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Give chance a chance

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ABSTRACT **How did I get to become a cell biologist? Or, more generally, why do things happen the way they do? The answer provided by the philosopher Democritus and later adopted by Jacques Monod is "everything existing in the universe is the fruit of chance and necessity." While I read Monod's book *Chance and Necessity* as an undergraduate student, little did I appreciate the accuracy of this citation and how much of my scientific trajectory would be guided by chance.**

A CHANCE ENCOUNTER WITH CILIA

Take my interest in primary cilia. Did I intend to study cilia when I started as a postdoctoral fellow with Peter Jackson at Stanford? I did not have a clue what a primary cilium was back in 2003, so the answer would be a categoric no. Back then, I was set on understanding mitotic exit in mammalian cells. Some groundbreaking work had just been published on the role of the Cdc14 phosphatase in triggering exit from mitosis in budding yeast, and the Jackson lab had initiated a molecular analysis of the mammalian Cdc14 orthologues. But while mitotic exit was clearly a fundamental and exciting problem, the mammalian Cdc14 phosphatases simply would not willingly fit in this pathway. Despite repeated efforts and much hard work, I ended up spending the better part of a year going nowhere (at least scientifically). Then, in the summer of 2004, an undergraduate student named Trip Adler came to the Jackson lab, and it became my responsibility to find him a suitable project. For lack of a more creative idea, it was decided that Trip would conduct a yeast two-hybrid screen using the *Xenopus* Cdc14 orthologues as baits. A typical day for Trip would start with a drive to Santa Cruz at 4 am to surf at dawn, followed by a return to the lab at midday to monitor his yeast plates and set up some cultures. Somewhat miraculously, we completed the two-hybrid screen, and one hit was particularly intriguing. Here was a protein named ALMS1, the product of a gene mutated in the hereditary disease Alström syndrome, which is characterized by obesity, retinal degeneration, cardiomyopathy, and kidney anomalies. Even though I had never been scientifically drawn to the study of human diseases, I could not help becoming fascinated by a gene product whose dysfunction would cause such a constellation of symptoms. Still, nothing was known about the molecular activity of ALMS1 or the etiology of Alström syndrome, so I kept puttering along on the (dead-end) Cdc14 track.

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Nonetheless, I kept trying to get my hands on every bit of literature published on this curious disease. And one day things clicked. An article from the *Journal of Pediatrics* (Michaud *et al.*, 1996) made a connection between Alström syndrome and Bardet-Biedl syndrome (BBS), based on the overlap in symptom presentation. Most excitingly, a couple of papers on the localization and possible function of BBS proteins in primary cilia had just been published (Ansley *et al.*, 2003; Blacque *et al.*, 2004; Kim *et al.*, 2004), and primary cilia had just been shown to be essential for Hedgehog signaling in mammals (Huangfu *et al.*, 2003). I was hooked and shifted direction immediately, trying to understand what makes this little organelle so special. Here was an entire organelle about which I and nearly all my colleagues knew nothing; it appeared to be essential for processing a variety of signals and had been linked to several fascinating hereditary disorders. The potential for fundamental as well as medically relevant mechanistic advances was enormous. Framing a project and getting our first results still took a considerable amount of time (we published our discovery of the BBSome, a core complex of BBS proteins, in 2007; Nachury *et al.*, 2007), but I was confident I had now found a rich niche and all the hard work would pay off. I am particularly grateful to the trust given by my

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Abbreviation used: BBS, Bardet-Biedl syndrome.

advisor Peter Jackson, who gave me the freedom to radically change scientific projects during the course of my postdoctoral work.

In hindsight, the odds of tracing such a path from mitotic exit to primary cilia seem astronomically low, and such a trajectory could never have been planned. Thus, for the most part, it is chance that presented me with a novel direction. But necessity was also a key ingredient: studying the role of Cdc14A and B in mitotic exit was unlikely to yield an important publication, even less a faculty position. I was ready for almost any alternative opportunity, and when something exciting materialized, nothing was there to hold me back.

A CHANCE MOVE TO THE HOME OF MITOTIC SPINDLES

Next, take my work on mitotic spindle assembly. Did I intend to work on mitosis or microtubules when starting graduate school? Not for a single second. I joined the lab of Karsten Weis (winner of the 2006 ASCB Early Career Life Scientist Award) with the sole intention of studying the role of the GTPase Ran in nucleocytoplasmic transport (Nachury and Weis, 1999). Yet, at the very same time that Karsten decided to move his lab from the University of California, San Francisco, to Berkeley, where his lab was next to the lab of Rebecca Heald (winner of the 2005 ASCB Women in Cell Biology Junior Award), a string of papers were published that demonstrated that Ran itself functioned in mitotic spindle assembly, the central theme of Rebecca's laboratory. How could the timing of Karsten's move have fitted so perfectly with the link between his research and Rebecca's? Pure unadulterated chance, and a phenomenal opportunity for someone halfway through graduate school to work on one of the most exciting mechanistic problems in cell biology at the time. Figuring out how Ran regulates spindle assembly required some creative approaches to dissect the molecular intermediates between Ran and microtubules. I benefited from the joint expertise of the Weis and Heald labs, which showed me how the whole of a collaborative group is much greater than the sum of the individual parts. Depleting mitotic extracts with Ran itself and subsequently assaying spindle assembly (Nachury *et al.*, 2001) seemed like the most natural experiment to do, yet it is highly unlikely such an experiment would have been done if the Weis and Heald labs had not been so tightly connected.

CHANCE YIELDS A TRANSFORMATIVE HYPOTHESIS

Finally, take our recent discovery of the tubulin acetyltransferase (Shida *et al.*, 2010). My previous studies of the BBSome had primed us to consider a role for the BBSome in tubulin acetylation (Loktev *et al.*, 2008). But how were we to identify the tubulin acetyltransferase? It turned out that the purification of BBSome-associated proteins from retina recovered one single entity, an uncharacterized gene product named C6Orf134. No domains were to be found in C6Orf134, and this BBSome-associated protein was quickly destined for oblivion. Without much hope, I contacted my close collaborator Fernando Bazan (then at Genentech), a wizard at uncovering distant similarities between proteins using secondary structure–guided alignments. Within 5 min, Fernando emailed back that C6Orf134 looked very much like Gcn5, the prototypical histone acetyltransferase! We have since then validated C6Orf134 as the tubulin acetyltransferase, but chance played a major role in the generation of the hypothesis. If I had not known Fernando, none of this work would ever have been initiated.

FINAL THOUGHTS

1. Don't be afraid to fail. Failure is part of the scientific progression. Most importantly, failure is a temporary condition ("giving up is what makes it permanent," in the words of Marilyn vos Savant). Had the project on Cdc14 worked, I would not have been open to explore a fundamentally new direction.

2. Cultivate scientific relationships. "My" best ideas have come from open discussions with some phenomenal colleagues. So these ideas are not really mine, but they are better ideas because of it.

3. Love what you do. Let's face it, you will earn less (a lot less) than your friends who went to law school (or than Trip, who is founder and CEO of Scribd, one of the hottest start-ups of 2009). You will not become famous (Trip has his own Wikipedia page and gets interviewed on NBC, I do not). You are doing science for the fun of it. I deeply cherish (and now mostly reminisce about) those moments of burning intensity when faced with a novel discovery. The times when you look under the microscope and utter, "Oh my god…"

4. Give chance a chance. As trite as this may sound, one has to be prepared for the unexpected. Carefully laid out plans may work out well for some (they certainly help with getting fundable scores on grants), but random events big and small can open up horizons one never envisioned.

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I am forever grateful to my mentors Karsten Weis, Rebecca Heald, and Peter Jackson for giving me the freedom to pursue what might have seem like random directions at the time. Sitting now at the other side of the desk, I can fully appreciate the challenges of providing scientific freedom to lab members, while keeping a coherent research program supported by renewable grants. Thank you all; I could never have made it to where I am now without your generosity and support. Research in the Nachury lab is supported by grants from National Institutes of Health/National Institute of General Medical Science, the March of Dimes, the American Heart Association, a Searle scholar award, a Sloan fellowship, and a Klingenstein fellowship.

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