



After the Fact | From Lab to Life: Making Cancer Treatment Less Toxic

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TRANSCRIPT

Ziyang Zhang, assistant professor of chemistry, University of California, Berkeley: We know cancer is driven by a certain protein, a certain gene, and if we can shut it down, we can shut down cancer. And then you ask, “We should talk to the chemist. Why don’t they just find a molecule?” Now, it turns out, “why don’t you just find a molecule?” is not that simple to answer.

Gabriela Domenzain, host, “After the Fact” podcast: Welcome to “After the Fact.” For The Pew Charitable Trusts, I’m Gabriela Domenzain. I’m a former journalist, a communications manager, and I am one of the newest hosts of the podcast.

The American Cancer Society projects that 2.1 million people in the United States will be diagnosed with cancer in 2026. But research shows the cancer mortality rate declined by 34% from 1991 to 2023, averting approximately 4.8 million deaths.

But even with the advancements in treatment and reducing deaths, a cancer diagnosis can be devastating.

I spoke to one of the scientists who is working to find new treatment methods. Ziyang Zhang is an assistant professor at UC Berkeley in the Department of Chemistry. He’s also a 2023 Pew-Stewart Scholar for Cancer Research.

His lab is producing cutting-edge research that will help develop more effective therapies and avoid damaging healthy cells—and it all starts at the chemical level.

Gabriela Domenzain: Thank you so much for being here, Ziyang. So, I’m going to start with the chemistry of this all. Tell me a little bit about the work that you do in your lab.

Ziyang Zhang: In my lab, we use chemistry as our primary tool to interrogate biology. That might sound a little too abstract, but really, one possible outcome is we may find a new molecule that could stop a disease. That has been one of the most intriguing and exciting goals of my research.



Gabriela Domenzain: So what makes cancer, cancer?

Ziyang Zhang: People have been asking this question for decades, and we now know cancer is cells from ourselves that, at some point, received instructions to grow in an uncontrolled way. We know in some extreme cases, it only takes small changes to the DNA inside a cell. And then it expands, it grows into a bigger cell chunk, and then it grows into a bigger mass, and then it grows into a tumor.

It's more complicated than I described, but the point I'm trying to make is it's a series of genetic changes inside the cell that gives a perfectly normal cell the license to become something we call cancer. It's not always one thing, and some people will say cancer is not a single disease, it's a group of thousands, or even more, diseases.

Gabriela Domenzain: What initially sparked your interest in chemistry?

Ziyang Zhang: I grew up in China in the 1990s. I was quite a nerdy kid. But it wasn't until high school that chemistry came into the curriculum. And to be honest, I hated it at the beginning because it was a lot about memorization than to understand why things happen. I really hated textbook chemistry, but I loved my teacher because he's one of those people who would say, "OK, this is what you need to know from the textbook, but let me show you something cool." And he would actually bring experimental kits into the classroom.

But the turning moment for me was when I realized that chemistry is about creating a molecule. And a lot of it is like solving a puzzle. So, that part of chemistry really piqued my interest. And that's how I got started. There is also a sub-direction in chemistry known as total synthesis, whose goal is to make molecules that occur in nature but can only be isolated in tiny, tiny amounts. So we know these molecules are important, they have very fancy structures, but we don't know how to make them.

And then I realized there seems to be a gap between the people who can make molecules and the people who are searching for molecules that can do a particular thing. And that's when I got introduced to this idea of using chemistry to kill cancer in a way that is selective and effective. And I applied for an undergraduate research position and I started doing experiments.

Gabriela Domenzain: So, you went to the University of Peking and then continued your studies in the United States.



Ziyang Zhang: Very luckily, I was offered a position at Harvard University as a grad student. And that really broadened my skill set, but I also got to experience a different culture.

Gabriela Domenzain: Had you been to the United States before?

Ziyang Zhang: No, not at all.

Gabriela Domenzain: What's the first thing you remember about it?

Ziyang Zhang: One thing I realized is that people have more in common than differences. It's a human tendency to want to ask, you know, what's different or what do you not agree upon. But in the department, we're just a bunch of grad students who are all interested in science, and we can always communicate with chemistry.

Gabriela Domenzain: Right now, what are the ways in which we fight cancer—whether they're natural, by your own body, or different kinds of therapies—and how are these methods working together and evolving?

Ziyang Zhang: Cancer is driven by a certain protein or a certain gene. We know it's important. And if we can shut it down, we can shut down cancer.

And then you ask, "We should talk to the chemist. Why don't they just find a molecule?" It turns out "why don't you just find a molecule?" is not that simple a question to answer. It requires the ability to make new molecules but also requires the ability of knowing what molecules to make. So when these things come together, it is chemistry that gives us the tools.

You mentioned that the body fights cancer, it's true. Our immune system helps us fight cancer by eliminating them at very, very early stages.

These days, you know, a lot of it eventually becomes diagnosed cancer, and then the patient has to undergo some sort of therapy. I think that part is still important because when it becomes so prominent that it is detected, and, in a way, it's kind of a last resort if the body can't fight it.

Gabriela Domenzain: You've said that there are good therapies, bad ones, and also the best ones. What sets these kinds of therapies apart, in your opinion?



Ziyang Zhang: Yeah, the best ones don't cause any side effect, eliminate the cancer, and perhaps teaches your body to prevent the cancer from coming back again. I don't think we have anything that's even close to that yet, but that would be the best drug.

And a good drug would be something you can give to a cancer patient that shrinks a tumor, makes the patient live better, and extends their expected lifespan. And I think that if we can come up with things like this, it would directly lead to patient benefit.

As for bad therapies, I can't actually come up with any examples, because looking back in history, you can always say, "Oh, I can't believe that drug even got approved," but maybe that's the best thing they had at the time.

Gabriela Domenzain: Speaking of the therapy, my parents were doctors, so I was around all kinds of talk about chemotherapy. My mother specialized in breast cancer, and I heard about it all the time. And it's often said that the cure is worse than the disease. Can you explain why chemotherapy is so harsh and causes all kinds of side effects, and possible diseases in the future?

Ziyang Zhang: Full disclosure, I'm not a physician, so your parents probably know more than I do in this field. But from a chemical standpoint, many drugs that developed in the early years of cancer therapy were actually derived from extremely toxic molecules.

A class of drugs derived from the same chemistry as mustard gas, which is a chemical weapon. It was some chemical effort that really tamed this type of molecule to a level that's safe enough to use as a therapy that enabled some of the early cancer chemotherapies.

They do kill cancer cells, but they also kill normal cells—most prominently many blood cells. That is a big source of the bad reputation of chemotherapy. And now we can find molecules that are more selective for the bad cancer cells.

Gabriela Domenzain: OK, you just mentioned something that I've never heard before. Chemotherapy is like mustard gas, or comes from mustard gas? Talk to me more about this.

Ziyang Zhang: It's fascinating to think about, but it's true. There are molecules known as mustins, these have the same chemistry, which are present in mustard gas. And the rationale is that if the mustard gas chemistry can do something to cells if we use just



use them at the right dose, then perhaps these can kill cancer too. And these molecules probably do more damage than is necessary for treating cancer, but in the 1950s and 1960s, that's what we had.

Gabriela Domenzain: The fact that a weapon of war was used to save lives is fascinating.

Ziyang Zhang: Yes—it's paradoxical, right?

Gabriela Domenzain: Exactly. Ziyang, let's go into precision therapeutics a little bit more. How do they provide better treatment for patients?

Ziyang Zhang: The solution, in my opinion, is to really think about what makes cancer, cancer. And if you understand that, can we stop exactly that? So, at a very high level, a precision cancer drug is just a drug that only kills cancer but nothing else. And cancer actually comes from normal cells, so this is a really difficult job to do, right? So we've been trying very hard to find ways that can kill cancer better, but ideally, we would be killing cancer only.

Gabriela Domenzain: That's interesting because chemotherapy attacks all the cells that are reproducing quickly, which is why we lose our hair and mucous linings get dry. So, precision therapy would be: Yes, we're attacking those cells, but only certain ones, so that you don't have all of these side effects?

Ziyang Zhang: Yes. Cells proliferate for different reasons. The instructions given to the cell to grow actually can originate from different things, depending on what these cells are. And for cancer cells, in many cases, we know what they are. So, once we understand what the bad players are, we can say, let's just stop that. Stop the instruction for cancer, but not the instructions for others.

Gabriela Domenzain: Could more research help on the prevention side of cancer?

Ziyang Zhang: Absolutely. Absolutely. I think preventing cancer is definitely a better approach in many ways. And a lot of it has to do with lifestyle changes.

Another exciting area is vaccines. And we know that for a type of vaccine known as HPV vaccines, it has been extremely transformative in cancer prevention in women, and that prevents a certain type of virus-induced cancer.



The science is extremely sound, and we have clear data showing that it works.

Gabriela Domenzain: Let's talk a little bit about what you think the most impactful finding or moments in your career has been.

Ziyang Zhang: Since we're talking about cancer, I would say it's about this oncogene called K-RAS G12D. We have known that it's a potent cancer driver, but in 2019, there was no therapy against this mutation.

I was able to get inspiration from nature—the molecules made by nature. And I borrowed the chemistry from a natural product called novolactone and used that to design a compound that can react with this oncogene. That led to the direct inhibition of its function.

So, we can take the compound I made, treat cancer cells with it, and we can see that the cancer cells stopped growing, and, over a few days, die in the dish. And we can do more nerdy investigations looking at the signals that these oncoproteins are trying to send to the cell, and we see the signals are gone.

I would say for me, as a chemist, that's a very satisfying moment because it really started with asking how these natural products work, in a chemical way. We can learn this lesson from nature but integrate it with some of the newest discoveries—but now we can target this new mutant.

In the end, chemically, it was very simple, but if you go through this logical thinking, you would say, "We should do that." But why didn't we do it? Because, you know, it's about the right timing, having the right realization, and doing the science. So, I was very excited about the finding.

Gabriela Domenzain: You brought it to life and made it something that could help other people.

Ziyang Zhang: Yeah, we're still very excited to see if this could eventually translate to patient benefit. But yes, that was the beginning of the purpose, and now we are coming back to it.

So, if you ask me, I say chemistry is a big part of the solution. It's going to be.



Gabriela Domenzain: If you had a magic wand, Ziyang, what would you accomplish in your lab?

Ziyang Zhang: If I could name one thing I would like to eventually do, is to come up with a molecule that eventually becomes an approved drug that helps patients.

Gabriela Domenzain: Do you think it's possible?

Ziyang Zhang: Definitely.

Gabriela Domenzain: Thanks for listening. You can read more about Ziyang and his work at pew.org/afterthefact. There you can also read a [recent article he wrote](#) in Pew's *Trend* Magazine. If you have questions or feedback you'd like to share, you can write us at podcasts@pewtrusts.org, and you can also leave us a review wherever you listen to podcasts. For The Pew Charitable Trusts, I'm Gabriela Domenzain, and this is "After the Fact."