From Toothpaste to Tumor: How AMG 510 is Revolutionizing Cancer Therapy

INTERVIEW WITH: MARGARET CHU-MOYER

BY: ANA SOFIA BRITO, ELLA KAUFMAN, AND TIANA GAO

Dr. Margaret Chu-Moyer *is a medicinal chemist currently working as the Vice President of Research and Head of Small Molecule Therapeutic Discovery at Amgen. Dr. Chu-Moyer graduated with her bachelors of science in Chemistry from University of California, Berkeley and soon after pursued a PhD in Organic Chemistry from Yale University. Chu-Moyer and her team are currently working on the discovery of various small molecules that can help to inhibit the growth of cancer tumors. During our interview, Dr. Chu-Moyer shared her insight on various aspects of the medicinal chemistry field. Additionally, she described the process she and her team went through during the discovery of her most recent successful inhibitor of the solid tumor KRAS G12C, AMG 510.*

BSJ: You have mentioned that you were fascinated from a young age by how chemistry is seen everywhere in daily life. How do you think your younger self would react to your current work in medicinal chemistry?

MCM: I always loved chemistry, but I did not really understand what chemistry could do in a human-centered field, like medicine. I always thought medicine was more biology. I remember at Berkeley, I took a biology class, but I did not like it. As a result, I did not think there would be any way that I could work in medicine.

Even when I was at Berkeley, I was extremely interested in how medicine works. At the time, I thought, well, since I get medicine from a pharmacy, they must be the ones that are understanding and making the medicines. So, my freshman year I volunteered at the health center with the pharmacy department, and my job was to count the pills into bottles. After doing this for a while, I realized that pharmacies are not responsible for discovering how these medicines work. I realized that the folks studying how those chemical compounds are actually going through and interacting with the biology of the body are called pharmacologists, not pharmacists. But nobody told me when I was a freshman anything about pharmacology, so I did not really know.

Luckily, as a sophomore, I happened to be sitting in an organic chemistry lab, next to a guy who said, "I'm going to do some research over the summer." So I thought I should go try some research too. I asked the professor if I could work in his lab in the summer and once I did that, I got a lot more exposure to the possibilities of organic chemistry. Even while taking the class, there might have been some discussion about natural products and how natural products can be drugs and used as medicines. Penicillin, for example, is a small molecule of organic chemistry and is used in medicine. However, I still had not made the connection at that time, even as a sophomore in college taking organic chemistry.

Then people in the lab started talking about getting a job after graduating in medicinal chemistry. They started to talk a little bit more about what that means; you would use organic chemistry to make molecules that might become medicines. So now, I think I understand what a molecule does when you ingest it into your body to give that medicinal effect much more than when I was in pharmacology..

Once you get into medicinal chemistry you then need to think about how different drugs last in the body and how different drugs should be administered. So now I think, wow, how cool is it that when I get a prescription, as a medicinal chemist, when I open up the

pamphlet and look at the chemical structure, drug-drug interactions, dosing, frequency, and side effects; I understand all of it. So it is a very cool career. I have been in the field for 30 years and it always changes; every time you work on a project for a different potential drug, you learn something new. It is not the same every day, you keep learning.

BSJ: How has your research experience and the relationships you built at Berkeley helped propel you along your career path and prepare you for your current role at Amgen?

MCM: My foundation from Berkeley, I think, really helped me. After Berkeley, my husband was working at a pharmaceutical company. I interviewed at this company and the individual who hired me was a Berkeley postdoc who knew of me as an undergraduate student. He interviewed me while I was still in graduate school and waited six months until I finished school to hire me at Abbott. At Abbott, he taught me how to do research in an industry environment. We wrote a paper together, which he taught me how to do. So, I learned a tremendous amount from him. Of course, I should not have skipped the professor from Berkeley that I mentioned earlier with whom I worked for two and a half years. So, I have had good mentors in my work career which is very important.

Now, I am looking to give back to Berkeley as I am on the Scientific Advisory Board for the College of Chemistry. But I am so grateful for the education that I got at Berkeley. Honestly, I can say that my work in science has always felt so well grounded, because I learned all that as an undergraduate, and was able to build everything on that. So do not underestimate how important your degree is from Berkeley.

BSJ: One of your research group's latest accomplishments is the discovery of the Covalent Inhibitor for KRAS, AMG 510. Why has the KRAS protein, for years, been so difficult to control? What about it, structurally or chemically has made it such a pinnacle of cancer advancement and cell proliferation?

MCM: This is very dear to me and close to my heart. I will end this part with a patient's story, because obviously, what is important are the patients who benefit from this therapeutic. KRAS is interesting in the sense that probably in the 80s, it was already known that it was the primary oncogene that made tumors grow. That was 40 years ago. People wanted to drug KRAS because they called it the master regulator. When it is on, it makes cells grow, and when it is off, the cells stop growing. Your cells are always growing and dying, and KRAS does this for every cell in your body. But, when there is a mutation, it gets stuck in the on position—that is how tumors grow. The cells keep growing and you get a bigger tumor. For a small molecule to work, it needs to be able to bind to KRAS. KRAS, for many years, was thought to be undruggable because it was pretty smooth. There were no crevices, no place for a molecule to stick itself into. People tried for a long time but were not able to drug KRAS. Around 2012 or 2013, there was some work by a professor at UCSF, who was able to show that there was actually a little pocket in KRAS.

You do not see it in the crystal structure normally, but if you have a molecule in there, you can see it. Think of playdough. If you put your thumbprint in it, there is a pocket. The same with KRAS. If you get a small molecule to go in there, it will make that divot. This UCSF professor published that, but we were already working on it. However, we cannot publish because it is competitive.

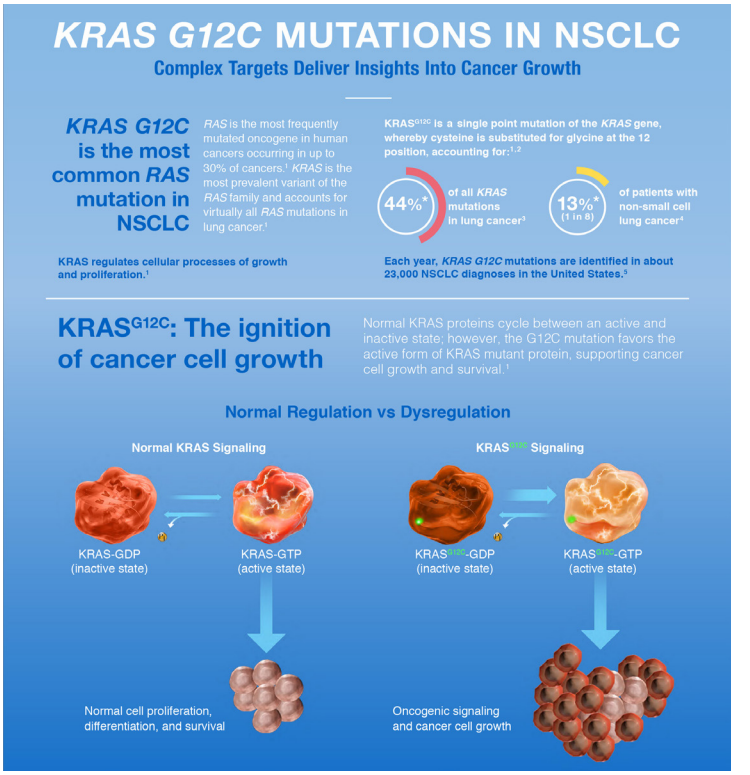

Figure 1: The KRAS gene mutates into KRAS G12C, supporting cell proliferation. KRAS G12C is a single-point mutation of the KRAS gene, in which the amino acid cysteine is substituted for glycine at the 12 position. The RAS gene family is the most frequently mutated oncogenes (mutated genes) in human cancers, and KRAS is the most prevalent variant, appearing commonly in solid tumors. KRAS mutations disproportionately affect patients with lung cancer.

Now, the question was if you could bind to the KRAS protein without being toxic. Because, if you have a nucleophile (in this case, the KRAS protein) in your body and you bind to it, similar to a cysteine residue, the concern is that it will become a hazard in your body. It is highly reactive and it alkylates everything within your body. This led to side effects seen with initial KRAS drugs such as rashes. So no one believed that would be feasible. However, at this period, it was beginning to become achievable as our understanding of chemistry and technology was expanding, allowing us to control the reactivity of these electrophiles. So they would only interact with the nucleophile you intended. This was a major scientific breakthrough.

We researched this for some time. Then, when we finally announced that we had a development, around 2019, we disclosed that we had finished our initial clinical trial. Surprisingly, we observed a reaction in cancer patients who had this particular KRAS mutation. So instead of glycine at position 12, which is the standard, individuals with the cysteine mutation at that position have cancer. This cysteine residue is what our molecule binds to, effectively deactivating it. As a result, tumors do not grow. In fact, they diminish. So, when we first shared our findings in 2019, it indicated that we had tested patients with the G12C mutation. These treatments are not for every patient; they must have the mutation for it to be effective. This is known as targeted therapy. Then, by 2021, we received FDA approval in May. From the time we first synthesized the molecule to its approval, it took just over four years, which is half the usual duration. Not only was the target initially deemed unattainable, but we also accomplished this in a relatively short time frame.

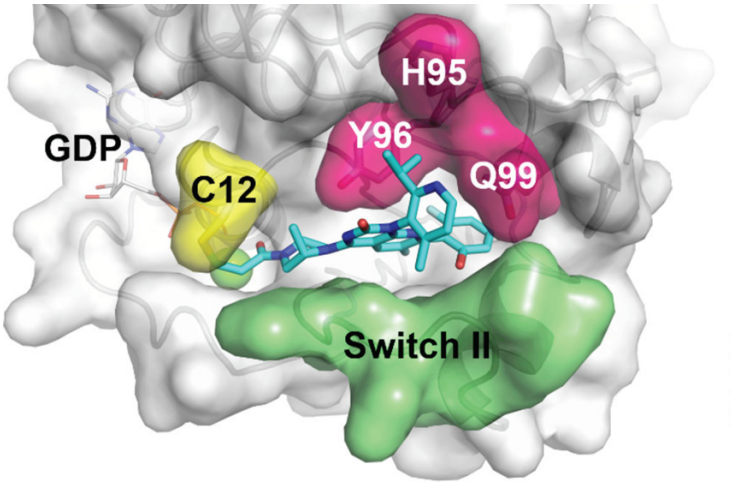

Figure 2: AMG 510 inhibitor binding model in the KRAS G12C protein. The Inhibitor AMG 510 engages the amino acids (H95/Y96/Q99) pocket (shown in magenta) and the Switch II protein pocket (shown in green) of KRAS G12C. The mutated gene is found in solid tumors and targets the substituted cysteine-12 amino acid (shown in yellow), permanently locking the protein in an inactive state and preventing further cell signaling.

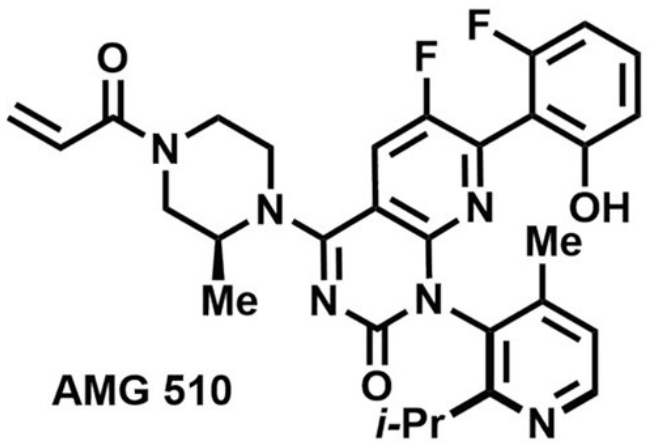

Figure 3: The AMG 510 inhibitor molecular structure. AMG 510 is a small molecule inhibitor that minimizes the negative impact on the normal cells of cancer patients. It offers a bright outlook for patients diagnosed with KRAS gene-mutated solid tumors who are faced with limited targeted treatment options.

Now, I will discuss the patients. This is the most rewarding aspect of our work, despite the challenges. My team comprised medicinal chemists who determined how to design the molecule to achieve the outcomes I just described. So, during the clinical trials, a lady from Amgen approached me. She was coming up to me crying, saying, "it's awesome that we are seeing these good results in phase one. My mom had lung cancer. And she had KRAS-G12C, lung cancer, but this was 10 years ago. Then, there was nothing for her because nobody had drugged it yet. She has passed now, but maybe other patients will have a chance with your drug." That was the first time I heard about someone knowing someone with this cancer.

Then the drug was approved on May 28, 2021. I had a message from a colleague I had not heard from in a long, long time. He says, "Margaret, I just want to tell you that my mom was diagnosed with KRAS-G12C, lung cancer, about a month ago. She's been on chemo, but the doctor had said once this is approved, he was going to change her to this therapeutic. I cannot tell you how much this means to us. It gives my family hope."

I have a second story from a close friend of mine who is a medicinal chemist. We grew up in the industry together; she worked at a different company than me, but we have known each other for a long time. Last year, she emailed me and told me her dad had lung cancer. In the beginning, when he was tested, he had no mutations. He was taking standard therapy. The tumors were growing, he could hardly breathe and could not go to the store. As it was growing, they took another tissue sample and found it was KRAS-G12C after about eight months of being on another therapy. She said she was going to the store with him to get the medicine, and he was going to start the new therapeutic. That was last September. They were not able to celebrate his birthday last year due to the pandemic, but they hoped to celebrate Christmas. Just before Christmas, she said her dad was doing better. He could breathe and could go to the grocery store. He was able to see his birthday. He was able then to see his first great-granddaughter be born in the spring of this year. And he is still alive.

Those are the things we kind of live for. That is why we do the hard work that we do. It is super hard to invent these medicines because your body does not want this foreign thing in itself; it does everything possible to get rid of it. You have to trick your body to keep it in there for a day. We have these tricks to change the molecule so that it will not get degraded by your body, so it gets stuck there. We have to do a lot of balancing acts to make these molecules do what we want them to do.

"It is super hard to invent these medicines because your body does not want this foreign thing in itself; it does everything possible to get rid of it."

That is what medicinal chemists do.

BSJ: What are the largest obstacles that AMG510 faces before it can obtain FDA approval and be available for public use?

MCM: I attempted to describe how hard it was to get to the molecule. We are approaching this on a research scale, so we are making a small quantity to be tested. If you want to deliver it to patients, however, you have to make it in kilograms, and thus scaling magnitude is quite hard to do. For instance, you can make dinner for yourself differently than you make it for 100 or 1000 people. Thus, scaling the process up was very challenging, and it was done during COVID. We had different kinds of chemists, who acted as process chemists, rather than medicinal chemists, figuring out how to make kilos of the molecule. They modified the chemistry to make it on scale and manufacturable. Like cooking, it takes an hour for a cake to cook, a process that cannot be expedited,

just as you cannot hurry chemistry. Our chemists did an excellent job of following these procedures. They were also able to alter several environmentally unfriendly reagents in the synthesis, thus improving the green chemistry status of the reactions. Our chemists received a Green Chemistry award for their excellent work.

Our team focused on facilitating the scaling-up process. In an attempt to pick the most accurate doses, we ran many clinical trials. It was crucial that the dose be designed to catch the tumor in an earlier phase so that the treatment has an effect. The clinical team undergoes an extensive approval process as well. It includes filing paperwork with the FDA and was initially approved in the US. It is now approved in 50 countries. On May 28, 2020, the day that it was approved, it was Memorial Day, and we were challenged with pharmacy closings. It was extremely gratifying to be able to deliver everything to patients as quickly as we could. In 2020, it was approved for lung cancer, and we wanted it to be approved for colorectal and pancreatic cancer as well.

A project I am very excited about is working with other mutations at the 12 position. Other common cancer-causing mutations, such as aspartic acid, are common as well. The cancer research community began to investigate the applications of our work to other mutations. AMG10 would not work on other mutations, though, because cysteine is doing a Michael chem reaction, but aspartic acid does not.

Now that we have learned some things working with KRAS-G12C, we have been working on what we call G12X. It is the next step in targeted cancer research because the patient population is even bigger. If we know that we can work on position 12, there are other similar mutations, like 61 or 13. G12X can address many of these different mutations. So you have just opened up the aperture for a new medicine.

"There are still an abundance of unknowns, and thus there is a need for bright, young scientists in cancer research."

I am super excited about this program because more cancer patients can be helped but with a different molecule. So this is an even more challenging prospect. But we continue to learn.

BSJ: How do you see the future of cancer research evolving?

MCM: If you are interested in cancer research, there is so much happening. When people talk about curing cancer, there are certain areas like blood cancers where sometimes you can get to a cure where people go into remission, and they do not come back out of remission. But in general, we do not know how to cure cancer, and most of the time you are simply trying to extend life. However, cancer is really smart and mutates frequently. If you start treating somebody, and it works for a while, it eventually will not work anymore. So how do we get around that? A cure is where we want to be, but I think that is years away. What we can do now are targeted therapies, which do not typically have extreme side effects.

In addition, there is a lot of immunotherapy for cancer now where mostly antibodies are conscripting the immune system to identify and kill a foreign cell. This approach has been very popular in the oncology field. What we are trying to do is combine targeted therapy and immunotherapy for a stronger effect. There are still an

IMAGE REFERENCES

1. Figure 1: Amgen. (2019). KRAS G12C Mutations Diagram. Amgen. https://www.amgen.com/newsroom/press-releases/2019/10/the-discovery-of-amgens-novel-investigational-krasg12c-inhibitor-amg-510-published-in-nature.
2. Figures 2 and 3: American Medical Society. (2019). Comparison of the GDP-KRASG12C binding modes. Journal of Medical Chemistry. https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b01180#