employees at Almanor, Naval, presented on how his expertise using genome editing techniques would fold into the goals for Almanor, "I'll be employing CRISPR interferase and high throughput chemical screens to identify gene networks that are dysregulated in a diseased state. And to be able to validate assays and then validate druggable targets." This application of genome editing, CRISPR interferase or CRISPRi, was not targeted to itself be a therapeutic, but rather a tool for discovery and learning more about the molecular mechanism of disease. A portion of the funding the Nielsen lab was receiving was to produce heart cells that could be used in Naval's CRISPRi experiments.

For the Nielsen Lab and Almanor to partner in this way, their interests needed to be aligned both legally and epistemologically. As Nielsen described how this work should be organized to the lab after Naval's presentation, "there's sort of general organization around this but the organization at this point actually has to do with the IP (intellectual property) people [lawyers] wanting to make sure that the scope of each of these things was narrow enough that we could actually deliver it without causing any trouble." Trouble could arise when the deliverables of the lab, engineered heart cells, are produced by an organizationally diffuse team or contain multiple proprietary parts. This was likely, however, since the Nielsen Lab hadn't invented the CRISPRi technique, but collaborated closely with the labs that did. Nielsen elaborated, "So for instance, here, the deliverable is a method to make CRISPRi in iPS cells, in iPS cardiomyocytes. So if there's a problem with transferring cells from, like there's some technology that is from the Weissman lab or from Stanley [Qi] or some other sorts of things where you can't physically [transfer them to Almanor]... The cells are made and we can publish on them, but for some reason we can't transfer the cells because the cells contain other proprietary things or something like that. That has to be worked out at one point. *The only thing that is important on this front is really the knowledge*." Here, Nielsen explains how norms governing the transfer of technology between organizations can easily become entangled with the research aspirations of for-profit partnerships. Because the materials of science are routinely the products of multiple organizational actors, Nielsen recommended relying on the transmission of protocols and know-how (i.e. "knowledge") as a way to circumvent the challenges of physically transferring materials.

This strategic separation of "knowledge" from the materials of science helped justify the alignment between the academic laboratory and the biotechnology start up by providing an epistemic approach that accommodated the legal requirements of the partnership. Because CRISPR-Cas9 was seen as a revolutionary technology, the experience using genome-editing technology and the tacit knowledge required to carry out new experimental protocols was highly coveted by researchers in industry who hoped to test the potential of the technology. This shaped specific facets of the agreement. The deliverable to the company from the Nielsen Lab was a method, not the specific products of research; and Naval was the right hire for the startup precisely because his experience with CRISPRi allowed him to produce the data that the company would need during its first phases of research.

Taken together, the development of the IGI, an interstitial organization, and the creation of Alamanor, begin to exemplify how the alignment of academic and industry organizations in the field of genome editing is coupled with the articulation of an epistemic and moral order. This order is experienced differently by different scientists, resulting in a moral economy that is stratified by one's position in the laboratory. The tensions that arose from this, however, were overridden by a) the organization's ideological commitment to the use of genome editing for clinical development as an

inherent moral and scientific good, and b) the authority of senior scientists. The exchanges I observed between lab members illustrated how the benefits of collaborative relationships with emerging start-ups can come into conflict with the values and goals of younger, less-established scientists and how the moral economy of genome editing intersected with the interests of both senior scientists and their universities who stood to gain a great deal from licensing technologies developed in their laboratories. Partnering with industry was, in fact, good science because it funded the production of the experimental techniques and protocols needed to use CRISPR technology in the lab and then translate these into what scientists saw as socially impactful products (drugs and therapeutics). As one of the senior scientists put it, "a Nature paper is not the ticket to the real world."

3.4. Affective and Moral Ordering

In addition to shaping the structural arrangements between the actors surrounding CRISPR technology, the ubiquity of academic-industry partnerships shapes scientists' views about what CRISPR technology is and the moral imperatives that drive what it will be. Because CRISPR has such a wide array of applications, the scope of the technology was a matter of active contestation. As I explore in greater depth in Ch. 4, broader public debates about genome editing have already attempted to articulate two moral lines that are problematic to cross: the use of CRISPR for germline modification and its use for enhancement. This leaves a wide ocean of clinical applications for genome editing under the general umbrella of somatic editing. As other analyses have pointed out, because our delimitations of the normal and pathological are socially constructed and shift over time such lines can become quickly blurred (Benjamin 2016a). Academic scientists at the center of the development of CRISPR-Cas9 and the technologies derived from it saw market forces as necessarily shaping what the scope of CRISPR-Cas9 technology would be. These forces were experienced and internalized by scientists as anxieties and fears that are constitutive of the moral economy of genome editing science.

Fear and "Real-world" Genome Editing

In one late-afternoon meeting of the "CRISPR Developers" workshop, a group of graduate students, postdocs, two PIs and I spread out in a small classroom, huddling over lukewarm coffee and oversized cookies at our desks. One scientist in IGI leadership with extensive experience in industry expressed,

> "I will admit my sort of deep anxiety for CRISPR is sort of the story... and don't laugh, I'm dead serious... is sort of the story of the Segway. If you've ever ridden a Segway, it's amazing. I mean, it takes five seconds to learn, it's super-fast, it's super safe, it's amazing! It's just… nobody uses it. I mean, police do use it and tourists in San Francisco. So once upon a time, there was a world where people thought that everybody would be riding Segways everywhere, and it has become a niche thing. *So my raison d'etre is to try to make sure that pretty much CRISPR everything*, at least that is impactful to the real world, is not niche, and is in fact quite widespread."

For him and other scientists, the fear of obsolescence was one that they learned of through the fate of other commercialized technologies. In one weekly lab meeting, a postdoctoral student expressed a similar worry. Remarking on the organization of projects in the lab, he argued that their relevance hinged on CRISPR-Cas9 being the most cutting-edge technology. His fear was that someone would

invent the iPhone for CRISPR, "Steve Jobs, he killed the iPod with the iPhone. Killed it. What if we are the iPod?" This affective expression, fear, was multifaceted in that it reflected insecurity about the continuity of relevance, funding, and individual scientists' careers. It was also a fear that evinced an inflection in the meaning of science identified by Max Weber that, at its heart, science "*cries out* to be surpassed and rendered obsolete," (Weber 1919:11). Under the conditions set by academic capitalism, instead, scientists working in the fast-paced field of genome editing expressed a near constant preoccupation with new techniques outpacing the technologies they were committed to or their competitors in other laboratories laying claim, via publication or patent, over more efficient, or powerful genome editing tools.

A different kind of fear shaped how scientists understand commercialization as a means through which to bring about societal benefit with CRISPR technology. In the same workshop above, the IGI scientist explained, "The tiles of IGI interest whether by medicine, plant, microbe, tools, and society all wrap around CRISPR-Cas. The mission, in sort of an emic form is to discover then develop and then deliver CRISPR-Cas solutions that improve the human predicament." For medicine, this meant their goal was to, "make sure that the CRISPR footprint in biomedicine is as broad as possible." A graduate student frustratingly seeking something more specific probed into the imperative, "but what does that mean?" "Well, so that means we are going to perform both structured and unbiased discovery. If we see something interesting, we will try to convert that into a proof of concept. Then, critically, and this is the last step that I think might surprise some of you... […] we're hopeful to go from that proof of concept to something that's actually *real-world robust*," [italics added].

This scientist's account of "real-world robustness" boiled down to whether and how CRISPR technology developed in academia would be taken up by industry. In walking us through this, he illustrated for the small audience of grad students, postdocs, and PIs how the scope conditions for genome editing technologies were shaped by the biotech and pharmaceutical industry. He explained how in order to fulfill its mission of ensuring biomedical applications of CRISPR were as broad as possible, the IGI needed to navigate the research and product pipelines of for-profit entities in a shared competitive field. He then surveyed the firms in the genome editing industry, "at least on the publicly-held front, these five are putting editing into the clinic and are public. […] There's a large number of companies that are starting now to use CRISPR for various biomedical applications. Sort of the practical reality is that if you look at the pipeline of these, […], certainly what's in the pipeline for these for the next five years is, round numbers, maybe 10 diseases. 10. One, zero. That's not very many."

The main obstacle to the broad adoption of CRISPR in the real world, this researcher went on to argue was fear,

> I'm going to walk you through what the obstacle is and what we're doing to try to address it. So the first obstacle, why is there not more [diseases], is this: It's fear. […] a key factor in the sloth of adoption of editing, in particular in pharma pipelines, is frankly fear. Pharma is afraid. This is not a small molecule. This is not a biologic. This is strange. And I speak to big pharma a lot, and let me assure you, it is really hard to convince somebody from a company with a hundred-billion-dollar market capitalization that they should be investing in this sort of stuff.

While the novelty of genome editing was experienced by scientists as a point of excitement, to the pharmaceutical industry this risk of adoption was greater. This was, in part, because the material components of CRISPR-Cas9 technology (an enzyme that cuts DNA, called a nuclease, and

a set of genetic instructions for where to cut, called a guide RNA) didn't have clear pre-existing regulatory standards of efficacy and safety. The there was a deeper anxiety shared between academic scientists and industry: the risk of an "adverse event".

Senior scientists in the field inherited the anxiety of an "adverse event" from their observation or, in some cases, participation in the technological predecessor to genome editing, gene therapy. On multiple occasions, both in bioethics workshops and in technical scientific talks, the trajectory of development of gene therapy was a touchstone. As one scientist put it during a lab meeting, "My worry is that you will kill people in trials, […] the same thing that happened for gene therapy," (Field Notes, October 2015). As briefly reviewed above, gene therapy is a different molecular approach to treating human genetic diseases where DNA is inserted into patient's cells using a virus. In both this lab meeting and the workshop above, the senior scientists recounted the case of Jesse Gelsinger, a teen-age patient who died in 1999 in a clinical trial for gene therapy, one of them explained, "[his] disease was treated by gene therapy, conventional gene therapy, not editing, and there was a severe adverse event due to insertion mutagenesis. And the field of gene therapy felt as if somebody poured liquid nitrogen over it. The FDA just shut the thing down." Senior scientists shared this history with younger scientists, explaining how for several years this resulted in a public loss of confidence in the approach, funding losses and extensive regulation of any gene therapy products. What was often overlooked in scientists' recounting of the Gelsinger case was that a financial conflict of interest on the part of academic scientists was found to have influenced academic scientists' assessment of the clinical risks of the trial (Yarborough and Sharp 2009). These histories informed how senior scientists managed the uncertainty over how the tools of the lab bench would be translated into the clinic.

While the field of gene therapy had begun to recover by the time CRISPR had begun clinical development, the threat of regulatory freeze pervaded. For the scientists observing the development of early clinical trials for genome editing, "the biggest victory in all of this is not the fact that we are sort of in the clinic, but the fact that nobody has died." The IGI scientist continued, "we therefore, right now, are living in this sort of halo where things are still okay while perpetually being afraid that something bad might happen. This is just the name of the game for clinical development. It's just how things work."

Scientists in universities made their own market predictions to assess the direction of research and construct a pathway of development for CRISPR technology. In discussing which of the 4,000 genetic diseases they should study outside of the 10 that industry had decided to focus on, one university scientist argued, "the question is which ones... what's the cost to develop and which ones have a positive return on investment because anyone... if you think this is cookie-cutter, any disease that has a positive return on investment should just be more capital and then it should be a solvable problem." I further probed into this logic during the Q&A of the workshop and asked the group of researchers why the IGI should broaden the biomedical footprint of CRISPR to, "CRISPR everything." To the scientists at the meeting, my question was naïve,

> **Senior Scientist:** Well, I think my response to that would be that once something's proven in principle, it's profitable by a very generous definition. There is capital and things can scale quickly, and that's the difference between the world 200, 300 years ago and now. When something's proven in principle, the ability to replicate it, scale it, deploy it is pretty simple.
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> **Senior Scientist 2:** The biggest advance or kind of most radical thing that has happened in biomedicine is in vitro fertilization, […], but before it was actually done

> a lot of people just thought it was basically criminal, and there was no research funds for it [sic.]. But as soon as kids started getting born, then it just changed the way people look at it. So, you have to realize that I think the advance of somebody who really has a serious disease and is better (from treatment with CRISPR), and then having more and more of those, that that kind of success is, I think, very powerful.
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> **Senior Scientist 3:** I cannot agree with you more strongly. […] I am convinced that the next half century will see editing therapies for common disease. These will be cardiovascular, neurological, gastrointestinal, musculo-skeletal, so the broad categories of killers. I think that the technology will have to be de-risked largely through the monogenic space and cancer first.

For genome-editing scientists working under the moral economy of academic capitalism, the Latourian mantra, "once the machine works, people will be convinced," takes on a distinctly market-based quality. Taken together, the responses this group of scientists reflect an expectation of inevitability in the progression of both technology and the market. Scientists' arguments of what kinds of diseases should be treated with genome editing were typically warranted by the belief that, "if I don't do it, someone else will." As I explore in Ch. 4, this warrant also surfaces when scientists respond to highly publicized controversies surrounding genome editing (Hurlbut 2019). Moreover, the optimism with which these scientists responded to my question also serves to counterbalance their fear of a severe adverse event, resulting in a speculative epistemology supported by a belief that once one successful case of therapeutic recovery occurs or a clinical trial is completed and consecrated by the FDA, other biomedical applications will quickly follow.

Re-framing Genome Editing Discourse: The Genome Surgery Center

To bring about its goals, the IGI attempted to develop a framework of meaning and an organizational model to support the expansion of clinical genome editing. To address the costs of clinical development some scientists in the IGI proposed the idea of a Genome Surgery Center that would partner with pharmaceutical companies for chemical manufacturing. The discursive framing of clinical genome editing as "surgery" aimed to make the practice of genome editing more legible to physicians and patients. It also brought connotations that were distinct from CRISPR as a drug, for example, it could instead be thought of as an urgently needed intervention or a one-time procedure to correct a "mistake" in a patient's DNA. This section draws from observations at a series of meetings held to develop a plan for the Genome Surgery Center to unpack the affective commitments of scientists engaged clinical genome editing. In this imagined center, scientists hoped to enroll patients to clinically test genome-editing therapies outside of the traditional pharmaceutical-clinical context with the idea that medical universities would stand to gain from greater autonomy when engaging in partnerships with industry. Scientists developed the concept of gene surgery on the one hand as a discursive strategy to construct CRISPR as a medical device instead of a drug, and on the other to competitively position their applications of CRISPR against the clinical uses being pursued by larger for-profit CRISPR companies.

During a regular bioethics workshop, one of the senior scientists who advocated for the metaphor explained that the IGI needed an organizational model to address the narrow and risk-averse focus of the genome editing industry. He explained with sarcasm, "so you have four large companies looking at editing a 30-base region in the genome that will increase fetal hemoglobin [for the treatment of sickle cell and thalassemia] and probably have a therapeutic value. But this is the genie in the bottle. […] 30 bases out of three billion bases (in the human genome). So, let's just say

that there's a little bit of opportunity." In other words, the human genome is so large that potentially any genetic variation that has consequences that are described as either pathogenic or is associated with an increased risk of pathology is a possible target for surgical intervention. The metaphor of surgery was first proposed to describe the process of directed DNA mutagenesis, but as this scientist explained,

> "It is also a different regulation, different funding models, and so on. And so, when you think actually historically about physicians and surgeons, medicine and surgery essentially, you actually realize that it's actually quite different. […] They came from very, very different schools and very different approaches towards treatment, and they have very different traditions. Even today though, they're very different in the sense that physicians and medicine think about making drugs, […], where surgery is actually where you make new devices essentially on rare diseases."

This difference he explained, also contrasted in terms of the economic differences between surgery and medicine. "Surgeons when they did the first heart transplant, the first thing on their mind was not how to monetize the heart transplant, right? That was just not even on the table. […] The issue was how to do the next one, and how to do the next one, and each one was different in an iterative way. And so, we felt that this actually was a better sort of metaphor for how we go forward in terms of thinking about this process, because actually in genetic disease every single person is quite different and really need to have custom tools, custom scalpels." The model of surgery, he additionally argued, was better fit for efforts to treat rare genetic diseases, commonly described as "orphan diseases" which the pharmaceutical industry had historically neglected developing treatment for because they represent a small market. Under the model of genome surgery, the IGI could perform experimental gene surgeries under a framework of "compassionate use" and not charge patients.

From the outset, however, the discourse around clinical applications advanced by IGI scientists produced a set of affective expectations especially among those who would stand to benefit the most from genome editing therapies: patients with genetic diseases. The interaction between researchers and this interested public illustrates the downstream effects of the moralized goals of genome editing development. Since the burgeoning of CRISPR-Cas9 in the media, the biochemists and molecular biologists in the genome editing sphere have received thousands of emails and phone calls from patients, their advocates and interested members of the public. In these communications, patients described the popular sources through which they had heard of CRISPR-Cas9 and its therapeutic potential and sought treatment from academic bench scientists. In one email, for example, a patient described, "I have a haplotype form of Cystic Fibrosis. My genetic variation is c.1477C>T. You might be able to manipulate this gene in the lab. It might be an easy breakthrough research project for yourself or one of your assistant researchers?" These hopeful messages reflected the public facing discourse around how easy it would be to do genome editing, which was often simplified and hyped by reporters and documentary film makers who bridged scientists' work with broader audiences.

Unlike physicians, biochemists and molecular biologists do not receive training in clinical ethics, patient care or genetic counseling, resulting in a capacity gap when the work of the lab bench is quickly translated into the work of clinical bedside. Unsure of how to address the concerns of patients on a case-by-case basis in a way they felt was sincere and truthful to the way CRISPR-Cas9 is used in practice, IGI researchers sought out the guidance of bioethicists. In consultation with an ethicist and a biotechnology law professor, the IGI developed an organizational response by creating an online portal on the IGI website for triaging and addressing public inquiries. This work was then

taken up by graduate students who had then transitioned into science communication and outreach for the IGI. In most cases, the solution was to direct individuals to patient advocacy groups, rare genetic disease foundations, more clinically relevant research organizations and professional medical associations. The portal was additionally flooded by inquiries from high school students working on projects about the ethics and science of genome editing. At stake in these interactions was the production of affective expectations around a yet undefined and promissory technology.

Within the IGI, the medical needs voiced by patients were a strong motivator for the continuation and acceleration of their work. For the scientists I observed, this moral imperative was closely aligned with the imperatives of academic capitalism. For example, for one IGI scientist who had experience in industry, their motivation for delivering on the promise of genome surgery and their sense of how to do it tied both patients' experience of the severity of rare genetic diseases and the for-profit landscape. To kick off his lecture at a genome surgery workshop he began,

> "All right, so I know there are many clinicians in the room. I am not one, but I want to show you again as a *profession de foi*, something that has driven me passionately. Many people who speak about editing for disease or therapy of disease, start with patients. I always think this is a little bit manipulative, because why are you doing this?
>
> We all know the disease is bad. I don't know how many of you have seen a Rett's child, I want to show you a movie of a Rett child having a seizure to really highlight and to remind us all that when we think about, for example, safety, or when we think about urgency, we really have to frame those two issues in the context of what the patients are going through."

The scientists' hesitation with "being manipulative" suggests evidence of a recognition that biomedical researchers use patient suffering as an affective device to value their work for different audiences. Despite the recognition, he continued,

> "Rett is particularly pernicious for two separate reasons, it effects one in 10,000 girls, so it's as prevalent as hemophilia A, most mutations in male fetuses lead to premature termination of pregnancy's spontaneously. The rare males who are born with MECP2 mutations really don't survive much. Girls born with MECP2 mutations on the X chromosome develop completely normally until age two, they're in fact happy children and then they slow down […] really horrific symptoms. So, I don't want to spend too much time on this, the next slide shows Alexa having a seizure. This was sent to me by her mom. Alexa gets these about 10 or 15 times a day, you will also hear her hold her breath. Again, this is super hard watching, I don't want to be manipulative, I want to be deeply respectful of the child and her mom, but I really want us to remind ourselves what we're doing."

The small audience of high-profile scientists, senior gene therapy researchers, clinicians, a fundraising expert, and I quietly watch the short clip taken with a phone camera. There is a short pause, and then the scientist continues,

> "So, where are we? The mutation was discovered when I was a post-doc at NIH, so this was 20 years ago and for the subsequent 18 there was absolutely nothing. To the best of my knowledge no pharma is working on a small molecule modulator of this. There was no gene therapy effort and there was no gene editing effort. Despite

the fact that we know the mutation and we know the fact that the mutation is restorative."[29]

Very recently, in the past year, AveXis, which as you know was bought by Novartis for eight point something billion dollars. Who have very promising late stage data for SMA (spinal muscular atrophy) using AAV9 (a viral vector), have disclosed that they may advance an AAV9 based treatment for that. The good news is they dosed non-human primates and there are no adverse findings. Hypothetically suggesting that there will not be an adverse effect from excess dosage, but nobody knows.

The deep tragedy here, is that, I can tell you having just worked in one, is that no editing biotech will take Rett on as a project until the AveXis phase one completes. First of all, this will be Novartis, so this will be slower. Second, so best scenario (is) three years.[…] And AAV9 is tied up IP-wise for that modality."

The urgency of genome surgery, from the perspective of this scientist, was that despite a complete understanding of the molecular basis for Rett syndrome, there have been few therapeutic options for patients. Moreover, the competitive nature of industry was further delaying clinical development. For him, the affective basis for genome surgery weds a moral imperative to alleviate suffering with the neglect of the disease by industry. Instead, he recommended a hybrid model, the Genome Surgery Center, which would draw from the innovative potential of universities in the Bay Area to develop partnerships with chemical and pharmaceutical manufacturing firms under a non-profit model.

3.5 Genome Editing as a Mode of Production

The cases analyzed in this chapter highlight the affective tensions that undergird the organizational alignment of university laboratories and biotechnology startups. When new interstitial organizations like the IGI are founded, alignment with broader moral goals helps draw in philanthropic donors and helped legitimize genome-editing technology. By leaning into the hype around CRISPR-Cas9, scientists set in place a set of affective expectations about what the epistemic, moral, and clinical value of genome editing was. Patients and their communities who learned about the ease with which CRISPR-Cas9 was being used in the lab perceived the clinical translation of the lab tools to be imminent, reaching out to academic scientists for individual treatment. In reality, clinical translation, as understood by senior scientists had to happen in partnership with industry firms from biotech and big pharma. The "real world robustness" of CRISPR-Cas9 hinged on whether or not it could be commercialized. In the case of Almanor, scientists aimed to take the practices and techniques developed in the lab and use them as foundational R&D in a venture capital-backed start up. This decision, however, created tensions between the values that new scientists were receiving through their academic training and the norms of industry partnerships. Senior researchers alleviated these tensions by siloing moral concerns about conflict of interest to local organizational legal bodies tasked with managing the intellectual property agreements and

[29] A mutation can be characterized as "restorative" when, if the genetic mutation is "corrected" in the relevant tissue to a non-pathological form, a recovery of the phenotype can be measured and observed. For some mutations, after a certain point in a patient's development there is no recovery even if the mutation is "corrected."

appealing to an ideological division of interests between academia and industry; where academia is focused on developing "knowledge" and industry is focused on developing "products".

This chapter has additionally illustrated how scientists' understanding of and speculations about the biotechnology and pharmaceutical market can shape how different areas of research are valued. This, in turn, shaped scientists' decisions about what diseases would be valuable targets for the development of genome editing therapeutics. Moreover, in the case of the Genome Surgery Center, scientists assessed the competitive dynamics between industry firms and their fears of potential market failures in developing the organizational model for developing CRISPR-Cas9 into a biomedical platform with broad scope. These ambitions, however, were closely followed by a set of anxieties and fears about the decline of CRISPR-Cas9 as a technology, whether brought about by a regulatory freeze in response to a severe adverse event in a clinical trial or because it may be superseded by an, as of yet, undeveloped technology.

These tensions, between promise and fear, and between multiple forms of value, constitute a moral economy that pushes scientists to extend the reach of their inquiries by any means necessary. The continued relevance of genome editing rests on the production of such an order, where the interplay between, "once the machine works, people will be convinced" and "once all the relevant people are convinced, the machine will work" a fervent driver of scientific work. When paired analytically with an overall moral imperative that technological innovations are good, which is deeply internalized by scientists both in leadership and at the lab bench, this moral economy is a clear case of how scientists can become "caught up in the chain of progress" (Weber 1922). Taken one step further out, the conditions of academic capitalism continue to enable the constant revolutionizing of the instruments of production (Marx and Engels [1848] 1998, p. 54). In this case, when conceived as a novel mode of production with broad institutional scope, genome editing empowers biomedical scientists to re-draw the boundaries of the normal and the pathological wholly in genetic terms.

Ch. 4. Governance, Crisis, and the Normalization of Genome Editing[30]

> "There's nothing like actually moving ahead [with research] to teach us what the actual pitfalls are." – David Baltimore (Hesman 2019, *Science News*)

New technologies do not come with a pre-established set of rules for what they are supposed to be used for. This is especially the case for technologies with a wide scope of potential application, such as the CRISPR-Cas9 system, which is no exception to Abraham Maslow and Abraham Kaplan's law of instrument: that once you have a hammer everything starts to look like a nail.

Having explained how the moral economies of genome editing develop through partnerships between academic laboratories and industry, this chapter explains the role of scientific associations in decision-making, agenda setting and the development of normative frameworks. Here, I approach governance from a neo-institutionalist perspective, where "governance models are articulated systems of meaning that embody the moral order as they explain and justify the proper allocation of power and resources," (Fiss 2008, p. 29) and these systems of meaning are reproduced through myths and routines (Meyer and Rowan 1977). Looking at governance in this way allows me to unpack how discourse shapes the emergence of the moral economy of genome editing.

Despite the sci-fi futurism built into the hype of modifying human DNA, the institutionalization of genome editing is guided by practices of decision-making that can be traced to the 1970s. Through the development of genetic engineering and the genesis of the biotech industry, scientists embedded practices of self-regulation in the governance of new technologies. In some cases, senior scientists have maintained central roles in decision-making processes for almost fifty years, despite the growth in popularity of public engagement models of decision-making and the increased inclusion of bioethicists and STS scholars in science governance. An observation that I interpret here as an example of the tendency of experts form oligarchies through their permanence in bureaucratic governance structures (Michels 1915; Selznick 1953; Weber 1922).

Researchers' tendency to adhere to models of self-governance in genetic engineering can be understood as a function of the autonomy of science. The observation that at different points in time scientific disciplines have enjoyed varying levels of independence, has been a staple finding in sociological research on the autonomy of science. In the mid-Twentieth Century, Robert Merton argued that science had acquired institutional autonomy to set the direction of research, to legitimate itself and to evaluate the knowledge it produced (Calhoun 2010; Gieryn 1988; Robert K. Merton 1957; Merton 1974). The premise of these observations was that science, as a social institution, tries to set itself apart from other spheres of society and enjoys relative independence (Bourdieu 1975, 2004). In the United States, this was evinced by the policies deriving from Vannevar Bush's "endless frontier," which essentially established a relationship between science and the state where scientists

[30] Early versions of sections of this chapter were written in collaboration with Gordon Pherribo and originally appeared as a blog series through the Center for Science, Technology and Policy at UC Berkeley and Free Radicals, a non-profit science education group.

could work freely and decide for themselves what knowledge would benefit society (Bush 1945; Mukerji 1990; Zachary 2018).

Still, the metaphor of the Ivory Tower has been largely shown to be not only anachronistic, but overall misleading (Latour 1987; Shapin and Schaffer 1985; Sismondo 2011). Instead, work in STS has shown that science is thoroughly tied state and international politics and heavily contingent on the economic structures which support it. Subsequent work has further complicated the view of "science" as a monolith and has drawn attention to the contentious and sometimes messy ways in which different scientific groups vie for autonomy and power. Scientists are particularly effective at doing this by maintaining and policing the boundaries of their disciplines (Abbott 1988, 2001; Eyal 2019; Gieryn 1983). In this sense, the degree to which a scientific discipline can self-govern depends on the strength of those boundaries in the face of encroachment by political, economic, and cultural interests related to the pursuit of knowledge.

For the case of genome editing, I show how self-regulation has allowed the field to be organized by guidelines and standards of practice with high interpretive flexibility. These guidelines help entrench a distinction between somatic and germline (heritable) genome editing; making the former seem good and desirable, and the latter seem controversial. This distinction has profoundly structured the discourse of genome editing; for example, while the vast majority of biomedical genome editing research is focused on the development of somatic therapeutics and using CRISPR technology to better characterize the molecular basis of disease, the broader public and bioethical discourse surrounding CRISPR is focused on germline therapy. This has helped normalize clinical applications of modifying human DNA. This chapter then describes a controversial case in the field of genome editing to understand how positive deviance and crises of legitimacy can contribute to the institutionalization of a technology through mechanisms of boundary repair.

4.1. The Myth of Asilomar: The Origins of Self-Regulation

History reveals dynamic fluctuations in public excitement and hostility towards new scientific findings and technologies. The ebb and flow of how the public views the value, meaning and usefulness of science is useful for understanding why and how organizations responded in the way they did. In the US., scientists are largely entrusted with the ability to self-regulate when using new biotechnologies. This model of governance developed through one of genome editing's early predecessors which launched genetic engineering as both an academic field and industry in the 1970s: Recombinant DNA.

Recombinant DNA (rDNA) is a term used to describe a hybrid DNA molecule constructed in a laboratory environment that contains genetic elements from more than one source. The original experiments that developed rDNA modified the DNA of a simian virus to introduce foreign DNA into mammalian cells. This new technology was exciting to many scientists because DNA molecules previously unseen in nature could be produced in a lab environment. Following the release of the results from the first rDNA experiments in 1972, biochemist Paul Berg, one of the lead inventors of rDNA received daily telephone calls from scientists requesting the variety of plasmids he had developed to be used for recombinant engineering. A pattern that mirrors the requests that Addgene would come to manage today, after new CRISPR paper are published. Paul Berg's description of these phone conversations captures the idea that the uses of promising new technologies are not always in agreement with the broader moral frameworks of the scientific community: "'What do you want to do?' we'd ask. And we'd get a description of some kind of horror experiment and you'd ask

the person whether in fact he'd thought about it and you found that he really hadn't thought about it at all," (Rogers 1975).

In recognition of growing concerns by scientists working at the lab bench that these altered viral strains could be pathogenic and could possibly cause cancer, Berg convened a small committee of 10 scientists. This committee drafted a letter proposing a moratorium on experiments using rDNA and distributed it through the National Academies of Sciences (NAS) in 1974. In addition to the fear of misuse, there was fear that labs were not taking the proper precautions given the lack of experience using rDNA. Additionally, the current lab practices raised concerns about the health of laboratory researchers conducting rDNA experiments, which was not an unreasonable fear given that mouth pipetting was still in fashion. This voluntary moratorium on rDNA experiments by molecular biology researchers was lauded by their peers as evidence of the scientific community's ability to self-regulate. The halting of scientific progress and innovation in order to consider their social responsibility for the potential hazards of rDNA experiments had not been done before.

The moratorium must have sat uneasily with the scientists eager to finally tinker with DNA, however. At the behest of Berg's committee, the NAS organized a larger conference in 1975 to discuss lifting the moratorium and develop guidelines for moving forward with rDNA experimentation. This 4-day conference was held at the Asilomar Conference Center on the windy coast of Central California. The conference hall was dominated by molecular biologists and virologists. During the 1975 Asilomar conference, 140 scientists debated the ethics of genetic manipulation. The topics guiding the discussion were predetermined by the conference organizers, who were well-decorated academic researchers including many of those in Berg's circle. The organizers limited the focus to the physical and biological risks of rDNA and effectively discounted any discussion about the role of science in society. The scene is best captured by one of 16 reporters who managed to get into the conference, Michael Rogers from Rolling Stone: "Sandwiched between pool and ping-pong tables, researchers meet for the first time in months, and even in the middle of an overwaxed linoleum floor, their discussions suggest both the vitality of small boys with new chemistry sets and the electricity of back yard gossip. The excitement is unmistakable. Clearly these people think they are *onto* something," (Rogers 1975).

Arguments that opposed lifting the moratorium stressed a need for broader social issues to be considered and recognized that the scientific community alone could not regulate the development of rDNA technology. For example, Science for the People (SftP), a left-leaning association of scientists, wrote to the organizers of the 1975 Asilomar meeting with a series of concerns they felt needed to be addressed. They argued that having scientists be solely responsible for regulating new biotechnology, "is like asking the tobacco industry to limit the manufacture of cigarettes." The letter goes on,

> There are even broader social issues that must be considered. The growing preoccupation with technologies involving genetic manipulation, and parallel developments such as cell fusion and in vitro fertilization, all point to the application of these techniques for human genetic manipulation. Technology and scientific development, even when labelled biomedical, is not intrinsically socially beneficial. Specifically, technologies pointing to the modification of human genetic material must be examined with the greatest care to understand why they are being so eagerely [sic] developed, and for precisely whose benefit. (Science for the People 1975)

Despite this, scientists at Asilomar did not discuss the issues around human genetic modification arguing that such discussions would raise public alarm. Furthermore, biosafety discussions did not include populations that were more likely to be exposed to the health hazards of

engineered viruses, one of the most salient being an increased risk of cancer. The open letter from SftP urged that collective decision-making on lab safety include those most immediately at risk (technicians, students, custodial staff, etc.). Instead, senior, well-established scientists were in charge of setting the guidelines.

At Asilomar, the molecular biologists also debated the interference of legislation and the spread of misinformation by journalists. The general ethos of self-regulation was to protect the autonomy and legitimacy of science by creating norms and rules that the community could adhere to. This was not so easy, however; as one scientist at Asilomar put it, "Here we are, sitting in a chapel, next to the ocean, huddled around a forbidden tree, trying to create some new Commandments–and there's no goddam Moses in sight" (ibid.). Part of the public concern was that by tampering with DNA, scientists were "playing God" – and as another scientist told one of the reporters at Asilomar, "Nature does not need to be legislated. But playing God does." On the one hand, scientists favored some rulemaking. "Legislation," said one experimenter, "is inevitable. I can't believe that we'll be allowed to continue to control ourselves. But something that could set back the progress of science even more than legislation is if, in a few years, there's a sudden epidemic around Stanford, say, or Cold Spring Harbor." Others felt differently. Berg explained to the audience of scientists that "If our recommendation looks self-serving, we will run the risk of having standards imposed. We must start high and work down. We can't say that 150 scientists spent four days at Asilomar and all of them agreed that there was a hazard–and they still couldn't come up with a single suggestion. That's telling the government to do it for us." At this, James Watson, responded: "We can tell them they couldn't do it either!" (ibid.).

The scientists at the meeting also felt uneasy about the way these issues would be reported by the press and at first did not allow reporters to attend. A writer from Washington told the conference organizers, "A secret international meeting of molecular biologists to discuss biohazards? If the press isn't allowed, I'll guarantee you nightmare stories," (ibid.). For example, it was unclear whether the journalists in attendance should be allowed to record. As one reporter put it, after attendees voted, "the press was permitted their recording equipment. But it is not, by any means, yet permitted any real welcome," (ibid.). The complexity of the issue was well captured by Senator Ted Kennedy who commented, "It was commendable that scientists attempted to think through the social consequences of their work. It was commendable, but it was inadequate. It was inadequate because scientists alone decided to impose the moratorium and scientists alone decided to lift it. Yet the factors under consideration extend far beyond their technical competence. In fact, they were making public policy. And they were making it in private," (Culliton 1975). These traces of contention, between science and the state, and between science and the public, point to the ways in which science maintains its boundaries (Gieryn 1983) and the entrenchment of decision-making practices that center the autonomy of science.

While there was disagreement among the scientists in attendance, ultimately, the excitement over what experiments could be done with this new technology won over, and the moratorium was lifted with a conditional set of safety recommendations. The goal of these safety recommendations was to ensure that the products of rDNA experiments would remain in the lab. As South African biologist Sydney Brenner put it, "What I would like to do and what certainly seems incumbent to me, is to erect the highest barriers possible between my laboratory, where the work is performed, and the people outside" (ibid.). As the moratorium was lifted, new barriers were created and old ones were maintained: new biocontainment barriers were raised to keep genetically altered strains inside the lab, and social barriers to keep the publics, politicians and reporters from governing the trajectory of science were reinforced.

After the attendees developed provisional biological safety guidelines, scientists from academia continued to gather in small committees to further cultivate their vision of rDNA regulation. These meetings led to the creation of a new Recombinant DNA Advisory Committee (RAC) inside the National Institute of Health (NIH). When first created, the RAC was mostly made up of bacterial geneticists because most of the relevant research was being done in bacteria. Non-scientific members of "the public" were not included in the committee. Scientists at Asilomar felt comfortable having the NIH enforce the guidelines regarding rDNA research and house the RAC because NIH intramural labs had directed a large amount of monetary and infrastructural support towards molecular biology research in the 1960s. Involving the NIH would both strengthen the position of expert committees and grant them legitimacy in the face of public scrutiny.

The guidelines that scientists had finessed after Asilomar were taken on by the RAC as a set of interim rules for federally supported laboratories (Vigue and Stanziale, 1979). The intent of these guidelines was to reduce risks to lab personnel and provide guidance on how to conduct work using rDNA. In 1976, the NIH published revised guidelines in the Federal Register that classified different types of experiments and specific instructions for how to monitor lab work for those experiments. These practices of containment would become concretized and routinized in what is today known as biosafety.

However, six months after the guidelines were issued, it was clear they required revision. For example, the knowledge of infectious disease experts and environmentalists had been excluded from the guidelines. Additionally, issues around the role of industry in science emerged in the years that followed. Scientists at the NIH and in academia began to recognize that the accepted guidelines did not apply to research being conducted with private funds or in industry. The only way the RAC could enforce the NIH guidelines, after all, was by restricting or removing funding from laboratories conducting experiments that did not comply with the guidelines. In 1976, a Federal Interagency Commission was formed in order to review existing research in private and federally funded labs and determine whether wider legislation was necessary. The need for revision was voiced by Donald Frederickson, the director of the NIH and the RAC. Reflecting on the process, he wrote, "The more we embedded the Guidelines in inflexible administrative molds, the less chance there would be for timely accommodation of the tide of new information that was already rising." Frederickson also helped implement and advocate for public hearings to deliberate on the proposed guideline revisions and worked to increase public participation in the RAC by requiring non-scientific community members to be involved in RAC activities.

As applications for rDNA began to trickle into the public sphere, so too did awareness of the lack of transparency in the process of decision-making. At Frederickson's behest, the National Academy of Sciences convened a public forum in March 1977 in Washington, DC to discuss the merits and dangers of recombinant DNA research. Twisting the spirit of Frederickson's move toward establishing more formal inter-agency governance of recombinant DNA, other scientists used the inclusion of members of the public into the RAC as an argument to lobby against the conversion of guidelines into legislation because it signaled that scientists would work with the interests of the public in mind. In the decades that followed, scientists in the NAS lobbied to weaken the bureaucratic hold of the RAC (Anon 1978; Bodde 1981; Walton 1981). RAC members Allan Campbell and David Baltimore proposed to convert the NIH guidelines into a code of standard practice, rather than enforceable set of rules. Such a reduction in the institutional strength wasn't universally supported, as pointed out to the RAC by historian of science Susan Wright, "In the past year, there have been two serious violations of the guidelines, […] Dismantling the mechanisms that have been set up to enforce

the guidelines will be a signal to the small minority of scientists who pursue their research goals irresponsibly that high standards in research are no longer a matter of concern."

Fig. 8 Protestors and their banner in front of the panel of experts which included biochemist Maxine Singer, Paul Berg, and NIH Director Donald Fredrickson at the March 1977 National Academy of Sciences Forum on Recombinant DNA.

Memories of Expert Governance

The decision-making process surrounding Asilomar has been historically assigned a great deal of virtue in scientists' memory. Despite the public backlash, molecular biologists' efforts to prioritize public health and environmental safety over the opportunities for advancing scientific knowledge with rDNA were viewed as a noble sacrifice. When molecular biologists lifted the moratorium, it was praised as an act of solidarity within the international scientific community, with various biologists from the Soviet Union in attendance. Moreover, the Asilomar process had resulted in the creation of concrete forms of governance and oversight, including legally enforceable standards and new organizational bodies (Krimsky 2005). Asilomar would be remembered by scientists as an ideal model of consensus building. Conferences and special journal issues continue to remark on Asilomar as a key historical moment in modern biology (Krimsky 1982, Davatelis 2000, Berg 2008, N.A. 2015). The idea that scientific experts should get together to debate the merits and potential ills of the technologies they produce became synonymous with the "Asilomar model."

However, the pitfalls and complexities of the deliberations during and after Asilomar are often understated in these recollections When Jonathan Moreno, a prominent philosopher and bioethicist,

was asked about how contemporary genome editing technologies should be governed, he stated "there's a nearly reflexive tendency to think of Asilomar, but Asilomar has become for biology what Woodstock has become for youth culture—a mythology that's grown but that obscures how muddy the event itself was at the time," (Bosley et al. 2015). The cultural significance of Asilomar rests in how this myth set expectations for future decision-making in science and reproduced the assumption that publics are limited in their ability to contribute to decision-making processes.

Since 1975, the Asilomar Conference has continued to serve as a model for decision-making around new technologies. For example, in 2010, 165 academics and members of non-governmental organizations attended The Asilomar International Conference on Climate Intervention to discuss geoengineering. Following this conference, five general recommendations were developed with the intent of guiding climate engineering research to be safe, responsible, and effective.[31] The was set in place by proponents of Artificial Intelligence (AI) in 2017. Assembling at the Asilomar conference grounds in January, the attendees of the Beneficial AI 2017 meetings were leaders and researchers from academia and industry that developed guidelines for the future of AI research, ranging from data rights to the potential for super intelligence. These guidelines were named *The 23 Asilomar AI Principles* (Dutton 2018).[32]

As new gene manipulation tools were uncovered through the 2000s and into the early 2010s, the need arose again to have a serious conversation about new risks, hazards, safety regulations, and beneficial applications of these new technologies. These new cases of decision-making around biotechnologies would echo the social and political limitations of Asilomar and, almost as if carefully rehearsed, scientists continued to carefully manage the boundaries of governance. This is, to a large extent, what has happened with CRISPR-based genome editing.

4.2. Moral Distinctions: Somatic and Germline

Echoing Asilomar, to date, deliberation and decisions about genome editing have occurred in a narrow variety of venues. Most of them look either like conferences or panel-based workshops. At the larger end of the scale, the National Academies of Science, Engineering and Medicine (NASEM), the Royal Society of the United Kingdom, the Chinese Academy of Science and the Hong Kong Academy of Science have organized two international summits. Hundreds attend and thousands live-stream these conferences where experts go on stage to present their ideas. At smaller scales, scientists have held information-gathering sessions with local community members for specific projects (Esvelt 2019), like releasing genetically engineered mice on Nantucket island to curb the spread of Lyme disease (Mullin 2019). While these stages vary in the breadth of both audience and expertise, in the United States they continue to reproduce the dynamics of the Asilomar model.

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[31] Asilomar Scientific Organizing Committee (ASOC), 2010: The Asilomar Conference Recommendations on Principles for Research into Climate Engineering Techniques, Climate Institute, Washington DC, 20006
http://www.climateresponsefund.org/images/Conference/finalfinalreport.pdf

[32] N.a. (2017) The Asilomar AI Principles, published by The Future of Life Institute (Accessed online: https://futureoflife.org/ai-principles/)

At each of these sites the agenda for the institutionalization is set and the terms of debate are articulated. As I explore below, participants in these meetings tend frame the debates in terms of a juxtaposition of the benefits of applying this technology to treat hereditary diseases, like hemophilia and sickle-cell anemia, against the risks of its misuse in germline editing and human enhancement. In doing so, a key ontological distinction is introduced between germline cells (sperm, eggs and their progenitors) and somatic cells (all other cells in the body). This distinction has then been mapped onto the ethical and moral debates surrounding genome editing, eventually setting in place a moral equivalence where germline editing is framed as potentially immoral and deviant, and somatic editing is acceptable and morally normative. This distinction has largely inured genome editing as an institution and has framed the public discourse on genome editing.

The Napa Valley Meeting

An early catalyst of these decision-making efforts around genome editing was a closed-door meeting held on January 24th, 2015, in Napa, California. The meeting was conceived by Jennifer Doudna, which as she recounts was triggered by three events in the Spring of 2014: the publication of a study (Niu et al. 2014) in China where the CRISPR-Cas9 system was used to make changes to the genomes of macaque embryos (their plasmids were obtained through Addgene); a then PhD student in her lab, Samuel Sternberg was approached by a "passionate" entrepreneur who wished to start a in-vitro fertilization company that would make "CRISPR babies"; and a nightmare where a colleague invites Doudna to teach Adolf Hitler how to use gene editing, in the dream Hitler had a pig-face and asked, "I want to understand the uses and implications of this amazing technology you've developed," (Doudna and Sternberg 2017b). To address these growing concerns, Doudna deliberately drew on the Asilomar model, hoping to learn from the past. As one of the senior attendees noted, part of the goal of the meeting was to "get some wisdom from people who were who were uh around at the time, you know, at Asilomar! Because it smelled a lot like the same kinds of things will be brewing in the future. Almost sort of a Groundhog's Day kind of thing. You know, I just, you know, the same things over and over again." Here, I draw on interviews with participants of the Napa Valley meeting to understand how this meeting helped set the stage for broader discussions around CRISPR.

In addition to setting the focus on germline editing, the Napa Valley meeting also helped reify the cast of actors that would come to hold key roles in organizing subsequent deliberations. The Napa Valley meeting included a small group of 19 attendees, all of them affiliated with prestigious research universities. All but three of the attendees were scientists and two of the attendees had expertise in law and bioethics. This small group also included three senior researchers who had participated in the 1975 Asilomar conference, including David Baltimore and Paul Berg. These connections, for a few of the attendees were quite personal,

> "You know, I knew Paul Berg, we were in the same field, and I knew David Baltimore very well and Paul was immediately interested, [...] Uh, when we communicated, and Paul and I communicated by email, and I spoke to David directly. David was a little skeptical about what you know about what might come of it. And then you know, then people like, uh, Steve Quake were people who Jennifer and Jonathan (Weissman) knew, and they wanted Steve involved. Alta Charo was somebody that we knew from the Hughes, because she had been working with the Howard Hughes Medical Institute. And she had been she had been very instrumental in writing the Stem Cell Issues. And uh, I knew her, and Jennifer knew her from the

> Hughes because she had been a consultant to the Hughes for years on the ethical issues and had spoken to Hughes faculty at retreats, at Chevy Chase. Uh, and uh, let's see. *So the invitation list was pretty self-evident.* And Dana and I were graduate students (together)." (Interview, emphasis added)

In the view of another participant, this selectiveness was partly why the meeting was successful and productive. When asked about the atmosphere of the Napa meeting, one participant explained that the group was committed to "more clearly defining the problem and think about routes to solutions, rather than coming to grind their axes […] Jennifer should get credit for pulling together people with that kind of attitude, it really made it work."

The group assembled at the Carneros Resort and Spa, amidst a backdrop of rolling hills covered by rows of grapevines. The agenda of the meeting included a one-hour group discussion titled *Lessons from Asilomar*, as well as other three other sessions: *Legal Aspects of Genome Engineering*, *Future of Stem Cell Research*, and *Emerging Scenarios: Scientific, Political, Bioethical*. During the meeting, participants brainstormed strategies for exploring and discussing emerging issues with the aim of advancing genome editing research in a responsible way.

Issues around germline genome editing took up the bulk of the discussion. Members expressed genuine concern that germline genome editing (modifying eggs, sperm, and embryos in a way that genetic changes will be passed down through future generations) would prove too sensitive and volatile of an area of application and worried that the specter of eugenics and "designer babies" would threaten the availability of funding for biomedical applications of genome editing. Instead, attendees agreed that non-germline, or somatic genome editing was less controversial of an application. Somatic editing includes the editing of cells that make up muscle, skin, connective, and nervous tissues. Our interviewees suggested that little critical attention was given towards somatic genome editing. As one of the attendees Hank Greeley, a Professor of Law at Stanford University, discussed in a blog post the lack of attention given to somatic gene editing: "changing the genes of one person, who will die without passing those on to anyone else, just hasn't raised deep questions," (Greely 2015).

Somatic gene editing has its own unique set of political, economic, and cultural challenges. Lack of nuanced questioning of the potential consequences of somatic gene editing prevents much-needed conversations about product regulation, industry and market oversight, and genetic technology misuse that can reproduce social inequalities and disregard for patient's rights. One participant drew from their clinical background to elaborate on the implications for patients and their families, which they argued was not being taken into account by the small group of bioengineers and molecular biologists. They discussed how their medical experience made them more aware of implementation hurdles than some of the other attendees that were asking questions using a more theoretical lens. Hank Greely also felt that the preoccupation with germline genome editing also eclipsed important concerns about the use of the genome editing in non-human animals and plants, which they felt could have more significant environmental consequences. By the end of the day, participants agreed that more discussion was needed and drafted a report about these issues.

A month and a half later, the group published the report as a policy forum in *Science*, "A Prudent Path Forward for Genomic Engineering and Germline Gene Modification." The paper discouraged work on germline genome modification in humans until more research could be done (Baltimore et al. 2015). Additionally, it promoted the creation of educational forums to engage the public about the societal impacts of the CRISPR-Cas system, and stressed the need for transparent

research that evaluates the efficacy and specificity of CRISPR. [Add in and analyze quotes from the article]. While some interviewees acknowledged that a wide array of society's constituents needed to be included in discussions about the ethics of genome editing, the Napa meeting reproduced the outcomes of the 1974 Berg Letter: a small group of researchers set the basic framework for further deliberation and made a call for further deliberation. This time around, there was concerted effort to include a wider set of stakeholders.

Producing normative guidelines: The NASEM

Closely following the article in *Science,* an organizing committee was formed in the National Academies of Science to contribute to convene stakeholders. In this section I examine the formation of committees in charge of international summits and the outcomes of these gatherings to identify the political and bureaucratic dynamics that have driven the creation of guidelines that institutionalize genome editing.

The National Academies, which include the National Academies of Science, National Academies of Engineering and National Academies of Medicine (NASEM) is a non-governmental association of academics created in 1863 to provide science and technology advice for the United States by bringing together experts from a vast array of scientific specialties. Expert committees are formed to organize events and consensus studies to inform white papers and reports drawn from symposia, conferences, and workshops that discuss specific issues related to science policy. These committees are typically a group of between 10-20 people with "a diverse range of expertise and perspectives" (NASEM 2005).

But who is actually invited to participate? Who is considered an expert? According to current formal organizational procedures, NASEM staff first reviews the scholarly literature and then "consults widely with the institution's members and volunteers, knowledgeable authorities, and professional associations." Individuals are chosen based on the Academies' assessment of their knowledge and experience with the topic being investigated. When selecting candidates, one dimension of focus is the balance and disclosure of conflicts of interest (COI). To do this, the academies require selected participants to fill out a series of forms disclosing any potential conflicts of interests.

This is important to unpack because the NASEM acts as a quasi-governmental agency, allowing political interests to leverage the allure of scientific authority in their favor (Boffey 1975; Hilgartner 2000). The most recent forms available on the NAS website offer an account of what this process looks like. A conflict of interest is defined as "any financial or other interest which conflicts with the service of the individual because it (1) could significantly impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organization." Typically, this means that the individual must disclose if they or anyone close to them (e.g., a spouse, employer, or family member) is either employed by or owns part of a company that might benefit from the decision-making. A conflict could also include holding patents that relate to science being discussed. The NAS acknowledges that in some cases, conflicts of interest are unavoidable, in such cases transparency is held as an organizing principle.

Despite this process, the selection of individuals for NASEM committee members has recently come under scrutiny. Two salient weaknesses of this policy are that financial interests valued less than $10,000 are not considered conflicts of interest, and the selection criteria only focuses on "current" conflicts, ignoring the possibility that past engagements may influence committee

members' views. In part because partnerships between scientists in academia and industry are now commonplace, as was explored in Ch. 3, the variety of ways in which any individual can have a conflict of interest have ballooned. Since committee members are asked to voluntarily describe conflicts of interests, assessing the extent to which financial connections have been disclosed by the NASEM is difficult. For example, one study found that six out of 20 committee members from a genetically engineered crop consensus study had financial COIs that went undisclosed (Krimsky and Schwab 2017).

In addition to financial COIs, there are other ways a potential committee member might demonstrate conflict. One group of scholars characterizes non-financial interests as interests related to (1) the individual through personal beliefs, (2) other people through personal relationships and (3) the organization through organizational relationships (Viswanathan et al. 2014; Wiersma, Kerridge, and Lipworth 2018). Another group describes non-financial conflicts more narrowly as intellectual conflicts of interests in which an academic activity creates the potential to develop a strong attachment to a specific point of view that could affect an individual's judgment (Akl et al. 2014). Unfortunately, one of the problems with identifying non-financial conflicts is that they may not fit any definition of conflict of interest (Bero 2014). In addition to these steps, the NASEM sometimes opens the selection of prospective committees for public commentary for a period of time. For a month or so, individuals, companies, or interest groups may submit letters of concern and suggestions for the formation of the committee. These comments are then considered by the organizers of the committee and changes may be made to the final slate. Given these limitations to the COI process, it is unclear what mechanisms exist to ensure accountability and that the widest possible set of stakeholders are represented on committees.

The legitimacy of the NASEM is warranted by the ideological premise that experts' objectivity, especially as a community, will override any potential bias. This warrant stands in the face of most anthropology, history, philosophy, and sociology of science, which has shown over and over that science is a value-laden field where judgments are made based on researchers' values, models and data reflect their interests, and collective expert consensus is shaped by personal obligations (Frickel and Gross 2005; Hacking 1983; Nader 1996; Shapin 2008). As I explored in Ch.3, the biggest difference between the 1970s at Asilomar and today, is that a fully developed biotech industry and revolving door has developed between academia and industry. The social structures of academic capitalism, or neoliberal science, have transformed the moral economies of scientific work and obscure the processes by which power in concentrated in expert bodies being shaped by market dynamics that are often obscure to the experts themselves (Berman 2012a; Mirowski 2011; Rasmussen 2004; Sismondo 2018).

The Washington Gene Editing Summit

It was not, however, always obvious that the NASEM should be the one to host an international meeting and provide guidance to scientists working with CRISPR-based techniques. One interviewee explained how the Howard Hughes Medical Institute, UC Berkeley, and the American Society of Human Genetics all vied to host these discussions. Other professional associations had also already hosted their own conferences focusing on the technical advancements of CRISPR for the scientific community. As one of the Napa Valley meeting attendees explained, "I was on the National Academy Council and so I and two other people, Bob Horvitz and Mark Fishman, wrote a letter to President of the National Academy of Medicine, Victor Dzau. And said the Academy should do something to convene this set of people to talk about these issues. So, it was

a direct product (of the Napa Meeting), in fact, Jennifer (Doudna) was going to organize another much bigger meeting and I said, 'No, you know the Academy should do this, a big neutral body. You're not regarded as a neutral player here. So, you should be involved in planning and everything else, but the National Academies is a trusted voice that was founded to advise the government on matters of science.' That's what it's for."

Because of its expertise, legitimacy, and perceived neutrality, the Academies arose as the central host. The explicit aim of the initiative was to "provide researchers, clinicians, policymakers, and societies around the world with a comprehensive understanding of human gene editing to help inform decision-making about this research and its application" (Anon 2015). As such, the initiative acted as if it was an information funnel and filter with the task of producing reports. In pursuing this aim, the NASEM identified what areas of genome editing were controversial, which ones were more settled, and what the technical limitations of the technology were.

One of the first outcomes of this initiative was the organization of the first International Summit on Human Genome Editing held in Washington, DC, at the Academies in December 2015. The organizing committee included David Baltimore (as chair), Paul Berg, George Daley and Jennifer Doudna, all of whom played central roles in the Napa Valley meeting. The committee also included expert representatives from the Chinese National Academy of Science and the Royal Society of the UK. This summit invited US and non-US researchers to serve as speakers and discussants on the emerging societal implications of new genetic technologies. In a noted departure from the 1974 Asilomar meeting, the DC Summit also included a number of social scientists, including Charis Thompson, Catherine Bliss, Ruha Benjamin, and Jennifer Merchant.

Upon opening, David Baltimore, an organizing committee member of both the 1975 Asilomar Conference and 2015 Napa Valley Meeting, stated in DC, "We are taking on a heavy responsibility for our society because we understand that we could be on the cusp of a new era in human history." Rather than an exaggeration, this statement is a reflection of the role the scientific community has written for itself as the main arbiter of what should happen next regarding human genome editing. This sense of duty and the weight of lone responsibility exemplifies the ethic with the Academies Initiative operated.

After the meeting, the NASEM released a set of guidelines for oversight systems to govern the research on and clinical uses of human genome editing. While these guidelines pay lip service to some of the concerns voiced by social scientists and disability justice advocates at the Washington meeting, they actively neutralize any argument for establishing a more socially just science or preventing applications of genome editing that are racist or ableist. For example, in response to concerns voiced by some disability justice advocates that the biomedical expansion of genome editing could exacerbate stigma towards people with disabilities or parents of children who are born with disabilities, the guidelines argue that,

> "Public policy has shifted toward eliminating discrimination in employment or public services, and public investment in changing the social, physical, and employment environment to achieve this goal has increased, with measures ranging from accessible buildings to sign language presentations to aural signals for street crossings. The range of measures remains insufficient, however, and one cannot know whether this shift in attitude would have been even more dramatic if genetic screening and abortion laws had not made it easier to reduce the prevalence of birth defects. Nonetheless, this progress does to some extent address the concern that reducing the prevalence of disabilities will necessarily decrease empathy, acceptance,

or integration of those who have them," (Committee on Human Gene Editing 2017:127).

This inference, that existing successes of the organizing efforts of years-worth of disability advocacy and activism is coupled somehow to an increase in genetic screening and availability of abortion, reifies scientists' alignment with a pathological understanding of disability and misunderstands the contentions of disability justice activists. The committee opted instead for a permissive framework and minimized concerns about the use of genome editing for enhancement and germline modification on technical grounds. Arguing that at the time of publication, there was too much technical uncertainty to establish a firm position on germline editing. As they put it, "these criteria are necessarily vague" because different stakeholders would approach them different and cultural differences between societies would shape how they were interpreted. Rather than opting for a moratorium on germline editing, as had been raised by some during the DC meeting, they argued that existing government regulation was sufficient, and that genome editing should be guided by "voluntary self-regulation pursuant to professional guidelines," (Committee on Human Gene Editing 2017).

These guidelines have had a lasting effect on how applications of genome editing are governed. For example, subsequent guidelines and reports produced by other groups have iterated on the original 2016 guidelines (Nuffield Council on Bioethics 2019). While the guidelines provide a normative frame of reference for genome editing, their uptake in unclear and scientists adherence to the guidelines is not easily assessed. Instead, more practical guidelines like those found in Addgene's CRISPR 101 e-book are more likely to be bench scientists' first encounter with a set of guidelines and standards.

4.3. #CRISPRbabies: Crisis and Boundary Repair as Forces of Institutionalization

The NASEM organizing committee proposed to hold two additional international Summits, to be hosted by the other national associations that had participated. The second was planned to be originally held in Beijing, and hosted by the Chinese Academy of Science (CAS), but as Baltimore explained, "CAS did not want to have a 500-person meeting in [mainland] China and we needed that to accommodate the expected number of attendees, […] So they dropped out," (Begley 2018). Instead, the Hong Kong Academy of Sciences offered to sponsor the summit and host it at The University of Hong Kong (HKU). To understand how these meetings have contributed to the institutionalization of genome editing, I conducted ethnographic observation and participated in the Hong Kong Summit. My original expectation was to find that the Summits were largely performative exercises that would allow scientists to continue to reproduce the idea of self-governance. As such, I expected it to be a demonstration of technical advances in genome editing since the 2015 summit and perhaps some increased understanding of the state of genome editing in East Asia. Little did I realize the controversy that would be catalyzed as I made my way through the city.

On the eve of the 2nd International Summit on Genome Editing in Hong Kong, reporters from the Associated Press and MIT Technology Review published a story that effectively rendered the anticipatory and precautionary views of the ethicists and scientists that spoke at the Summit obsolete. The reports were confirmed later that same day by biophysicist He Jiankui, from Southern University of Science and Technology in Shenzhen (SUSTech), via a series YouTube videos,

> "Two beautiful Chinese girls named Lulu and Nana came crying into this world as healthy as any other babies a few weeks ago. The girls are home now with their mom, Grace, and dad, Mark. Grace started her pregnancy by regular IVF [in-vitro fertilization], with one difference: right after we sent her husbands' sperm into her egg, we also sent in a little bit of protein and instruction for a gene surgery" (The He Lab, 2018).

He's videos outlined both the experimental setup and the ethical principles behind a clinical project to develop an "HIV vaccine" by genetically modifying human embryos and implanting them. The story triggered an immediate response as organizers set the stage for the Summit and brought with it the attention of 1.8 million remote attendees and over a hundred reporters from Chinese and international news organizations. At the conference, scientists, ethicists, reporters, and a handful of social scientists all wanted to know how this experiment had happened. As the media frenzy continued, reporters pieced together more details of the project that gave birth to the first children who had been genetically engineered with the CRISPR-Cas9 system.

This section frames the ensuing events as a crisis of legitimacy. Following well-established theoretical and methodological traditions in the sociology of science (Jasanoff 2019; Mukerji 2007; Panofsky 2014), I use the openings afforded by the controversy to examine the normative environment of genome editing. Interpreted as a natural breaching experiment, the repair mechanisms that scientists deployed to address the crisis and re-establish the legitimacy of the field illustrate how the social order of genome editing is maintained. Amidst the inquisitions, many scientists responded by characterizing He as a rogue actor who had transgressed the consensus of the scientific community, assuredly classifying the situation as a case of individual deviance and criticizing both the ethics and the science behind the project. As one of the leading developers of genome editing technology, biophysicist Feng Zhang, conveyed, "He was an outsider [...] What he has done was not transparent. It was against the community's consent and it does not represent science" (Belluck 2018). Immediately after He gave his remarks outlining the details of his experiments to the genome editing community at the Hong Kong Summit, senior scientist David Baltimore, diagnosed the case as "[a] failure of self-regulation by the scientific community because of the lack of transparency."

Researchers in China and Chinese government officials condemned his work and charged that he had broken Chinese law and conducted research without the proper oversight. In the months that followed the Summit, He's whereabouts became unknown, with eventual reports claiming he was placed under house arrest. Pinning the weight of the criticism on He largely succeeded as a mechanism of social repair and boundary maintenance (Gieryn 1983) for both the organizations affiliated to He and, more importantly, for the emerging field of genome editing as a whole.

However, characterizing this just as a case of individual deviance fails to account for the social origins of experimental work. For example, research in the sociology of deviance points to the proximate sources of deviance, where risks and punishment are concealed by the local routines of organizations (Vaughan 1999). Organizational deviance has been conceptualized as, "an event, activity, or circumstance, occurring in and/or produced by a formal organization, that deviates from both formal design goals and normative standards or expectations, either in the fact of its occurrence or in its consequences, and produces a suboptimal outcome," (Vaughan 1999:273). Such an approach would focus on the local ethical oversight mechanisms in place at SUSTech and at the hospital where He conducted his experiments.

Even then, this would only be part of the social context in which He's experiments occurred. As transnational studies of science show, the circulation of materials, knowledge, technology, and people permeate organizational and national boundaries (Anderson 2009; Thompson 2008). In this case, the team of researchers involved in the experiment He led, involved multiple organizations and actors, many of whom reside in the United States. Indeed, subsequent reporting by investigative journalists has indicated that at least 8 U.S. researchers were a part of He's "inner circle" and knew about his intention to implant the embryos. Keeping in mind that the normative environment of genome editing is organizationally diffuse, I can interrogate how multiple normative frameworks, operating at different levels of organization, can interact. To do this, I build on sociologist Adam Hedgecoe's approach to the regulatory co-construction of organizational deviance (2014). Hedgecoe's extension of this Vaughan's theory of organizational deviance describes how regulatory bodies and formal scripts that govern organizations can be complicit in producing deviations, mistakes and accidents by fuzzy standards or by creating systemic gaps in reporting and knowledge (Hedgecoe 2014). Thus, rather than examining the local regulatory and funding conditions in China and further pursuing the argument that He or research organizations in Shenzhen had operated unethically, this I look at more distal determinants of deviance in the field of genome editing in the United States.

This approach brackets two important dimensions of the controversy. First, implicit in this framing is the assumption that because of the international scope of science, any explanation of scientific practice cannot be reduced solely to national context and preemptively obviates the cultural essentialism and orientalism that pervades academic and non-academic discussions of this controversy thus far. A complete account of the controversy surrounding He's experiments would incorporate primary data on SUSTech and the research environment in China to capture the proximate organizational mechanisms that contributed to the development of He's experiments and the local controversy among Chinese academic scientists and government officials. I only address these concerns in passing, and instead draws on examples of organizational repair mechanisms and cultural determinants that are endemic to U.S.-based genome editing scientists.

Second, like in Chapter 3, I approach the debates about the ethics of germline genome editing sociologically, looking at what scientists, lawyers and bioethicists ascribe moral relevance and virtue to. For example, many scientists rather than engaging with the issue on moral grounds, focused their attention on the technical rigor of Dr. He's experiments, arguing that his work was wrong because it was flawed. I build on Hedgecoe's approach and my theory of normalization to show how, in science, informal norms around innovation, like those contained in the 2016 NASEM guidelines and the broader political ethic of self-governance, can also produce deviations from more formal rules.

As I show below the interaction between multiple normative frameworks and over-reliance on self-governance conceals a culture of opacity and, in this case, moral ambivalence towards the practice of modifying human DNA. This ambivalence is moreover reified by the repair mechanisms that ensued following the He Jiankui affair. During the repair of the crisis, actors first aimed to reaffirm the moral status of genome editing and resisted arguments for a moratorium on germline editing by ejecting He from the field. They then moved to create yet another expert committee in 2019 that would focus on the establishment of technical standards and guidelines for germline genome editing. This response further normalized germline editing via the production of a permissive normative framework and further solidified somatic editing as a morally valuable and un-controversial goal for biomedicine.

I additionally argue that reactions to the controversy are less due to any concrete moral objection to germline modification on the part of the genome-editing community, but that instead, the case is controversial to scientists because it displays a system of positive deviance within science that contrasts with the image of the genetic engineering community as responsible, reflexive and self-regulating. It is through interactions between scientists, regulators, bioethicists, and journalists that a moral order that favors the institutionalization and re-legitimation of clinical genome editing discursively constructed. I trace how these actors reproduce a system of positive deviance, whereby scientific progress is rendered morally agnostic and research is rewarded for its inventiveness and cutting-edge rather than its concordance with the *illusio* (Bourdieu and Wacquant 1992) of scientific consensus and responsible innovation.

In effect, the case of the He Jiankui affair serves as a reminder that scientists can and *have* distinguished themselves by breaking with the consensus of the scientific community. In the language advanced by Fourcade (2004), these instances of *moral unhingement* are also characteristic of the moral economies of capitalism, of which the imperatives to progress technologically and scientifically are central as I've argued in Chapter 3. While scientists justify their work with strong moral and social promise, such as curing disease and alleviating patient suffering, in practice, researchers silo off the "ethics" of their work to oversight and regulatory bodies and opt instead for opaque accountability practices. This opacity and moral agnosticism are characteristic of science in a condition of rapid advancement and innovation like genome editing, where the impetus for treating disease and the potential for profit are great and where work is surrounded by moral and regulatory uncertainty.

ChiCTR1800019378: Evaluation of the safety and efficacy of gene editing with human embryo CCR5 gene.

At face value, clinical trial "ChiCTR1800019378" donned the bureaucratic trappings of a legitimate experimental protocol. He Jiankui's project had the approval of a medical ethics committee of the hospital where the trial would be conducted. Its protocol included a detailed informed consent form outlining risks and benefits to the participants. And the protocol was registered in and vetted by China's centralized clinical trial registry. The protocol further describes how its clinical and intellectual aims are aligned with the criteria set by the 2016 NASEM guidelines. Understanding how the crisis effectively breached the apparent legitimacy of the normative environment of genome editing necessitates a careful dissection of the experiments that would be described as "monstrous" and liken He to a "Chinese Frankenstein." Here, I summarize the specifications of He Jiankui's experimental project based on what is currently known to have been done as presented by He at the Hong Kong Summit and as represented in the documentation made available on the (now archived) He Lab SUSTech website.

Described as a clinical trial for an HIV-AIDS vaccine, the project aimed to use the CRISPR-Cas system to address a globally recognized health issue. The study objectives listed in the Chinese Clinical Trial Register (ChiCTR) read,

> "HIV-induced AIDS is a major medical problem that threatens all human beings in today's world, affecting the safety and health of all human beings. To date, there is no effective drug or clinical technique to completely cure AIDS. […] The only HIV-infected person who has been recognized as completely cured in the world is the 'Berlin patient'. At that time, the patient developed leukemia and was diagnosed as HIV-positive before the bone marrow stem cell transplant. The German doctor used a bone marrow matching to creatively treats leukemia in this patient with a rare

CCR5 genetic mutation existing in Western European population resistant to HIV-1."

He Jiankui's study aimed to introduce a deletion mutation for the CCR5 gene at the single cell embryo stage. This *CCR5* gene encodes a protein that is a co-receptor for HIV. Basically, it is like the hinge of the door that the virus uses to enter a cell. It was known in the literature that this specific mutation in *CCR5* confers immunity to HIV infection (Allers and Schneider 2015; Choe et al. 1996; Dolan et al. 2007; Lehner et al. 2011; Tebas et al. 2014). Additionally, the hospital approval form approved in March 2017 suggests that "individuals with *CCR5* 32bp-deletions have normal immune and inflammatory responses and are significantly resistant to multiple viral infections; therefore, gene editing on *CCR5* may be effective in blocking cholera, smallpox or HIV infection." He Jiankui also ascribes tremendous moral value to the study in the YouTube video uploaded on the eve of the Hong Kong summit, where he argued that HIV-stigma is rampant in Chinese society. He expanded on this affective warrant in his presentation in Hong Kong, where he recounted being deeply saddened by his experience visiting an AIDS-village in the Hunan province where 30% of the population has HIV. His proposal was also in alignment with other existing clinical proposals that targeted the *CCR5* gene and the activity of the protein derived from it.

As He described, to disrupt the activity of the *CCR5* protein, the components of the CRISPR-Cas system, Cas9 and guide RNA (gRNA), and sperm were injected into a fertile human egg from the donor parents. What He very explicitly called, "A gene surgery." Injecting sperm in this way is common procedure in in-vitro fertilization known as intracytoplasmic sperm injection (ICSI). Adding Cas9 in this step was also not a new procedure, as this was already being used by other researchers who study human embryonic development (e.g. Ma et al. 2017). He's team had ordered the materials for the experiment from U.S. companies: the Cas9 protein was acquired from Thermo Fisher and the gRNA from Synthego. Where Thermo Fisher is a major provider of laboratory equipment ranging from pipette tips to nuclear reactor monitoring instruments, Synthego is a newer biotech company specializing in genome editing tools that was notorious among those of us at IGI for giving away quality merch at conventions and sponsoring IGI social hour. According to the data reported at the summit, He performed these experiments on 31 non-viable and 19 viable human embryos before proceeding with the two embryos for the parents.

What was unprecedented was the decision to implant viable embryos. To carry out these experiments the project team recruited 33 heterosexual couples where the male partner tested positive for HIV. These participants were reportedly recruited from online HIV forums and patient support groups. As the informed consent form explains, the main objective is to "produce infants who have the ability to immunize against HIV-1 virus," on the theoretical basis that, "It would help these *CCR5* gene editing babies to obtain the genotype of the Northern European to naturally immunize against HIV-1 virus." Of these, one couple agreed to have the edited embryo implanted and carried the resulting twins to term. Throughout the pregnancy, the project team obtained tissue from both fetuses and amniotic fluids for DNA sequencing to analyze the outcomes of the editing experiment (at weeks 12, 19, and 24). This sequencing was done to test for possible mutations in genes that could lead to cancer, off-target sites where Cas9 may have introduced a mutation where it wasn't intended and to measure the effects on the *CCR5* target gene.

These experiments did not occur out of nowhere. He earlier presented extensive work validating and testing different genome editing procedures in mice and monkey embryos. Records show He presented at genome editing conferences in 2016 and 2017; at a CRISPR Revolution meeting at Cold Spring Harbor Laboratories, and at a Bioethics Workshop at IGI at UC Berkeley. He's position in the field is moreover affirmed by his invitation by NASEM organizing committee to

present at the Hong Kong summit itself long before any news of the project. The planning for this research program would also demand an interdisciplinary team, on top of He's expertise in bioinformatics and biophysics, including molecular biologists, gynecologists, epidemiologists who specialize in HIV, and IVF specialists,

Moral ambiguity: "We want to give Dr. He a chance to explain what he is done."

It was investigative reporter Antonio Regalado from the MIT-Technology Review who broke the news of the birth of genetically modified twins through this clinical trial the day ahead of the Hong Kong summit. As it turned out, He had previously hired a public relations consultant, Ryan Ferrel, who arranged exclusive interviews and media content with The Associated Press. The AP, under pressure, would then release their story exclusive in tandem to the YouTube videos released by the He Lab (Marchione 2018). He was scheduled to give his talk on the second day of the summit, which meant the first day would be deeply suspenseful, since nobody knew whether He would show at all. In the second session of the conference vice president of the Chinese Society of Bioethics, Qui Renzhong was asked during the Q&A how the He Lab's experiments could have been approved. Qui then slowly made his way to the edge of the stage, putting his hand up to his ear to focus in on an audience member who was translating the question to Mandarin. Qui made his way back to his chair on the panel and was handed a microphone, "Maybe this review is a fraud." Qui suggested that He had created a fraudulent medical ethics review and circumventing the institutional review board (IRB) of his home institution, SUSTech and had instead obtained approval directly from the hospital where the research was conducted. Indeed, SUSTech would later make a public statement claiming no knowledge of the trial. The rest of the day, other scientists speculated that the entire project may have been a forgery since no supporting data had been shared. The suspense continued to build up to the second day of the Hong Kong summit. During a modified session on "Human Embryo Editing" He entered the stage through a side entrance. With an entire section of the auditorium occupied by media crews, the sound of the camera shutters overwhelmed the stadium. Despite the session moderator's attempts to scold photographers with a threat to cancel the whole session, "Free press!" one photographer responded. Amidst the camera shutters capturing every gesture and presentation slide, He nervously made his way through the motivations, procedures, and results for the experiments, mechanically following his lecture notes.

Once it was more clear what experiments had occurred, the community's response became more apparent. Each slide presented by He was meticulously dissected to assess whether the take home message He offered, that the outcomes were as planned and that the twins were healthy, was accurate. Researchers on Twitter picked apart the technical details and strategy of his project, arguing that the editing was not as successful as He suggested.[33] In the end, other scientists with expertise in embryo editing for developmental research showed that the embryos of the twins varied in their genetic outcome and showed signs of mosaicism.[34] In theory, then, one twin was protected against HIV-AIDS and the other was not. Other critics pointed out that protecting against HIV-infection did not meet the criteria of treating severe disease, and was instead disease prevention lives in the blurred a form of enhancement (Greely 2019). In doing so, critics would fulfill sociologist

[33] See for example: Burgio, Gaetan (2018) https://twitter.com/GaetanBurgio/status/1067657557114679296; and Ryder, Sean (2018) https://twitter.com/RyderLab/status/1068128997656207361

[34] Mosaicism or genetic mosaicism which is when different cells in the same multi-cellular organism have different genotypes, such as that observed in the multi-colored fur of calico cats.

Ruha Benjamin's claims from the 2015 DC Summit, that "The distinction that is commonly made between genetic therapy and enhancement is not at all straightforward or stable. The bright line we may want to draw between laudable and questionable uses of gene editing techniques is much more porous than we may realize. Many practices that were optional yesterday are medicalized today, likewise traits as behaviors that we may regard as enhancement, may very well find their therapeutic justification tomorrow." More proximate dimensions of the controversy, such as the individual biography of Dr. He (Begley and Joseph 2018) and the regulatory conditions in China (Nie and Pickering 2018), were also proposed as explanations for why these experiments were conducted.

While the outcry against He Jiankui as an individual obscures this social reality of He's project, it was not lost on genome editing researcher Matthew Porteus who was tasked with interrogating He after his talk alongside the moderator of the session, British geneticist Robin Lovell-Badge. As I waited in line to ask the very same question, Porteus jumped the gun, "Who did you discuss this trial with, in terms of your mentors or advisors, other people, in terms of getting feedback on the consent process, trail design? Tell me sort of the scope of the team." To which He responded, "once we had some early data, preclinical, I presented at the Cold Spring Harbor Meeting in New York in 2017 and also at the UC Berkeley genome editing conference. Some of the audience (members) were in that conference too." As he answered, He began to gesture to the scientists in the front rows of the auditorium. "I received positive feedback and also some criticism and also some constructive advice. I continued to talk to not just scientists but also the top ethicists in the United States such as at Stanford, William Hulrbut, and I showed my preclinical data to many visiting scientists."

That He must have felt a bit blind-sided is an understatement. As the translated text of the medical ethics approval form for the Harmonicare Shenzhen Women's and Children's Hospital reads, "Ultimately, our research will stand out in the increasingly competitive international application of gene editing technology. This is going to be a great science and medicine achievement ever since the IVF technology which was awarded the Nobel Prize in 2010, and will also bring hope to numerous genetic disease patients." Indeed, physiologist Robert Edwards received the Nobel Prize in Medicine in 2010 and had himself gone against the consensus of his field and existing clinical safety in 1978 and facilitated the birth of the first "test tube baby," Louise Brown (Obasogie 2013). As one IVF expert told investigative journalist Antonio Regalado, "It was the same with IVF when it first happened, we never really knew if that baby was going to be healthy at 40 or 50 years. But someone had to take the plunge." He would continue to bring up Edwards at the Summit and meetings with the organizers. As Jennifer Doudna would recount, during a meeting held at Hong Kong's Le Méridien Cyberport Hotel lobby with He and some of the Summit organizers, "He was very confident in his work, and totally not understanding what an explosion he had caused," (Begley and Joseph 2018). Published personal accounts dramatize the end of meeting with He storming off in frustration after dropping cash on the table for the drinks.

This reaction can be understood in two ways: a) in terms of a broader culture of positive deviance in science.; and b) as evidence of moral agnosticism towards the ethics of genome editing. As described by Vaughan, "cultural understandings affect interpretive work, so that people may see their own conduct as conforming, even when the behavior in question is objectively deviant," (Vaughan 1999). This may very well have been the case for He. As he explained in the medical ethics approval form from March 2017, "in February 2017, the US National Academy of Science, Engineering and Medicine released a statement that experimental study on the gene editing of embryos as therapeutics for the treatment of serious diseases is ethically acceptable." The following logical step, to implant the embryos, was clearly off the table for in the NASEM guidelines, but was

not entirely dismissed. He Jiankui was not alone in interpreting the NASEM guidelines this way. The morning of He's session at the summit, the dean of the Harvard Medical School, George Daley, who was also one of the summit organizers, made strong moral argument in favor of germline editing drawing on the language three different guidelines and reports.

The moral ambiguity of the field towards germline editing is additionally clear from the statement released by the organizing committee shortly after the Hong Kong summit. A central framing, again, is the distinction between somatic and germline applications, "While we, the organizing committee of the second summit, applaud the rapid advance of somatic gene editing into clinical trials, we continue to believe that proceeding with any clinical use of germline editing remains irresponsible at this time." The rest of the statement, however, reads like as coherently as an astrological reading,

> "Making changes in the DNA of embryos or gametes could allow parents who carry disease-causing mutations to have healthy, genetically related children. However, heritable genome editing of either embryos or gametes poses risks that remain difficult to evaluate. […] Nevertheless, germline genome editing could become acceptable in the future if these risks are addressed and if a number of additional criteria are met. These criteria include strict independent oversight, a compelling medical need, an absence of reasonable alternatives, a plan for long-term follow-up, and attention to societal effects. Even so, public acceptability will likely vary among jurisdictions, leading to differing policy responses.
>
> The organizing committee concludes that the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at this time. Progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway toward such trials."

In some ways, He must have felt had sufficiently engaged in discussions around the ethics of germline editing and though he had actively contributed to developing and clarifying the uncertainty of CRISPR-Cas9's moral frameworks. His own YouTube videos and lab website outline a series of ethical principles that guided the project. As He explained, he had consulted bioethicists in the US, including William Hurlbut whom He met at the Berkeley bioethics conference. In a now retracted paper published in *The CRISPR Journal,* the flagship peer-reviewed genome editing journal, He along with four co-authors (including Ferrel, the PR specialist) outlined five "Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies": 1. Mercy for families in need; 2. Only for serious disease, never vanity; 3. Respect a child's autonomy; 4. Genes do not define you; and 3. Everyone deserves freedom from genetic disease. In affirmation of He's work, geneticist George Church, one of the authors of the *Science* paper from 2015 that came out of the Napa Meeting argued, "I think this is justifiable." (Marchione 2018).

Practices of credit attribution and norms of collaboration: "It was barely a collaboration, just like collegial feedback."

In one interview with *Science,* George Church*,* like Porteus, also recognized He's position in the field. Despite others' minimization, Church notes "he had an awful lot of company to be called a 'rogue,'" (Cohen 2019). *Science* eventually identified what they characterize as a "circle of trust" including a Nobel laureate—in China and the United States, business executives, an entrepreneur connected to venture capitalists, authors of the NASEM report, a controversial U.S. IVF specialist

who discussed opening a gene-editing clinic with He, and at least one Chinese politician. He's presentation at Cold Spring Harbor also included Hurlbut and an IGI postdoc. Later, Matthew Porteus would also admit that He had approached him beforehand seeking both methodological and ethical guidance. It turned out he emailed a lot of people for feedback. As most academics will recognize, a key normative framework that supports scientific work is rooted in a gift economy of credit attribution and patronage. As I explored in Ch. 3, these norms cannot be separated from the moral economy surrounding academic capitalism and scientists' entanglement in "the chain of progress" (Weber 1922).

He was by no means a stranger to U.S. norms around collegiality nor around partnerships between academic research and industry, having received his doctoral degree at Rice University in and his postdoc in 2011 at Stanford in Stephen Quake's lab. Quake also happens to be the co-president of the Chan-Zuckerberg Biohub, from which Nielsen obtained funding for his shift to projects that centered CRISPR-Cas9. Both He's doctoral advisor, Michael Deem and Quake served on the scientific advisory board for the Chinese DNA sequencing company, Direct Genomics, that He Jiankui started using software developed by Deem at Rice. As the postdoc at IGI who I interviewed explained to me,

> "He's a scientist, he's got American training, he knows kind of how we roll. And so he was managing or conducting these relationships facially as collaborations, or in my case was barely a collaboration, just like collegial feedback, […] It was kind of on the low end of what you'd acknowledge, but it wasn't inconceivable that you would want to acknowledge. […] It is immoral. And he put the wool over our eyes by acting like this was a collegial relationship when in fact it was he was manipulating us into giving information or at least not calling the authorities or anything on him."

This postdoc had shared technical know-how and been flown to Shenzhen to give a talk. The rest of his lab was quite upset that he hadn't shared the details of what was going on. His PI, at least, had cautioned him not to share any reagents or materials that would have more formally entailed a collaboration. After doing an interview with STAT news without consulting IGI leadership, the postdoc would then loose his position at IGI.

Legitimacy without laws

In an interview with the New York Times, Quake pointed to yet another competing moral framework that allows scientists to silo-off ethical concerns when collaborating: the legitimacy of organizational bioethics oversight. "But as these things unfold, you're in the moment, and you know, he's doing legitimate scientific research — many people would define it that way. He's got I.R.B. approval and his institution is regulating the human subject stuff and you sort of believe all that. […] To the extent that it wasn't obvious misconduct, what does a person in my position do? Encourage him to do it right, his research, right? I mean, that's what I believed I was doing," (Belluck 2019). While this is similar to how researchers in Nielson's lab shunted accountability to local organizational oversight bodies during their collaboration with biotech startup Almanor, relying on the regulatory framework and organizational oversight of a different country further illustrates how the legitimacy of genome editing, as an institution, is divorced from the legal management of scientific practice. Indeed, scientists pursuing clinical work must undergo ethics training for human subjects research both in the US and in China. China also has strict rules for conducting research with human embryos, despite Lovell-Badge's claim that, "[in China] pretty much anything goes; this is the Wild West," (Kelly 2019). Throughout the development of genome editing, scientists carefully

guarded their work from restrictive forms of control through self-governance. He Jiankui's experiments and the way they were revealed threatened the validity of scientific self-governance.

In response to this crisis of legitimacy, some scientists advocated for a moratorium. Feng Zhang, for example, issued a statement at the beginning of the Hong Kong summit, "Given the current state of the technology, I'm in favor of a moratorium on implantation of edited embryos, which seems to be the intention of the *CCR5* trial, until we have come up with a thoughtful set of safety requirements first." (Regalado 2018). A moratorium, while not an enforceable form of control, would be a stronger statement of control and a meaningful push for self-constraint. The most strongly worded position in response to the lukewarm reaction to He Jiankui's experiments by the organizing committee in Hong Kong came from the Center for Genetics and Society (CGS), a civil society group based in Berkeley, CA. Their statement to the NASEM organizers, with over 150 signatories (mostly academic), urged that "they (1) condemn in clear terms the rogue actions of the researcher who has taken it on himself to make a hugely consequential decision that affects all of us; and (2) call on governments and the United Nations to establish enforceable moratoria prohibiting reproductive experiments with human genetic engineering." (King, Darnovsky, and Hasson 2018). However, the chair of both of summits, David Baltimore, opposed a formal moratorium. When pressed on why by *Science News*, Baltimore explained,

> "It's largely a semantic issue. Statements made after the first summit and the second summit have avoided using the term moratorium. Consciously. Because that word has been associated with very firm rules about what you can do and what you can't do.
>
> I fully agree — and the whole group of us involved in the summits agree — that we're not ready to be doing germline modification of humans, if we ever are. You might say, "Well, that's a moratorium," and, in a sense, it is. I don't have a big argument about that.
>
> But the important point is to be flexible going forward. That's what's wrong with a moratorium. It's that the idea gets fixed in people's minds that we're making firm statements about what we don't want to do and for how long we don't want to do it.
>
> With a science that's moving forward as rapidly as this science is, you want to be able to adapt to new discoveries, new opportunities and new understandings. To make rules is probably not a good idea," (Saey 2019).

Baltimore's position may reflect his own experience with the moratorium on rDNA in the 1970s, which while lauded as an instance of great restraint, many scientists felt was excessive. In both cases, however, the self-governance of science demands tireless resistance to the imposition of formal regulation and the management of the boundaries of expert governance. The claim in CGS's letter that governments should enforce restrictions ran directly against this political boundary work.

A good example of how the genome-editing scientists maintained the boundary against increased government regulation in the United States was a hearing in November 2017 of the United States Senate Committee on Health, Education, Labor and Pensions. At the hearing, Matthew Porteus represented genome-editing scientists in academia, Katrine Bosley of biopharmaceutical company Editas Medicine represented the burgeoning CRISPR industry, and Jeffrey Khan, a member of the NASEM genome-editing committee, represented bioethics. Their testimony, in short, argued that no new regulations were needed

for CRISPR and affirmed existing oversight structures. Kahn, in his testimony, pointed to the 1965 Asilomar Conference on rDNA as the point of departure for the relevant policy history of genome editing and described how genome editing in humans falls under the jurisdiction of the NIH Recombinant DNA Advisory Committee (RAC). Porteus made sure to clarify the important distinction between somatic and germline editing to the committee and argued that "the current regulatory structure has been appropriate as researchers begin to bring somatic cell editing for the treatment of disease to clinical trials and ultimately to market as an approved drug." Bosley similarly claimed that, "Continued success in this field will depend in part upon Congress maintaining the robust, but flexible regulatory system over novel genetic technologies that has operated effectively since the first recombinant genetic research began over 40 years ago," (Alexander et al. 2017). Two years later, however, the RAC would be relieved of its regulatory role and re-assigned an advisory position in the NIH (Wilson 2018).

The U.S. congressional hearing on gene editing also alludes to the broader geopolitical conditions of the crisis over He Jiankui's experiments. In his opening statements, Senator Lamar Alexander put genome editing in the context of the 21st Century Cures Act, which authorized $6.3 billion in funding for the NIH in 2016, "CRISPR is just one of the amazing discoveries that have come from basic research funded, in part, by the Federal Government," (Alexander et al. 2017). With respect to regulation, Kahn described in his statement why the U.S. science regulatory context should avoid prohibitive policies due its effect on U.S. competitiveness in science, "Just last week in Canada, a major group of researchers called for change to their federal law that makes it a criminal offense with penalties of up to 10 years in prison for using gene-editing tools on cells that could lead to heritable genetic change in humans. The concern expressed by the group is that research has been stopped in ways that mean Canadian scientists are falling behind their international colleagues," (Kahn 2017). The testimony then explains,

> "There is no comprehensive [international] regulatory approach, however, the absence of which creates an opportunity for some jurisdictions to craft lenient or nonexistent regulation, leading to the emergence of so-called 'regulatory havens,' the encouragement of both scientific flight and medical tourism, and more near-term concerns around scientific leadership and competitiveness, and a loss of ability to control research that is outside of U.S. jurisdiction." (Kahn 2017)

In his questions to Kahn, Senator Tim Kaine shows how the boundary between science and the state is carefully coordinated to advance national goals, "That is a big concern. We would want to be the leader. We would want to remain in the leadership position in this based upon our institutions and individuals. How should we start to think about this regulatory issue so that we do not run into a position where we are chasing away—by tryng to do the right thing on regulation—we are chasing away innovation to other locations?" (Alexander et al. 2017:39). Kahn agreed, "This country has long, really forever, been the leader in science in the world and I do not think we want to cede that to anybody else." The consensus among the three witnesses was to keep faith in the FDA's current authority and that did not see any need for new legislation. As Porteus put it, "I hope that the FDA will be able to be flexible and adapt to new information to continue to put United States at the leading edge," (Alexander et al. 2017:45).

However, as *Fortune* would put in their headline in 2018, "China Is Beating the U.S. in the Gene Editing Arms Race," (Mukherjee 2018). After a group of researchers in China carried out the first clinical trial to use CRISPR in 2016, U.S. scientists described CRISPR as

a "Sputnik 2.0" (Cyranoski 2016; Davis 2018). For scientists in the United States, the apparent "lead" was due to a more relaxed regulatory environment in China, a position that overlooks China's ability to more readily produce new guidelines and regulations for biotechnology and bioethics (Nie and Pickering 2018). Only three months after the controversy surrounding He Jiankui, China's health ministry passed additional regulations and re-specified the penalties for research misconduct (Cohen and Normille 2020; Cyranoski 2019). In December 2019, He Jiankui took the full fall. He, along with two of his Chinese colleagues were fined and sentenced to prison after an internal investigation concluded that the ethics review documents were faked. As it turned out, manipulating human gametes, zygotes, and embryos for human reproduction was illegal when He's experiments were carried out, and had been since 2003, but the punishment for doing so was unclear. In doing so, China was disciplining an individual who it had invested quite great deal in, He Jiankui had received numerous distinctions and was recruited under Shenzhen's "Talent Peacock Plan" and China's central "Thousand Talents Plan," which are capacity building programs designed to attract elite scientists from around the world to Chinese academic organizations. By making an example of He Jiankui, the Chinese scientific community aimed to restore confidence in their work and signal their ability legislate quickly around emerging technologies. However, as Kehkooi Kee, a genome editing scientist from Tsinghua University, explained, he would now have to go through much more paperwork because of the new regulations and "the industry will develop at a slower pace, […] The government will be more cautious with research funds, and private organizations, such as charities and startups, will be less likely to invest," (Wang and Ting 2019). Echoing the sentiment of a letter signed by over 120 Chinese scientists describing He's experiments as "crazy," Kee expressed his frustration "I don't even want to call him a scientist — he is an irresponsible man," (Wang and Ting 2019).

For both scientists in China and in the United States, the management of the boundary between science and law was crucial to maintaining the moral order of the distinction between somatic and germline editing and re-establishing the legitimacy of measures of self-governance. As Jennifer Doudna and IGI scientist Bruce Conklin stated, "It is essential that this news not detract from the many important clinical efforts to use CRISPR technology to treat and cure disease in adults and in children," and "It is particularly troubling if the recent claims distract attention from the completely valid somatic genome editing," (Langelier 2018). That year, the United States NIH would allocate around $190 million over six years to a Somatic Cell Genome Editing Program to accelerate the development of clinical genome editing (Saha et al. 2021).

4.4. The Banality of Scientific Progress

The CRISPR-babies crisis did in fact distract attention from somatic genome editing, but in doing so normalized most biomedical applications of genome editing. This was in part because, once the crisis was framed and treated as a case of individual misconduct, the systemic pressures to revolutionize science and challenge the consensus of the field are obscured. To borrow from philosopher and political theorist Hannah Arendt (Arendt 1963), scientific progress, for the most part, is incredibly banal. As I described in Chapter 2, the day to do day of undergraduate volunteers, graduate students, and postdocs at the lab bench is tedius, highly routinized, and often stressful. Academic pressures to carry out experiments, manage teams, take courses, publish, move through a career, and succeed socially in the laboratory environment do not leave much room for considering

the moral and social dimensions of one's work. Beyond that, the way deviance in science gets metabolized through misconduct training reproduces Vaughan's thesis regarding the reproduction of practices that go against the broader moral order of society through organizational band-aids. In this section, I examine how existing ethics and professional misconduct trainings effectively constitute a case of the regulatory co-construction of organizational deviance (Hedgecoe 2014).

Understanding how the crisis surrounding He Jiankui's experiments is metabolized as a case of professional misconduct shows how a system of positive deviance, where individuals are rewarded for their breach of social norms, is perpetuated. Harvard University dean George Daley, who had made a strong case in favor of germline editing at the summit, argued "You can't control rogue scientists in any field. But with strongly defined guidelines for responsible professional conduct in place, such ethical violations like those of Dr. He should remain a backwater, because most practitioners will adhere to generally accepted norms. Scientists have a responsibility to come together to articulate professional standards and live by them. One has to raise the bar very high to define what the standards of safety and efficacy are, and what kind of oversight and independent judgment would be required for any approval," (Bergman 2019). So, what does scientific misconduct training actually look like?

I have observed a mandatory lecture on research misconduct three years in a row that is given at UCSF. The first 20min of the course are devoted to repeating how important it is to attend the weekly lectures and sign in for attendance. A teaching assistant carefully monitors the sign-up sheet, as the doctoral and master's students are threatened for signing in for someone else. To introduce the course, in the last lecture I observed in 2019, the instructor quoted the U.S. Congressional Hearings which led to the mandated research misconduct requirements for NIH funded research, "the foundation of public support for science is trust that scientists and research institutions are engaged in the dispassionate search for truth," (n.a. 1993). The instructor's interpretation and re-framing in his explanation illustrate a tension in ethos of science between conformity with scientific professional norms and the drive to push the edge of science. "This is actually how the public views this, and there's much of this which is actually true. Except one little piece here," the instructor uses his laser pointer to circle rapidly around the word "dispassionate" projected on the slide, "and that is we do not expect you to be in a dispassionate search for truth. You are at UCSF, you should be trying to kill it! You should be trying to figure out how to break the rules!" The instructor fumbled, realizing what he just said, "In terms of rules of science, not necessarily rules of ethics. But you should be trying to take hypothesis and turn them on their head you should be passionate about that, and we encourage that, we encourage you to challenge people's authority about how things are done." This division, between science and ethics is one which work in sociology of science has routinely shown to be fiercely ideological.

We can further interpret this in Kuhnian terms: the dialectic between revolutionary science and normal science produces a scientific ethic that diverges from the Weberian ideal of the dispassionate search for truth. Instead, the leading edge of science is advanced by a passionate and brave engagement with epistemic, semantic, and moral uncertainty. Scientists own adoption of the language of Kuhn's theory has led to an accelerated perpetual search for and expectation of more revolutionary tools. When coupled with the ideology of "disruption" that pervades the culture of innovation in the San Francisco Bay Area this contributes to a normative environment were risk taking is favored over conservative experimentation.

The lecture went on to discuss several significant cases of scientific misconduct, each story with their own moral lesson. First, the instructor described the case of Woo Suk Hwang from 2005, a researcher whose team had published results of a study showing they were able to transfer the

nucleus of a somatic cell from a patient into an enucleated oocye,[35] and then harvesting cloned stem cells from the embryo that would develop from this oocyte for research. At the time, this was a breakthrough in the field of reproductive medicine and stem cell research. Hwang became a national hero in South Korea. Turns out, Hwang had forged the evidence in his publications and had used oocytes obtained from his subordinates (Resnik, Shamoo, and Krimsky 2006). Hwang was sentenced to 10 years in prison. This example were used to illustrate the dangers of falsifying data, the dangers of nationalism in science, the consequences leveraging the power relations within the laboratory for personal gain.

The second was the 2010 case of Anil Potti, a cancer researcher at Duke University who fabricated datasets used to support the development of clinical trial to test how patient's genes affect their responsiveness to different cancer treatments and then lied about how many patients were enrolled in the trial during the reporting along with his collaborator and mentor Joseph Nevins. In consequence, Potti entered a voluntary settlement agreement and was merely prevented from applying to future federal funds for a five-year period. Potti continues to practice oncology, but is no longer affiliated with Duke. Nevins, for his part did not receive any major sanctions, even after emails were released that showed that Nevins actively attempted to silence the medical student who blew the whistle. (Xie 2015). The instructor further described how Duke's own administration had been complicit in the cover-up of the case for years. The Duke case was used to illustrate the misuse of federal funds, the dangers of misconduct for patients and the complicity of university officials.

These cases had been the same for the years prior. This time, the instructor added the He Jiankui case. After introducing the experiments, the rationale and setting the context, the instructor set up a discussion activity. As the slide screenshot in Figure X. describes, the set up describes the situation that He's collaborators in the United States experienced leading up to the Hong Kong summit.

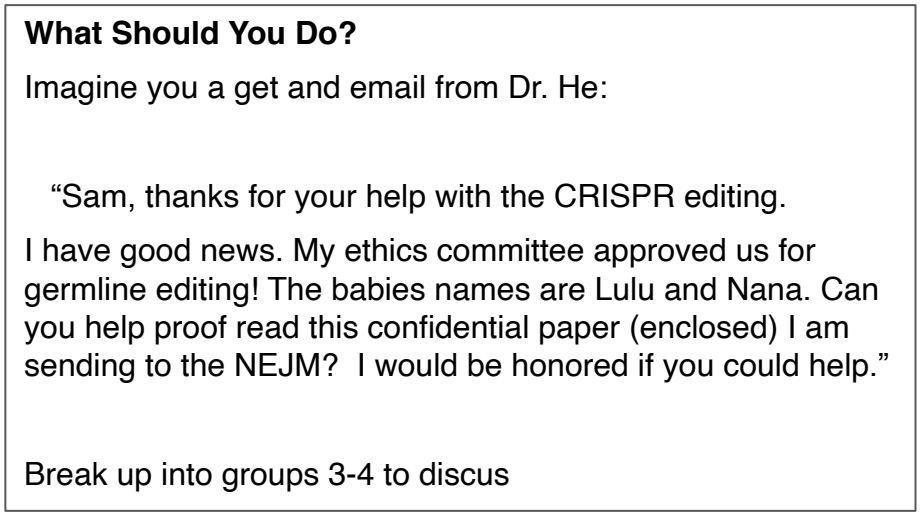

Figure 10. Presentation slide from research misconduct course.

[35] An oocyte is a precursor to an egg cell, an enucleated oocyte is one where the nucleus of the cell has been removed.

We then breakout into small groups to discuss the case. Having just conducted an interview with the IGI postdoctoral fellow who had been in correspondence with Jiankui He and had himself received a copy of the manuscript prepared for the New England Journal of Medicine, I was curious to see how the students' reactions would compare. The postdoc had been extremely distraught as a realization of his complicity in the project – difficulty sleeping, anxiety, and drinking. The students in my group had a hard time understanding how someone could have been in this position in the first place. In an effort to participate, I draw from the recommended actions from the previous cases to make suggestions to my discussion group, "Maybe I would go to the office of research integrity? Or talk to my PI?" We briefly discuss the risks and a few questions come up for the group: if you're PI is already a part of the project, maybe they already know? What jurisdiction does a university office of research integrity have over research done in another country? What were the laws in China anyway? We circle back for a broader group discussion.

The group discussion that ensued illustrates the formation of a moral order where deviance is normalized. One student responded, "I don't think you'd be surprised to get this email. Because you've already been helping." The instructor probes, "But what would you do about it?" "Well depends, because you are already in it, I'm already in it." Another student says, "You want to put it writing to show that you are against it." Another student contends, "From this email you don't have enough evidence to go tattle on someone." Snitches get stiches. The instructor then responds, in agreement, "You are right in your perception that you are involved, even if you just helped with guide design, the perception is going to be that you were involved and that could be very damaging to your career. […] Now you have to cover your tracks." This suggestion drew form Stephen Quake's strategy, which was to reveal to an inquisition by journalists that in his emails he had expressed concern over the consequences of the experiments, despite early encouragement. Porteus had also shown in emails in an internal investigation by Stanford University that he had challenged the idea that Jiankui's experiments could be done safely given the current state of the technology.

These strategies did in fact, "cover their tracks" but also illustrate the deep entanglement of scientific collaboration and deviance. Because scientific work is a deeply collaborative endeavor, its progression depends on moral economies that allow individuals to flexibly explore the boundaries of uncertainty in ways that can deviate from the public facing responsible conduct. Framing cases of deviance as solely the product of individuals whose interests were corrupted, be it by financial interest, competitive pressure, nationalistic fervor, or willful disregard for social norms, conveniently circumvents the systematicity and sociality of these practices. As I described in Chapter 2, the meaningful unit of scientific change, the scientific research program, cannot be reduced to individual interest and the cognitive dimensions of scientific problem choice, experimentation, and explanation are distributed between groups of individuals and their instruments (Fleck 1935; Hacking 1983; Nersessian et al. 2003). For participants in scientific research programs where genome editing tools are merely a piece of the day-to-day grind at the lab bench, recognizing what is a case of misconduct or lapse of research integrity in clouded by the fluctuating ontology, epistemology, morality and semantics of genome editing. Moreover, the broader moral narratives surrounding the applications of CRISPR technology for somatic editing normalize it daily use.

Courses like this one I've observed fall under the policy framework of responsible conduct of research (RCR), which treats individual ethics as a matter of professional training. The institutionalization of RCR in the 1980's and 1990's in the United States across biomedicine and only later in engineering has been a part of the development of the legitimate basis for self-regulation. Acting as an alternative to punitive and reactive models dealing with scientific misconduct, RCR aimed to develop a culture of individual responsibility and commitment to norms

of integrity and virtue (Steneck and Bulger 2007). Empirical assessments of RCR trainings have, for some time, shown that the teaching approach, topics, and measurement of success varies across institutions (Kalichman and Plemmons 2015; Mastroianni and Kahn 1999). Current research into life scientists' perceptions of RCR training suggests that researchers view questions of ethics as questions of compliance and are seen, frankly, as a drag by participating students (Antes et al. 2010; Kalichman 2014; Peiffer, Hugenschmidt, and Laurienti 2011). The limitations of research misconduct and "ethics" trainings are not unknown to scientists and there has been a meaningful push toward reforming ethics education and governance (Anderson 2009; National Academies of Sciences, Engineering, and Medicine 2017c). In one report from the NASEM, this was framed by bioethicists in terms of a distinction between *microethics* and *ethics:* where standard graduate STEM research training attempts to promote a culture of responsibility, professionalism and ethics through mandatory training on integrity, falsification of data, adversarial workplace dynamics, authorship, etc., i.e. the *microethics* of research. On the other hand, discussions of *macroethics* (e.g., impacts on society, issues of equity and justice, disability rights, etc.), have traditionally been left out of life science training (Herkert 2004).

A reliance on a compliance model of social control lies at the heart of the justifications articulated by Stephen Quake regarding the legitimacy of He's institutional review board, and other academic scientists' reliance on the technology transfer offices for ensuring the legitimacy of their partnership with biotechnology start-ups. In an archetypical example of the decoupling of formal routines and their practice as myth and ceremony (Meyer and Rowan 1977), empirical studies have shown that IRBs can diverge widely in their decision-making (Abbott and Grady 2011; Dyrbye et al. 2007; Goldman and Katz 1982; Levine 2001; Stair et al. 2001; Stark 2007, 2011). These divergences pose an increasing challenge to contemporary biomedical research because scientific collaboration networks are diffuse and involve multiple academic and non-academic organizations. a meta-analysis of RCR's effect on ethical decision making suggested, that "RCR instruction may not be as effective as intended and, in fact, may even be harmful," leading to researchers showing more closed off decision-making and leads to less transparency (Antes 2010). Antes and colleagues suggest this may be because either part of what students learn is that ethical situations ruin people's career through sanctions and should therefore be avoided and not discussed, other people are untrustworthy, or after having training, students perceive that they can make decisions without involving others.

In short, RCR training reifies the notion that "sanctions for scientific misconduct are primarily symbolic" (Hesselmann and Reinhart 2021:414). As a recent empirical study of the administrative processes of universities and journals investigating cases of plagiarism, falsification and fabrication in science argues, "the punitiveness found in the scientific community thus seems to be less of a result of individual attitudes or moral inclinations; rather, it emerges as a result of the problems related to making visible actions that are rare and incidental," (Hesselmann and Reinhart 2021:434). By making visible select cases of misconduct and emphasizing that they are rare and the product of individual failures reactions to cases of deviance, like the case of He Jiankui's experiments, serve two mutually supporting ideological functions: on the one hand, they protect the self-governance of science and re-cultivate public trust in community-controlled normative frameworks by re-specifying and affirming the boundary between science and non-science (Gieryn 1983); on the other, they obfuscate the moral ambivalence of scientific progress by reducing the spread of accountability through the networks of collaboration that sustain and perpetuate scientific research programs.

Ch. 5. Conclusion: Towards a Biopolitics of Genome Editing

"I'm going to have to science the shit out this." – Mark Watney (Matt Damon), *The Martian,* 2015

"A rat done bit my sister Nell.
(with Whitey on the moon)
Her face and arms began to swell.
(and Whitey's on the moon)

I can't pay no doctor bill.
(but Whitey's on the moon)
Ten years from now I'll be payin' still.
(while Whitey's on the moon)

The man jus' upped my rent las' night.
('cause Whitey's on the moon)
No hot water, no toilets, no lights.
(but Whitey's on the moon)"

- Excerpt from Gil Scott Heron's *Whitey on the Moon* (1970)

As the lab and I sat around the long table Monday morning in September 2015, arguing over whether strawberry-cream cheese is a legitimate option for bagels, our PI, Samuel Oak, comes in oddly looking both frustrated and excited at the same time, "What did you guys think of the movie *The Martian*?" A few of the folks in the lab had gone to see Ridley Scott's new science fiction film where Matt Damon, a botanist, survives the harsh conditions of the Red Planet by MacGyvering his way around a wrecked station on the desolate surface. Oak explains how if Damon had CRISPR all his problems would have been solved, for example, he could have used a genetically engineered potato that would tolerate low water and poor soil, Damon himself could have been genetically engineered to withstand colder temperatures with a mutation in the *ACTN3* gene. The ethos of the film is captured by the line, "I'm going to have to science the shit out this." The lab continues to imagine and describe applications for CRISPR that would enable space travel. Just four years later, researchers on the International Space Station performed a series of genome-editing experiments with CRISPR to study the corrosive effects of ionizing radiation on human DNA. The hope is that eventually CRISPR might be used to protect astronauts from the effects of radiation so they may venture into longer expeditions into the void (Stahl-Rommel et al. 2021).

Gil Scott Heron's spoken word poem pokes at the absurdity of the will to progress underlying late-stage capitalism. This absurdity is also poked at by Karl Mannheim in *Ideology and Utopia,* for Mannheim the ideology of science is over-determined by the utopias it builds for itself. A utopian ideal is a central driver of scientific inquiry. In STS terms, scientists' ideology are constituted by sociotechnical imaginaries, or visions of the future that simultaneously justify and drive scientific work (Jasanoff 2004). CRISPR, in quite a few ways, is revolutionary to the predominantly white scientists because it is an actualization of the utopias that were first articulated when the molecular basis of heredity, DNA, was characterized in the early 20th century. Outside of the lab, however, genome editing boasts the transformative potential of a general-purpose technology.

This dissertation has been an exercise in exploring how would one study the construction of general-purpose technologies, like electricity or the steam engine, ethnographically. The

transformation of the means of production, i.e. objectified and instrumentalized nature, has been an important object of inquiry in sociology, as exemplified by Karl Marx's technological determinism (Bimber 1990; Mishra 1979) and more recently, Ruha Benjamin's theoretical framework of the New Jim Code (Benjamin 2019). In beginning to explain how the idea and discourse of genome editing technology is being rendered into a durable set of practices that become taken for granted, I contribute to our understanding of the role of technology in mediating the relationship between the production of knowledge and the production of social order. I have here sought to explain how the practice of modifying human DNA with CRISPR technology is being institutionalized, seeking to describe what the work of institutionalization looks like and who carries it out.

I have argued here that scientists have managed to advance genome editing fairly autonomously and with great speed. In Ch. 2, I described how scientists at the forefront of genome editing generated new practices through the management and metabolization of the uncertainty of CRISPR technologies. This is because the structure and content of the research itself shaped how the technology and its application are constructed. In this sense the technology stands in a dynamic relation to the questions scientists sought to answer because the biological mechanisms that made CRISPR work were not completely understood by scientists. At face value, CRISPR tools work differently depending on what you use them for and in what organism. CRISPR departed from its predecessors because of the ease with which genome-editing practices spread across the life sciences with the bureaucratic holds of intellectual property offices temporarily removed by the plasmid repository Addgene. With every plasmid request comes a new research program and a graduate student, research associate or undergraduate student must grind at the lab bench to successfully perform experiments.

While the incentives to share material reagents and best practices through Addgene begins to explain the moral economy of open science, it stands in contradiction with the inclinations that come with the deeply entangled relationship between non-profit academic laboratories and for-profit biotech startups and pharma companies. As a means of production, genome editing has proven to be the technological basis for a global market sized at $5.1 billion in 2020, and by some projections expected to reach $11.2 million in 2025 (Markets and Markets 2020). In Ch. 3, I analyzed the role that academic capitalism plays in the development of the moral economy of genome editing. I show how the imperative to treat diseases and expand the institutional scope of genome editing is moralized in a way that couples market value and clinical/therapeutic value. By making human genome editing normative, the organizations built around CRISPR, like the Innovative Genomics Institute, set in place a set of affective expectations for both the scientists at the lab bench who are committed to contributing to society through science and patients with rare genetic conditions.

These affective expectations are then amplified during public conferences and meetings that do double duty of advertising technical breakthroughs in genome editing and performing public governance. In Ch. 4, I traced the origins of the political basis for expert self-governance in biotechnology and showed the close relation between the governance models that were operationalized in the 1970s in response to the development of rDNA plasmid technology and the deliberations held around CRISPR. I then unravel the formation of the decision-making committees that have producing existing normative recommendations and guidelines for genome editing to show how they helped entrench a moral distinction between somatic and germline editing, where applications of CRISPR to modify the DNA eggs, sperm and embryos in a way that will be passed to down to future generations is seen as requiring greater moral concern and editing other cells in the body is assumed to be morally unproblematic. This distinction has largely inured the practice of modifying DNA and has allowed therapeutic applications of genome editing to expand without

requiring the development of additional regulatory protections. Ultimately, the permissive guidelines developed by expert committees help obscure a culture of moral ambiguity towards the institutional boundaries of genome editing.

As I describe in Ch. 4, in 2018, the outcomes of this moral order brought the genome editing community into a crisis of legitimacy upon the realization that He Jiankui and a team of researchers in Shenzhen had implanted genetically modified embryos in a woman's uterus. I use this case to show how organizational deviance in genome editing emerges because of the mismatch between the normative frameworks of self-regulation and the cultural drivers of scientific progress. Ultimately, the ejection of the Chinese scientist leading the project, He Jiankui, from the field is best understood as the maintenance of the boundary of genome editing to restore legitimacy and insulate the field from the imposition of regulations and laws by state governing bodies.

In this final chapter, I conclude by describing two theoretical takeaways from this analysis, each reflecting a different side of the same phenomenon of institutionalization. On one side, my analysis of the relationship between technological change and scientific progress re-kindles interest in the normative drivers and mechanics of scientific change, the form of revolutionary science in the 21st century. On the other, I here begin to outline the components of a future analysis of the subject of biomedical applications of genome editing, what might be described as the biopolitcs of genome editing.

5.1 The Normative Structure of Scientific Change

By framing scientific change as a case of organizational transformation and the institutionalization of practice, I have incidentally brought back in the structural analyses of science that had their heyday in the mid-twentieth century. These internalist studies are perhaps best represented by the observations of Pierre Bourdieu, Thomas Kuhn, and Robert Merton. In their characterizations, the productive advancement of scientific work was a function of the dynamics and relations of scientists to each other and the practices they develop for evaluating knowledge claims. In arguing that genome-editing scientists shape the institutionalization of CRISPR technology by controlling the terms of discourse and setting the agenda of public deliberation through self-governance, I have described a case of how the autonomy of modern science manifests under the conditions of academic capitalism and transnational networks of scientific work.

My critical and transformative addition to Kuhn's model of scientific research is that in becoming "normal" scientific practices become normative. This relationship between two interconnected cultural processes of normalization and normativisation is deeply symbolic and is not unique to science, but has been localized to the field of medicine since the mid-eighteenth century (Canguilhem 1968; Foucault 1975, 1994, 1995). Normalization is about articulating a moral frame that both makes the practice seem natural or commonplace. In that sense, the postdoc in my lab who described my project as concerned with describing how CRISPR is "becoming boring," is spot on. As genome-editing technologies became ubiquitous throughout laboratories in the life sciences, their revolutionary hype as a laboratory instrument began to wane. For a graduate student in a molecular biology program, for example, it was no longer enough to merely show that you were able to use the CRISPR-Cas9 system to test the function of a particular gene in your cell line of choice as way to obtain a peer-reviewed publication. The bar had been raised. Part of this process accounts for how a practice or concept becomes *unmarked* or cognitively taken for granted through the stabilization of discursive elements (Zerubavel 2018). For the case of genome editing, for example, I have described how metaphorical understandings of the technology become a feature of readymade

accounts of how the CRISPR-Cas9 system works. One particularly effective strategy for rendering a practice normal is to standardize it. Standard protocols and routines that allow practices to be more easily replicated in different experimental situations. Standardization of practice and language, in this sense, is a fundamental feature of the production of a new social institution as terms and behaviors become codified in glossaries, textbooks, step-by-step guides and professional reports (Star and Lampland 2009; Timmermans and Almeling 2009; Timmermans and Epstein 2010).

In order to explain how a practice or concept becomes normative, I have focused on the interplay of the varying value frameworks of academic biomedical research. Rather than identifying an ethical framework based on principles (Merton 1974), I have described the moral economies of both daily laboratory life and the performance of expert decision-making in public conferences and governance bodies. This more intersubjective analysis of the interactions between scientists has pointed me to the affective dimensions and drivers of normalization. While normalization describes a process, 'moral economy' describes the system of affect and emotional commitment that guides behavior. Part of what makes moral economies work, is there is a push and pull between opposing sentiments (Daston 1995), such as between hype and fear, between passion and disinterestedness, between communalism and individual merit. When something is normalized, it becomes articulated with that system (web) of affect and emotion such that people either see something as both normal and normative. While for Merton, lapses in scientific conduct were 'extremely infrequent' (Merton 1957:651), I have here suggested instead that deviance is endemic to cutting-edge science in the 21st century and that a system of positive deviance drives science to push the limits of community consensus. By doing so teams of actors coordinate to challenge how things are done and revolutionize their fields. While this occurs through the coordination of teams and is governed by norms around collaboration and credit attribution, punitive practices make visible cases of individual deviance and corruption to maintain the boundary of legitimacy and authority that preserves the self-governance of science.

Through the careful management of its boundary, scientists are able develop stable relationships between stakeholders in positions of authority. This underscores the point that "the key to institutionalizing a value is to concentrate power in the hands of those who believe in that value," (Stinchcombe 1968:108–12). This suggests a renewed interest in the characterization of scientific subfields as autonomous or heteronomous.

5. 2. Biopolitics and the Institution of Genome Editing

A parallel story here is not about *how* a technology or set of practices is institutionalized, but a story about *what* is being institutionalized. This line of inquiry is motivated, at its core, by the work of Troy Duster. Duster argued that genetic technologies and genetic ways of thinking about health, illness, and human difference have become increasingly ideologically penetrant since the mid-20th century (Duster 1996). Duster's theoretical framework of the prism of heritability, offers a useful analytic for understanding the justifications and moral imperatives behind scientists' efforts to make modifying your DNA and your children's DNA a widespread practice. As I described in Ch. 3 the moral economies of genome editing frame CRISPR as an inherent good. The framing of genome editing as *surgery*, exemplifies this normalization. It first articulates genome editing to medicine by imports a model of pathology that makes certain genetic variants deviations from a healthy standard. The language of surgery connotes the control, precision, and necessity of a medical procedure to *restore* that gene to a healthy state. Clinical genome editing is thus a powerful contributor to projects of normalcy, "a regime of beliefs and practices, emanating from science and medicine, which are

preoccupied with eradicating disability and which prize a typical body," (Frederick 2017). Normalcy projects are part and parcel of the biopolitics of contemporary societies, that is, the system of norms and formal policies aimed at shaping human life (Rose 2001). As Rose described, contemporary biopolitics works through a "rhetoric that celebrates the potential of biomedicine and biotechnology to improve the health, welfare and quality of life of individuals [but] obscures the threat that new biological practices of control will coerce, restrict and even eliminate those whose biological propensities are believed – by doctors, parents or perhaps even by political authorities – to be defective," (Rose 2001:2). Future sociological research is well-positioned to not just understand and observe as has been suggested (Saha et al. 2018), instead sociological work should proactively to dissolve this obscurity (e.g. Benjamin 2016b).

The distinction between somatic and germline editing has already helped inure genome editing as eugenics. The distinction has proven to have enduring impact on how funding priorities are set and has served to dispel opposition to the rapid commercialization of clinical applications of the CRISPR-Cas9 system. While early deliberation over the implications of editing the human germline is critical, these concerns have largely eclipsed the ethics of somatic genome editing. This prioritization has produced a substantial ethical and regulatory vacuum because somatic genome editing is being more widely developed and relates more directly to a majority of biomedical researchers who use the CRISPR system. This has left these applications to be assessed on a case-by-case basis by pre-existing governance bodies such as institutional review boards (IRBs), and the Center for Biologics Evaluation and Research (CBER) of the U.S. Food and Drug Administration (FDA), both of which are limited by their statutory roles. At the same time the moral ambiguity surrounding scientists' responses to the He Jiankui case leave the door open for future germline applications of genome editing tools once the safety and legitimacy of these tools has been established through somatic applications.

To turn to Duster's prism metaphor, beyond its ability to refract the biomedical gaze, the prism has now been sharpened to the point where it can be readily used to intervene at genomic sites of difference. This transformation of the prism has immediate implications for patient communities of rare genetic diseases which have been historically orphaned by biomedicine (Navon 2019). To return to the case of Victoria Gray, which I started with, sickle-cell patients anemia patients have raised the concern that they will bear the burden of risk in experimental treatments for therapies that will ultimately be unaffordable to their communities. The normalization of genome editing also has broader implications as scientists target genes involved in diseases with complex social etiologies like asthma, heart disease, and diabetes. Unless a more diverse set of voices is not included (e.g. patients, their families, nurses, disability justice advocates, health disparities researchers, and scientists in training), then the risk is high that genome editing will reproduce racial health inequities.

Methodological Appendix

There is no one way to study how a new technology is constructed. In part, this is because each technology will impose its own demands on the social scientist as its use, discourse and material constitution will uniquely co-determine the social structures and ideology behind and in front of it. In both an epistemic and ontological sense, a technology in construction is a moving target. Here, I review the methodological strategy that supported the collection of data on the development of CRISPR-Cas9 technology and emphasize the ways in which the epistemic assumptions of participant observation enabled me to follow the target, trace its movement, and shift my own position rapidly in response to where I, and my informants, thought the target would be in the near future.

My introduction to CRISPR-Cas9 began at the first Cold Spring Harbor Laboratories (CSHL) "CRISPR Revolution" meeting in September 2015. At a registration cost of $955, this was by far the most expensive conference I had ever attended and felt like a gamble since I did not know

anyone in the field, nor had I conducted any pilot observations in the Bay Area. In the end, the gamble paid off, as the wave of excitement over this new tool that had swept the conference attendees swept me up as well, as I spoke with the most disciplinarily eclectic cast of characters I had ever seen at a scientific conference. To briefly paint this picture, CSHL, founded in 1890 in Long Island, New York, embodies the eerie feel of a quaint New England village on a scenic hillside next to Oyster Bay off the Long Island Sound, where inside each building are floors of high-tech wet labs and way more basement floors than necessary. After hours of lectures and posters sessions, I conversed in the pub with an unlikely pair, a plant biologist from Saudi Arabia who was using CRISPR to edit tobacco and a developmental biologist who had edited the African clawed frog to study hormones. Along the walls of the pub, hung portraits of prominent affiliates of CSHL, including eugenicist Charles Davenport, who would serve as the director of CSHL where he founded the Eugenics Record Office in 1910-1939. It was this juxtaposition that would fuel my sociological interest. On the one hand, it was the most cross-disciplinary conference I had seen, where a new technology was the focal point of every branch of the Life Sciences, on the other, it was situated in the context of institutions with deep legacies of fueling white supremacist ideology to shape societies from the genes up. Eugenics, or "the E word" as one scientist put it, would rarely come up in my observations.

In part because of my unique positionality at the conference as the only sociologist listed in among the registrants, and as someone who had training in the philosophy of biology and bioethics, I knew I would need a methodology that could account for my own role in the landscape of genome editing. It would also need to be a methodology that was nimble enough to keep up with the shifting target that is genome editing. It was by great fortune that I began this inquiry under the guidance of Michael Burawoy, whose elaboration of the extended case method of participant observation has provided scaffolding for the project. The Manchester School of social anthropology, where the "extended case method" was first articulated, aims to observe and account the discrepancies between a social group's normative principles and their everyday practice in relation to social forces at higher levels of abstraction, like colonialism or capitalism (Gluckman 1961; van Velsen 1979). In this methodological appendix, I expand on how I have adapted the hallmarks of the extended case method: comparison, iterative engagement with theory, and reflexivity. In doing so, this project innovates on traditions in laboratory studies that have tended to follow more situational and inductive practices of data collection (Clarke, Friese, and Washburn 2017; Clarke and Fujimura 1992; Latour and Woolgar 1979). By relying on comparative data from multiple sites, the extended case method can trace decentralized social processes that would otherwise be difficult to reliably observe. The extended case method is additionally well suited for examining the claims outlined by the literature regarding which actors have greater influence over the process of institutionalization because of the method's emphasis on a more abductive interplay between theory and data.

6.1. Triangulating Multi-Level Processes

To understand the relationship between the production of knowledge and the production of social order, I have centered a process-based understanding of science. What this means is not that the social phenomena I analyzed were conceived as linear phenomena with a beginning, middle and end, but that they were the product of actors engaging in practices that meet challenges and develop in relation to multiple levels of complexity. Actors' organizations, networks, histories, and contingent situations mattered to how they engaged in practices of experimentation, collaboration, self-regulation, and conceptual development. Because CRISPR was in continuous re-definition, development, and expansion, I was drawn to theories of institutionalization that stress how social

phenomena are only momentarily stable and rely on routinized structures, internalized myths, and moral economies for their reproduction. To frame the problem of the emergence of genome editing as a problem of institutionalization meant that I would need to capture multi-level data to understand the interplay between those different levels of complexity over time (Harmon et al. 2019). This is where the orientation of the *extended case method*, to "to move from the "micro" to the "macro," (Burawoy 1998:5) comes in and where I align it with the theoretical orientations of work on the microfoundations of institutions (Harmon 2020). Rather than pursuing a middle-range theory, existing theories of the microfoundations of institutions are modeled off the epistemic assumptions of the classical "boat" model of social causation, which draws attention to the individual-level mechanisms that underly broader system-level phenomena.

However, the temporal indeterminacy of institutionalization as a multi-level process generates two empirical problems. The first puzzle that this generated was first pointed out to me by Scott Frickel, when I first described my project, "How will you know when CRISPR has become an institution?" In other words, how does one measure that genome editing practices are stably reproducing across different organizational situations by different actors? From a methodological standpoint, this framing reproduced the ethnographic problem of when to stop. The second problem relates to relationship between units of analysis that exist at different levels of social organization and abstraction, which I return to at the end of this section. To step up to these challenges, I operated under the principle that I could, in principle, never stop conducting participant observation as I would shift according to the developments of genome editing, becoming a perpetual biographer of an ongoing process. To gain traction as I conducted these observations, I would also rely on two well-established heuristics in sociology: comparison and triangulation.

Comparative Ethnography

Throughout my research I conducted three different comparisons. The first was between contemporary genome-editing projects, both within laboratories and between different organizations. The second was temporal, comparing genome editing with recombinant (rDNA) genetic engineering technologies developed in the 1970s and their accompanying practices of decision-making and self-governance. Third, I compared laterally between contemporary innovations with a similar scale of economic transformation, having spent a summer conducting participant observation and developing an interview protocol for inventors and regulators in the field of automated vehicles. These three comparisons helped identify the conditions for case-to-case transfer logic across laboratories and helped generate additional sub-questions for the project.

The first comparison paid off from the gamble at CSHL, as I met the two PI's who would allow me to join their labs among the gaggle of graduate students after their talks at the CSHL meeting: Andrew Nielsen and Samuel Oak. Both PIs were open to my observation and welcomed my participation in lab meetings. Asking only that I keep the technical details of their experiments private and wait until they had published the results of their teams experiments before publishing my own accounts. These observations were largely facilitated by my assignment as the "resident ethnographer" and the apportionment of my own bench space in the lab in one of the labs and as the "in-house sociologist" in the other. The comparison between these two sites was crucial, as the similarities and differences between them generated fertile grounds for tracing how genome editing was being put into practice. At first Nielsen, was unsure of why I would choose two biomedical laboratories, suggesting that I would have maximized my comparison by studying a plant biology lab. However, doing so would have exponentially expanded the reach of my inquiry, as the funding

landscape and history of plant engineering is widely different than biomedicine. With both labs oriented towards biomedical applications of CRISPR, I could better focus my observations and account for the internal heterogeneity of how different diseases require different applications of genome editing tools. While both labs focused on biomedical applications of genome editing, as reviewed in Ch.2 the different orientations of the PIs and structure of their research programs led to different pathways of adoption. Additionally, a crucial distinction was that both were situated in distinct organizational environments in same regional hub, the San Francisco Bay Area. As I indicate throughout, my comparison highlighted the inter-dependence of both labs, as they interacted under the umbrella of the Innovative Genomics Institute and worked together to problem solve and shared materials, know-how, and resources. In this way, I could study the scientific environment of genome editing from distinct vantage points.

This participant observation was carried out from 2015 to 2019. Observations were conducted by following post-docs, graduate students, research assistants and undergraduate volunteers during their day. Most of the recorded observations came from attending weekly laboratory group-meetings and project-specific meetings. Lab meetings are concentrated and routinized sites of interaction and served as a window into the way post-docs and research associates pursued specific parts of the research program as a team. During weekly group-meetings an individual member of the lab would give a power-point presentation on their ongoing work, show results, discuss major challenges, and describe planned future experiments. Each week, a different member of the lab would present. In a few instances, researchers from other laboratories would present their work, often as part of a collaborative opportunity. Lab meetings are also where lab members valuated experimental practices and techniques in at least two ways: the epistemic value of different techniques was debated according to their ease and data output; and clinical value of different applications were assessed according to their contributions to the laboratory's research program and the broader impacts of those techniques in the market.

In addition to observations and interviews in lab, I attended approximately 65 workshops, webinars, and conferences on genome editing. Observations at major conferences included both hearing plenary speakers give talks about the state of their research and poster sessions where I could ask typically younger, presenters about their work. At these sites, scientists went on stage to present not only their work, but also their visions for genome editing as a whole. In a few circumstances, patients' narratives were also put on stage to recount their experiences of their diseases and opportunities for treatment. Two regular workshops self-named the "CRISPR-Users" and "CRISPR-Developers," were particularly informative for situating the two research programs I studied in relation to work in other laboratories. The two groups were originally one group and diverged because differences arose between those who practically wanted to apply the tool in the pursuance of their own research interests and those who were keen to innovate on CRISPR-Cas9 techniques. While the categorical distinction between users and developers quickly falls away in practice, as researchers in both groups must tailor CRISPR-Cas9 to the specific conditions of their research programs, the self-identification of the groups and the questions they raised during the workshops gave me purchase on how different laboratories manage the technical uncertainty of CRISPR and the use-scope of the CRISPR-Cas9 system in biomedical research. Additionally, weekly seminars at IGI offered a continuous stream of presentations from researchers in industry, in different fields (including microbiology and plant biology), and different countries. In addition, I was invited to attend a lab meeting and interview members of a third biomedical lab affiliated with the IGI. This further helped me understand the local position of the Nielsen and Oak labs in IGI.

My choices of sites were guided by both the field, such as what conferences members of the lab were presenting at, as well as by previous theories of scientific change, such as the technical standard setting meetings of professional associations. For larger conferences and smaller elite meetings, I selected formative moments—what Hardy and Maguire (2010) call "field-configuring events"—where I could directly observe individual actors as they attempt to define, assert, and contest genome-editing discourse with each other and their professional communities. To identify additional formative moments outside of the routines and networks of labs in the Bay Area, I followed existing theories of the politics of science (Benjamin 2013; Frickel and Gross 2005; Frickel and Moore 2006) and of processes of standardization (Star and Lampland 2009; Timmermans and Epstein 2010).

Throughout my observations I triangulated my findings with interviews and archival data. These additional streams of data allowed me to identify gaps in my observational schedule and pointed me to additional sites where I might trace the development of guidelines, technical standards, and governance for genome editing. Over the course of this fieldwork, 50 semi-structured and ethnographic interviews were also conducted with members of the lab and experts as a way to deepen my understanding of the projects that post-docs, graduate students and technicians were working on and to probe about their attitudes regarding genome editing and the lab's relationships with funders and industry partners. These interviews helped me understand actors' affective commitments, personal challenges, and aspirations, as well as, their position in their subfields and the norms of their organizations. During these interviews, I asked my senior informants to guide my observations and I invited them to critique my project. This meant I had to be open about what I was trying to understand. For example, one of my PIs urged me to go to Addgene and helped me enter their network. I was also encouraged to obtain data on genome-editing laboratories in Cambridge and Boston. My PIs argued that there I would find a "different culture of science" that was more competitive and business oriented. They then connected me with a colleague who worked at a genome editing start-up so that I could better understand the differences between for-profit ventures and non-profit academic science. Doing so allowed me to better situate my geographically-specific observational data.

I also built an archive of about 880 documents from a wide range of mostly online sources. To immerse myself in scientists' public environments I followed key actors from the field on Twitter, as well as, bioethicists, biohackers, CRISPR biotech companies, more junior presenters from conferences, professional associations, and science journalists. From these I pulled discussion threads that reflected scientists' disagreements, excitement and sharing of key research breakthroughs, biotech spin-offs from academics, as well as general musings and memes about scientific life. I also collected news articles that communicated both general trends in the field, the findings of specific publications, and quotes from interviews with actors in the field. To understand how to interpret scientists' claims in news articles, I included a subset of questions in my interview guide regarding their interactions with journalists. As one scientist explained to me, "There's no way to avoid feeling screwed over. [But] it is our responsibility as publicly funded scientists to communicate our work." I additionally collected clips from science fiction films, documentaries, and television series that brough "genome editing" to the public eye. The other outsiders observing and doing qualitative research alongside me at large CRISPR conferences were novelists, playwriters, film makers and comic book writers looking to add detail and depth to capture the futurism of modifying human DNA. These cultural representations and their fidelity to the actual usage of CRISPR mattered to the scientists I spent time with, as depictions of CRISPR as a biological weapon, such as in *Rampage* (2018) where an albino gorilla, wolf and alligator are mutated into skyscraper destroying monsters, countered the depiction of CRISPR as clinically safe and ethical. Finally, a key subset of these archival data concerns meetings of professional associations

that aimed to establish ethical and technical guidelines. These guidelines were anchors for the process of institutionalization and serve to constrain the terms of debates over the ethical and social implications of modifying human DNA.

Cross-Temporal and Lateral Comparison

In addition to comparing to other research programs within the emerging field of genome editing and across its usage in different biomedical laboratories, I looked to the history of biology to identify similar revolutionary technologies and contemporaneously to identify other technological breakthroughs with similar anticipated economic impact. Historical comparisons helped me better understand the uniqueness of genome editing as a case and to trace the genealogy of the family of practices that constitute genetic engineering in the laboratory. These broader comparisons served as tests of inference, where I could identify the limits of my own analysis and learn from previous scholarship on the construction of novel technologies.

I identified three historical antecedents that were key to understanding the institutionalization of CRISPR: rDNA, PCR, and a family of stem-cell technologies. Recombinant DNA (rDNA) technologies, discussed in Chapter 4, gave rise to genetic engineering as a field and catapulted the biotechnology industry. Previous sociological research on rDNA helped me identify the legacy of these technologies for how university laboratories build partnerships with industry and how biotechnologies have been historically governed in the United States (Krimsky 1982; Owen and Powell 2001; Powell et al. 2005). PCR is a fundamental technology in modern science as it enabled the production of DNA itself, rendering it visible and material for experiments. Like CRISPR, PCR became a fixture of the repertoire of practice in any laboratory. However, PCR did not have as wide a scope of application and was relegated to a black box on the lab bench. Paul Rabinow's anthropological account of the development of PCR and the place of the personalities and egos of individual scientists in its commercialization was an early touchstone as I learned what CRISPR was a case of (Rabinow 1996). Finally, accounts of the stem-cell debates in the United States and the politics of these reproductive technologies served as a model of how the expectations for the clinical power of new biotechnologies are built (Benjamin 2013; Thompson 2013). These comparisons helped me identify path-dependent forces that shaped the conditions for the institutionalization of genome editing. Previous literature, for example, has described mechanisms of resistance to the imposition of regulation from governing bodies, like the enrollment of the NIH into rituals of self-governance, careful maintenance of the boundaries of expertise, and production of an ethical choreography that legitimizes controversial practices.

As a heuristic exercise not reported on in this dissertation, I additionally compared genome editing to automated vehicles (AV) as part of a larger project on the regulation of emergent technologies, *The Capacity Challenge: Governing in an Era of Rapid Scientific, Technological, and Economic Change* (NSF award #1735661). In 2018, I attended the largest AV conference in the United States where engineers, regulators and investors debated the safety, efficacy and regulation of self-driving cars, buses, and freight trucks. These observations were coupled with semi-structured interviews with experts in the field. Like genome editing, AV has transformative potential and its advocates used promissory discourse to build hype around the technology. However, accidents during tests had recently set back the field, as cities tightened the rules for on-road testing. While the response to unintended consequences between the two technologies was similar, i.e. improved technologies will reduce the uncertainty that leads to unintended consequences, the outcomes for each differed. For example, during these observations and interviews we learned that the reach of the Department of

Transportation and its history of collaborating with manufacturers differs from that of the FDA, which acts only through a centralized organization and evaluates projects as an arbiter not as a collaborator. Because of this, AV manufacturers could more flexibly move from state to state depending on how tightly local transportation authorities regulated on-road testing. This lateral comparison helped me better understand what makes clinical biotechnology a unique case of innovation and helped me flesh out the external validity of my findings.

Near-Decomposability of Social Units of Analysis

A key epistemic move in sociological inference is the delimitation of the boundaries of the case and its identification with other similar cases (Ragin and Becker 1992). Because genome editing was still in-formation, I have treated it as a largely a theoretical bound 'case,' rather than a case of a discrete subfield of the life sciences or as a case of a well-bound technology, (Tavory and Timmermans 2009). This insight, in addition to being informed by the extended case method, better reflects the data I was collecting. More than a subfield or technology, "genome editing" was a framework for clustering various practices for modifying DNA under the umbrella of a novel metaphor for directed mutagenesis. However, "frameworks" are not directly observable units of analysis and the processual account I developed here highlights the interplay between individuals, practices, organizations, and communities. Thus, rather than treating the complexity of social phenomena as a hierarchical system, whose parts can be neatly decomposed into units and sub-units, I operated under the assumption the societies are *nearly decomposable* (Simon 1962). This assumption allows for the individual agency of individuals and their interactions to be central, but not reducible, to how the ontology of social structures is understood. For economist Herbert Simon, this means that, "(a) in a nearly decomposable system, the short- run behavior of each of the component subsystems is approximately independent of the short-run behavior of the other components; (b) in the long run, the behavior of any one of the components depends in only an aggregate way on the behavior of the other components," (Simon 1962:74). Given this assumption, the units of analysis for a study of institutionalization following the extended case method must span multiple levels of complexity.

This is where concepts that help encapsulate the interaction between actors, their organizations and their work come into play. For example, in Ch. 2, I re-specified the unit of adoption from the laboratory to a scientific research program. A research program is an articulated set of practices, questions, and research projects that are enacted by a constellation of researchers and experimental tools. In this sense it is a cognitively distributed system (Nersessian et al. 2003) and avoids the hagiographic pitfall of treating scientific innovation as the product of sole actors or sudden moment of discovery (Bourdieu 1975; Hagstrom 1965; Kuhn 1962; Laudan 1978; Robert K. Merton 1957). I have additionally discussed the interplay between different actors and the moral economies that shape their normative environments. The concept of the moral economy similarly accounts for how internalized expectations and emotional forces productively constrain actors' behavior and practice. Because it is an intersubjective unit of analysis, I use it to describe how practices can become morally normative over time and in relation to patterns of alignment that exist outside of the control of individual actors, namely late-stage capitalism. In that sense the concept helps bridge my empirical observations of actors in the field and historical trends, like the commercialization of academic biotechnology.

6.2. Reflexive Positioning

Despite the systematicity these heuristics afforded me, I was regularly intertwined with the phenomena I was observing. Because of the extended case method's focus on reflexivity, this was more of a feature than a bug of the analysis. Beyond my use of previous theories of science and empirical studies of innovation, here I briefly account for my own position as the participant observer and unpack my entanglements in the field.

As a white, Mexican American man in their late twenties, the intersection of my identities in the lab was unique beyond my academic training as a social scientist. The only other Mexican American person in the lab was the dishwasher, with whom my observational schedule seldom overlapped. The two labs where I conducted the bulk of my observations were quite diverse, including Chinese, Chinese American, Eastern European, Filipino, Korean American, Pakistani American, Spanish, Thai, and Vietnamese American graduate students and research assistants. But most of the postdocs in the labs were white men, only two of the twelve postdocs in the labs were women of color. Indeed, Black and Hispanic representation in STEM is durably low (Woolston 2021). Outside of the lab, at conferences, expert committees were more white and more demographically homogeneous. Despite this, I largely attended meetings with little resistance. I believe this is because I present as white and look younger than my age, posing little threat by virtue of my presence. This allowed me to inhabit a pre-existing role in the lab, as more senior scientists, like my PI and some postdocs, came to treat me as a curious and eager mentee.

As a social scientist, I was sometimes co-opted into the process of legitimation on a handful of occasions. For example, I was invited by IGI administrators to participate in a meeting with a potential philanthropic funder who was interested in supporting humanistic and bioethics research on genome editing. More commonly, I participated in lab meetings asking various questions about the reasoning behind experimental techniques and offered suggestions for resolving coordination challenges the lab encountered. For example, I presented on the normative dimensions of collaboration in science, disability justice approaches to genome editing and reported back to the lab from larger conferences and symposia they had not attended. My participation in a monthly bioethics working group also meant that I was actively involved in the production of normative discourse around genome editing. Additionally, once socialized as a member of the lab, I became invested in scientists' careers and the outcomes of their projects.

This growing responsibility was framed explicitly by the principal investigator of my lab in one interview: "If you are invited into someone's house and you see a fire hazard, it is irresponsible not to say anything. Not only that, but it is bad science to wait until the house burns down and then say, 'I know how and why there was a fire.'" The tenor of the fire hazard metaphor wasn't made explicit, but I interpreted this as a call-in to identify potential social and ethical controversy that might impact the lab. While this never materialized into a feedback mechanism for the lab, it hinted at how my place in the lab was understood by scientists in leadership. In the other lab, I would be introduced more as a biographer of the lab's work. Were the PI would routinely explain to any visitors that I was writing a book about him and that I should help write the script for the, now defunct, bio-terror drama *C.R.I.S.P.R.* produced by and starring Jennifer Lopez (Boddy 2016).

Ultimately, I was seen as an asset, adding disciplinary diversity to the PI's already interdisciplinary laboratory. As the PI of another lab put it after Nielsen introduced me as the resident ethnographer in the lab, "I want one!" As IGI, I would come to be involved in the "societal" arm of the organization and was invited to various meetings that they thought I would find interesting and where they could showcase "their" sociologist. While I never received monetary compensation, I was invited to help put together a large NSF grant proposal to study the ethics of genome editing and was hired into a research assistant role for an empirical bioethics project housed

by the IGI. This loose organizational affiliation afforded me access to some closed-door meetings, where lack of security clearance for the building and buy-in from senior scientists would have been prohibitive.

6.3. Limitations and Opportunities

As with any study, there are several limitations based on the methodological choices I've made here and my own positionality. Here, I unpack the empirical questions these limitations entail and identify fertile grounds for future research on the sociology of genome editing and biotechnology more broadly.

First, while my position as a graduate student allowed me to enter the field in the role of a mentee, it meant that senior scientists saw higher-level conversations as not appropriate for my participation. I was thus sometimes excluded from planning meetings with IGI directors, high-profile funders, and university officials based on rank. This meant that my vantage point was sometimes closer to that of someone working at the lab bench, than someone setting the agenda. Because I maintained enough distance from the organization to avoid a potential conflict of interest, some of its inner workings were opaque to me, especially around funding and hiring. Instead, I was only able to study these indirectly through my interviews and during informal discussions with the lab.

Additionally, because my project has focused on the institutionalization of genome editing in biomedicine, I am unable to account for the role of CRISPR's wider set of applications in non-human animals, plants, and microorganisms. These applications also have tremendous economic potential and are quickly leading to changes in the state of the art in agriculture and industrial biotechnology. Leasing Cas9 patents to agricultural giants, in particular, was a priority for universities vying for a stake in the genome editing market. There is ample opportunity to conduct research on the adoption of the CRISPR-Cas9 system in other areas of the life sciences, such as biochemistry, microbial biology, environmental science, and plant biology. The distinct regulatory, disciplinary, and organizational conditions of radically different areas of research will likely show unique ways in which breakthrough technologies are adopted. My project also skirts the question of how applications in these different fields can interact and impact the normalization of CRISPR's application in the field of biomedicine. For example, how might the use of genome-editing tools to engineer mosquitoes that won't carry malaria impact how public health organizations frame clinical genome editing? There is ample opportunity to connect streams of research to develop a more complete picture of CRISPR's normalization across social worlds.

An additional limitation of my study design is that I've conducted research in laboratories in well-funded and elite organizations near the core of Jennifer Doudna's IGI. Most scientists adopting CRISPR-based techniques operate under tighter organizational conditions. Conducting research on research programs in conditions of resource scarcity is likely to show how the relative low-cost of CRISPR technology significantly changes the opportunity for those scientists. As I described, in Chapter 4, global policy asymmetries and global inequality in science funding cannot be disentangled from the institutionalization of genome editing in legal and regulatory bodies. The U.S. based focus of this study not only punts on the development of genome editing guidelines in Europe but ignores CRISPR's impact in the Global South. Furthermore, I have only indirectly examined how biomedical genome-editing research in for-profit biotechnology and pharmaceutical industries shapes genome editing. Comparing how CRISPR technology is used between small regional biotech startups and international pharmaceutical giants will likely reveal additional mechanisms by which

industry actors are able to capture the development of standards of practice and push ahead of academic actors.

Lastly, because of my reliance on observational data, my understanding of broader field and network dynamics is partial. In-depth ethnographic studies can be complemented by bibliometric and network studies that can help map the broader terrain of research being shaped around genome-editing technologies. For example, studying co-authorship on patent applications will likely yield fruitful insights regarding the relationship between the production of knowledge in academic laboratories and the production of technologies, drugs, and devices for the market. As CRISPR-Cas9 continues to become ubiquitous across scientific specialties, in different labs and in different economic sectors altogether, its development as a general-purpose technology is likely to closely follow. This presents an opportunity for tracing broad institutional change and the development of new social structures.

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