Science Will Win Podcast
Season 5
Episode 3 Transcript

Jen: We have a saying that's, we say time is life and, uh, we really do believe that we need to work with urgency to move things forward. It's just hard work and good science. And so, I hope people will engage with us and learn about what we do because we're just people who really want to make great medicine.

[Transition into Theme Song]

RAVEN: Welcome back to Science Will Win. I'm your co-host Dr. Raven Baxter aka "Raven the Science Maven." Here with my co-host and partner—

RON: Dr. Ron Gamble.

RAVEN: And we're back today to cover a topic that's near and dear to my heart as a molecular biologist. It's time to get into molecular glues!

[Theme music ends]

RON: So we're talking about like, sticky glue, like super glue?

RAVEN: Well, so we *are* talking about molecules that stick proteins together, right? Which maybe doesn't *sound* that exciting. But, guys, trust me when I say that this is a big, big deal when it comes to treating illnesses like cancer and potentially a whole bunch of other cool applications.

RON: And can you tell us whyyyyyyy?

RAVEN: I mean, you know I would *looooooove* to. Let's start with a metaphor. Imagine you're at a speed dating event.

RON: But I'm definitely a taken man!

RAVEN: Yes you are. But this is just for the analogy! So at this speed dating event, let's say it's at a swanky bar with dozens of people milling around. They got name tags on. You're spending maybe 5 to ten minutes bopping from table to table. And you're having a lot of small talk. Right a lot of "get to know you" conversations. And you're meeting all

kinds of different people. An accountant. A mortician. A snake charmer. People you might never encounter in your day to day life.

And a lot of them for you…aren't matches. Not your type. A lot of people just don't click. But at the end of the *night*, you see a few newly formed couples leaving together. Couples that you'd think would never in a million years have gotten together in any other way.

RON: So I get *charmed* by the snake charmer. Hehe.

RAVEN: Exactly! You and the snake charmer are so different, but speed dating brought you together. And that's kind of like what molecular glues are doing with the proteins in your cells.

RON: They're sticking them together?

RAVEN: Yeah, and making something happen that wouldn't happen otherwise in the body.

RON: And I know you used to work with molecular glues. So you've got extra expertise here. When we think about making two proteins or enzymes stick together—why is that important? What can scientists do with that?

RAVEN: I mean it's really exciting to be able to manipulate proteins and get them to interact with each other. Proteins are like these little machines in your body that do work, and it's a very intricate system. There's a lot of understanding that needs to be developed to be able to use and even create molecular glues.

So, there's two basic categories that scientists have sorted molecular glues into, and these categories are based on how these molecular glues affect protein-protein interactions in the body.

First, let's talk about Type I molecular glues. This category of molecular glues induce NON-NATIVE protein-protein interactions. So this can mean forcing an interaction between two proteins that wouldn't normally interact. And that takes us right back to that speed dating analogy, with you going home with the snake charmer. In a million years, we wouldn't expect that.

This first category of molecular glues might also be used to block a protein's normal activity in the cell, stopping it from carrying out its typical biological function.

Why would we want to do this? Well, let's say you've had a kidney transplant, and your doctor is worried about your body rejecting the new organ. So they might prescribe a drug intended to inhibit the activity of mTOR—a protein involved in a whole bunch of cellular processes—cell growth, protein synthesis, transcription—you name it. It's a very, very, very busy protein.

So by inhibiting this protein's function, you can also inhibit the body's normal response to reject a new organ after a transplant. So that's really useful to be able to do.

RON: I'm guessing there's a Type II category as well?

RAVEN: Yep!

Type II molecular glues work with existing NATIVE interactions between proteins to ENHANCE their function or PREVENT them from being inhibited.

An example for this would be drugs that bind to the protein cereblon, reprogramming it to help get rid of the proteins responsible for causing/spreading cancer. That's a process we'll talk more about in a second.

RON: Okay, so for the test—there's two main categories of molecular glues. But they're both involved in protein-protein interactions. And we can either enhance or inhibit existing interactions or create novel interactions. Am I keeping up?

RAVEN: Like you always do! And there are so many potential applications for molecular glues in therapeutics. Targeting autoimmune disorders, inflammatory conditions, neurodegenerative diseases.

RON: Woah. That's a lot to unpack.

RAVEN: Yeah, I could literally talk for hours about molecular glues. I love them so much. But I think it would help to narrow the focus a little bit now.

In drug development, one of the earliest areas of innovation tends to be oncology—finding and testing novel treatments for cancer. And molecular glues have been really exciting for researchers in this field. We sat down with Jennifer LaFontaine, the head of oncology medicinal chemistry at Pfizer. She's gonna help walk us through the cellular processes that scientists are using to target cancer-causing proteins.

Jen: One of the most, um, common ways that we think about molecular glues as molecular glue degraders, and what that means is we'll bring in another protein that will tag that rogue protein and, and tell the body, eliminate that rogue protein, degrade it. It allows us to improve cancer outcomes.

RAVEN: And this is a different approach to fighting diseases like cancer than, say, older, much more widely available and used treatments like chemotherapy.

Jen: So when we think about chemotherapy, chemotherapy works because it's generally toxic to dividing cells, but as we know, all cells divide, it's just a matter of the rate at which they divide. And for a cancer cell, they're dividing more quickly. And so you're kind of taking advantage of the kinetics of that, right? If they're dividing more quickly, you're going to be able to stop that with something that targets that.

RAVEN: But unfortunately, many other cells in the body are also dividing quickly. For example, the cells in the gut turn over relatively quickly, too.

RON: So chemotherapy drugs can end up targeting non-cancer cells, too. Which isn't ideal.

RAVEN: Right**.** And things can get really out of whack with the body. But with molecular glues, it's a whole new story.

Jen: Our approach is completely different. We're not just targeting dividing cells, we're targeting specifically mechanisms that drive tumors, that drive cancer cells.

RAVEN: Molecular glues offer a much more targeted approach.

RON: Sounds like the difference between painting a whole room in big strokes with a huge roller brush versus working on a small canvas using little, detailed strokes with a tiny round brush.

RAVEN: Right! But getting this targeted isn't easy!

Jen: So one of the biggest challenges with designing molecular glues and specifically molecular glue degraders, is that you're leveraging a protein that interacts with many proteins throughout the body to tag them for degradation. So to get a specific interaction with just those two proteins can be challenging. And oftentimes we start from a starting point that's not very selective, and we have to

do a lot of optimization and work to try to weed out any other interactions that would be unproductive or harmful and just have that one protein ideally tagged for degradation. And so that's where the challenge comes in.

RAVEN: If the cancer-causing protein you're trying to degrade is a locked door, you don't want your molecular glue to be a skeleton key—something that could open *any* other locked door. You want to create a key that unlocks that one specific door to get the desired outcome.

RON: Which in this case, is stopping cancer from spreading in the body.

RAVEN: Right. Another important piece of this puzzle is that molecular glues are really *small* molecules.

Jen: So they'll tend to be in a molecular weight range, four to 500, maybe a little bit more or less. That's a great range, um, for drugs. And that's typically where our small molecule drugs will sit. If it's too small, we tend to not be able to get, the specificity or the potency that we need. If it's too big, we might not be able to get it into the body productively and get it to where it needs to go.

RAVEN: Small molecules work better to get proteins together that typically wouldn't be able to attach. They can fit into the little pockets on the surface of proteins that larger molecules just couldn't.

To be able to get rid of a cancer-causing protein in a cell, you need to send it through that cellular garbage disposal system—yes, our cells have a *cellular* garbage disposal system– and it's utilized through a process called ubiquitination.

RON: Say that 3 times fast.

RAVEN: Ubiquitination, ubiquitination, ubiquitination. Easy.

[laughter]

RAVEN: So when we're talking about molecular glues when applied to cancer drugs, we're often talking about THIS process. You'll remember that not EVERY molecular glue is involved in protein degradation—they can do a lot of other things like we talked about—but for cancer, a lot of times, we're all about ubiquitination.

So, remember earlier I said that proteins are these molecules in our bodies, and they all have jobs to do? Well, if ubiquitination is the process in which we dispose of trash in a

cell, you can think of these molecules, these other proteins involved, as like the waste men. The workers who come and help to facilitate the carrying out of the trash.

And so for ubiquitination to work, you have to tag that cancer-causing protein with a molecule called ubiquitin. And surprise! We have little helpers in our cells, our helper proteins, that actually do that.

There's an enzyme—called an E3 ligase—and that is an enzyme responsible for attaching ubiquitin to a protein.

But here's the challenge: a lot of proteins don't easily bind to that enzyme. So the protein—the one that's causing cancer—can't get recycled.

But you can use a molecular glue—which are really small molecules—to stick to that troublesome protein and change its surface, suddenly making it possible to bind to that E3 ligase enzyme—the trash guy.

> *Jen: So when we design a molecule that interacts with a protein, often the both the molecule shape can kind of, um, change to contort itself to that a binding pocket, for example, or a surface. But also the protein can change when that molecule binds. And so what we found is that the molecular glues often bind along the surface of both proteins and, um, both proteins shaped shapes can be influenced by that binding event. So it's kind of miraculous that it actually works because you're asking both proteins as well as a molecule to do something very specific.*

RAVEN: And it took many decades for scientists to reach this point—understanding those protein-protein interactions and how to leverage molecular glues to drive *new* interactions.

> *Jen: So compounds that serve as molecular glues have been known and actually have been used as medicines for many decades.*
>
> *But amazingly, the underlying molecular glue mechanism of how they interact with the proteins and kind of glue those proteins together was not really well understood until about a decade ago.*

RON: I'm sensing it's time for a history lesson…

RAVEN: Big time. Jennifer explained that one of the earliest examples of a molecular glue used in medicine was a drug called Thalidomide.

> *Jen: So thalidomide is one of the first molecular glues. We didn't call it that at the time. It was a compound that was initially brought to the market to treat morning sickness.*

RAVEN: Thalidomide was introduced in the late 1950s. And doctors were really hopeful that they'd found a drug that could make pregnancy a little easier on women…But they didn't appreciate that two forms of the compound had different activities in the body.

> *Jen: It really wasn't well understood, how it was working. It's also is a compound that, um, is, it has two mirror images that are interconvertible. Think of it as having a handedness. It has a right handedness or a left-handedness, right. When you interact with a protein, it matters, which handedness that protein exhibits, but thalidomide in the body ended up having both handedness and caused unwanted side effects and hit a target which led to birth defects.*

RON: So is thalidomide just not used at all anymore?

RAVEN: Actually, it is. Just *not* for morning sickness – doctors stopped prescribing it to pregnant patients in the early 60s. And around 1964, a new application was discovered! A doctor was seeing a patient with leprosy who was dealing with a lot of really unpleasant skin lesions. And, amazingly, this doctor found that thalidomide cleared this patient's skin within a few days.

RON: So you have a drug that didn't end up working for its original purpose. But that got repurposed to treat something else.

RAVEN: Yeah. And once researchers realized thalidomide worked well for leprosy patients—they started to test it on other inflammatory conditions. By the early '90s, they'd figured out that thalidomide could also inhibit the growth of new blood vessels. And that gets them thinking…Could this type of drug interfere with the growth of tumors?

RON: Wait…can you walk me through the connection between stopping blood vessel growth and treating cancer? Like explain it to me like I'm five.

RAVEN: I'm so glad you asked because you KNOW I wanna talk about it.

Basically, cancerous tumors need oxygen and nutrients to grow. And red blood vessels supply those things to them. So if you want to stop tumors from growing and spreading, you want to cut off those lifelines.

New blood vessels get formed through a process called angiogenesis. And thalidomide works as an anti-angiogenesis drug, meaning it inhibits that process of forming new blood vessels, which helps cut off the oxygen and nutrients a tumor needs to survive.

So that's the logic behind applying thalidomide to oncology.

> *Jen: Interestingly, once they've elucidated the, the targets, for thalidomide and other related what we call IMIDs, it was found that they actually can have a very beneficial effect in multiple myeloma. And that has gone on to be very successful as an approach.*

RAVEN: So by the early 2000s. We've got thalidomide and the other "IMIDs" that Jennifer mentioned. We've got a better understanding of what types of conditions they're useful in treating. But at this point, we're still discovering effective molecular glues … serendipitously.

RON: Right. By happy accident. Which is not the most streamlined method for drug development.

RAVEN: Definitely not. But with these early discoveries, scientists began to understand, "Hey, these are molecular glues!" These drugs can tag cancer-causing proteins for degradation in the cell. And once we understand that, the next big question is—

RON: So, how can we make this happen on purpose?

RAVEN: Exactly. That's the next hurdle.

> *Jillian: I think the field of molecular glue design is still transitioning from a phase of serendipity to a phase of like rationality.*

RAVEN: That's Jillian Spangler, an associate research fellow at Pfizer who works with molecular glues.

> *Jillian: Rational drug design means that you have a protein target in mind, or in this case probably two protein targets in mind that you wanna glue together. You can visualize that by thinking about the protein structure, and then think about the*

space in between those two proteins and come up with a molecule that you think is gonna fit in that pocket or in that space. Design it, make it and it works.

RON: So basically, she's an artist and these molecule are her beautiful original creations.

RAVEN: Totally. And like art, it can be really fun and creative but also quite complicated, right? They want to get this right.

I've done this work. This is what the synthetic chemists at Pfizer are engaged in right now. Building out huge databases of molecules that scientists have discovered or built from scratch over the years and screening those to find potentially effective molecular glues. But we also have a lot of great tools now that can make this a lot more efficient. AI has been really great in helping speed up this process.

[new music cue]

RON: So we sent our production team to Pfizer's La Jolla campus to get a glimpse at that whole process.

RAVEN: Starting with Jillian—she's one of the researchers building those molecules from scratch.

Jillian: My day-to-day job is to look at the data, think about what molecules we should be making and how those molecules could eventually become potential therapeutic drugs.

RAVEN: Jillian's work is way, way upstream of clinical trials and large scale drug production and treating patients and all that good stuff. Jillian has a very big checklist of properties a molecule needs in order to potentially work as an effective therapeutic someday.

Jillian: At Pfizer typically the small molecules we bring into the clinic are dosed orally, meaning the compounds are formulated as tablets, and a patient is able to swallow that tablet, the molecule goes from the mouth into the stomach and then into the, the intestines. And when it's in the intestines, it actually has to be absorbed. It has to then pass through the liver without being broken down, and excreted. And then from the liver, it has to get distributed to, to the rest of the body tissue. So the compound needs to have the properties that allow it to be soluble.

Be able to go into the liquid that's in your stomach. It has to be resistant to the body's natural ability to actually clear molecules out. So our bodies are well tuned at trying to get rid of foreign substances, which these compounds are. So we have to be able to evade the body's natural ability to clear out foreign substances and then the molecule needs to actually be absorbed into the intestines, and needs to be able to pass through the intestinal lining and get distributed to the rest of the body. And if you have cancer in a particular part of the body, the molecule needs to be stable enough that it can then get to the tumor tissue, and actually get to the target.

RAVEN: And then there's the *practical* concerns that design chemists like Jillian have to consider.

Jillian: The starting materials need to be affordable enough. We try to make our chemistry green enough that we're not creating a ton of waste when we actually make the molecules. So there's tons of different facets of a project that go into drug discovery.

RAVEN: So the next time you take any kind of oral medication, think about Jillian behind her computer, with that long checklist that her molecule has to get past before it's ready to move into the next stage of drug development.

RON: So…she's like a bouncer, only letting the best molecules in the lab.

RAVEN: Exactly! Then, there's the next stage, when scientists at Pfizer actually start creating that molecular glue in the lab.

[lab ambience from La Jolla]

RON: Our team's first stop at Pfizer's La Jolla campus was a visit to a synthetic chemistry lab, where we met Joyann Donaldson.

Joyann: My name's Joyann. I'm a medicinal chemist here at Pfizer. So as a medicinal chemist, I work in the lab synthesizing new molecules that could eventually, hopefully become a new therapeutic for cancer patients.

RON: In other words, Joyann takes new molecular glues from the design phase into the tangible, physical world.

Joyann: We make molecules that get tested. Eventually we're hoping to find the one that has the best balance of a variety of different properties and then that molecule will then go on into the clinical trials.

RON: Joyann says that making a molecule from scratch is actually pretty similar to cooking or baking.

Joyann: We combine different reagents just like you would imagine eggs and flour and sugar. They have to be combined the exact correct reagents. They are pseudo baked, at a specific temperature for a specific amount of time to ultimately make a product just like, again, cooking or baking. Usually there's two or three or even tens or 20 different chemical reactions that go into making a molecule.

RAVEN: Then there's the next stage, when scientists at Pfizer actually start creating that molecular glue in the lab.

I worked in high throughput drug discovery where we were testing thousands of molecular candidates against many different types of cells. So that requires robots.

So we actually have computer scientists on staff who were training robots to help us find those drug candidates. And the drug candidates were made by our chemists, who worked in house. And we tested drug candidates on cells, and that's what my job was. I would grow cells. I would put them in these robots that computer scientists were helping to teach. And the chemists would give us the drugs.

We would apply them with the robot onto the cells and then monitor them and do experiments. And so it is very similar to working in a kitchen. If you think of what a chef looks like—they wear those white coats with the hats. I mean, we almost look like chefs wearing lab coats and everything, huddled together, working towards getting this final product.

RON: And just like a team of chefs in a kitchen, Joyann and the other chemists in her lab rely on sophisticated tools and equipment to help them get through all that work. Like our good friend the rotary evaporator – commonly known as a rotovap.

[lab sounds]

Joyann: This tool is used to quickly evaporate solvent. You can imagine boiling water takes a long time, but if you can pull vacuum on it and then boil it, you can

remove much faster. Similar to high altitude cooking, in which case, uh, water boils at a lower temperature.

RAVEN: The rotovap in Joyann's lab is around the size of a large espresso machine. It's got a glass round-bottom flask that the machine spins in a water bath.

[sounds from the rotovap]

RON: The rotovap is a really common but also really useful piece of lab equipment.

It helps you efficiently boil off the unwanted solvents from your sample. Solvents, in case you don't know, are liquids that can dissolve other substances, making a solution, with the most common solvent being water. So getting rid of that solvent with the rotovap will bring you a step closer to making a molecular glue into a medicine.

[more sounds from the rotovap]

Joyann: So you can see that the solvent's starting to come and it's bubbling and you're starting to see a solid form where there used to be a liquid that looked like water, although it wasn't water.

RON: Just like that, the sample is solvent-free!

RAVEN: Woohoo! Alright. This process is pretty routine for scientists like Joyann. And honestly, for me personally, when I would be in the lab, I would steal away into the chemistry section and stare are the rotovap going round and round and round. Especially when I was waiting for my experiments to finish. It's a little hypnotizing, I'm not gonna lie. But I will say that it's really cool that something so minor and routine to us scientists contributes to something that is such a bigger picture.

Joyann: Most of the time when we're making molecules, we're the first person who's ever made that molecule. So that's also quite, you know, exciting and figuring out how to do something that somebody's never done before is also pretty exciting.

And obviously the passion for trying to make a molecule to help save patients that are living with cancer is also something that, you know, really gives you purpose in life and working in the lab.

RAVEN: Molecules that come from design chemists like Jillian might pass through a number of other specialized labs at the La Jolla campus.

> Neal: So all of my reactions are generally less than one milligram each. It's like a grain of salt. Yeah. It's, it's very small.

RON: That’s Neal Sach, another research fellow at Pfizer. He works in a lab on the same campus as Joyann.

> *Neal: In terms of my lab, we are still finding the best ways of putting the atoms together of the molecule. So whether it's a molecular glue or it's a cancer compound, it's much the same for our lab. We are basically working out the best way of stitching the molecules together.*

RAVEN: In a high throughput chemistry lab like Neal’s, researchers use machinery and robotics to conduct hundreds or even thousands of experiments each day to optimize chemical reactions.

Let me explain more about what these labs look like. So, when you walk into a high-throughput drug discovery lab, there’s a lot of equipment. There’s centrifuges that rotate solutions at high speeds to separate things out from each other using gravity—really, centrifugal force.

You have to think about, also, things that humans can’t do efficiently on their own that we would require robots for. So drawing up thousands of aliquots of liquid at a very minute scale and then distributing those aliquots evenly into like thousands of wells—we need a robot to do that.

We've got robots that can incubate large volumes of cells and take pictures of every single well. Like, let’s say you have a thousand plates that each have 96 wells. So, now you’re looking at 96,000 plates and making sure you’re checking for cell viability. You’re checking to make sure everything is at the right temperature. You’re exchanging media in these cell wells.

I mean, there’s so much technology in these labs. And it is incredible.

One of the things that you’re also gonna see in these labs—in addition to these robotics and processing machines—is a glovebox.

RON: So the glovebox is essentially a vacuum-sealed cabinet—about six feet tall—with a glass front that has two holes—or “ports”—with big, black or blue rubber gloves attached, you can just stick your hands inside. The gloves protrude into the cabinet and allow researchers to safely perform experiments inside the sealed area.

> *Neal: So when you are dealing with air sensitive materials like precious metals such as palladium or platinum that are sensitive to oxygen we’ll run reactions inside of the glove box so that those are not spoiled by the oxygen in the ambient atmosphere…So in this ambient atmosphere, we’re at about 20 percent oxygen, which is 200 parts per million. And you can see the reading on the box here that our oxygen level here is 40 parts per million. So I guess that’s almost 4 or 5 magnitudes less oxygen. So by that measure, our compounds in there will last about 4 or 5 magnitudes more than they would outside of the box. So say for example, we had a reagent out here, I mean, some reagents out if we brought outta the box out here would just catch fire because there's enough oxygen that they'll spontaneously combust.*

RON: The glove box keeps the carefully controlled atmosphere on the inside from reacting with the normal atmosphere on the outside. I’ve seen what happens if you’re not so careful with volatile reactions…and let’s just say, things can get…hot! Safety first!

> *Neal: …we have nine parts per million water in the glove box, so it's extremely dry. Just kind of imagine it as being a, a desert on Mars. There's no water, there's no oxygen. You definitely wouldn't wanna breathe in there…*

[sounds of opening the glove box]

RAVEN: So, high throughput drug discovery work looks a lot different than what they teach you in school or what you might do in a classroom or at home, right? There’s just so much quantity happening all at once. It’s not just one experiment at a time. You’re often doing dozens and dozens of experiments at the same time. You’re often testing dozens and dozens of variables at the same time. And oftentimes, you're using really small quantities of reagents to get that done. That way, you can get results faster.

> *Neal: When you're running 300 reactions a day, you can really find solutions much faster, but you need the technology to do that. If we can use relatively little resource to fix reactions very early, it speeds that transition into development, um, and allows us to go from milligrams to kilograms much faster. And that means ultimately we can get medicines to patients quicker.*

RON: After hanging out with Neal in the high throughput chemistry lab, our team made one last lab visit—the purification lab.

[noises from the purification lab]

> *Neal: So this is a machine, um, that uses this to separate components of a reaction. So oftentimes when we do chemistry and reactions, we don't get a perfectly pure profile. And it can be quite difficult to remove those impurities from our desired compound.*

RON: The purification lab is where a new molecular glue will visit *after* it's gone through Joyann and Neal's labs but *before* it's ready for its first rounds of testing.

> *Neal: And when we do the testing, we want to make sure that any biological activity we get is solely due to the compound that we wanted to make. So removing those impurities, which could affect that is important.*

RAVEN: Once a molecular glue compound is purified, it can start the early stages of testing. And if the results of those look promising, —and, of course, the compound is proving to be safe and effective during early trials—a molecular glue can finally enter the clinical trials phase.

> *Jillian: …and in oncology, our clinical trials we generally go directly into sick patients… And there it's looking for two things. Are the patients that are getting our drug, are they receiving exposure? Is the drug actually getting into their body? And if it's getting into their body, is it having the effect that we want? Is it shrinking the tumors? Is it leading to a decrease in their tumor volume?*

RON: And now that we're talking about patients again, I want to understand how much molecular glues could be a game changer for cancer treatment.

RAVEN: This is what's so exciting about this new modality. Because molecular glue degraders can target cancer-causing proteins in that really specified way, they can avoid the damage to healthy cells in the body that other treatments cause.

> *Jillian: What chemotherapy agents do is kill all of the rapidly replicating cells in your body. So that includes your tumor, but it often also includes other normal tissues in your body. Um, the bone marrow, the, the cells in your GI tract, all those cells are turning over rapidly. And so there can be a lot of toxicity*

associated with chemotherapy agents because they tend to be non-specific. They just kill everything that's replicating.

RAVEN: Molecular glues don't have that problem. Which is amazing news for the countless cancer patients who have experienced the side effects from treatments that really take a toll on the body.

Jillian: Patients when they're undergoing chemotherapy, right, they vomit, they lose their hair, they lose weight because the normal tissues in the body are affected by the medication that you're giving them. I think a lot of times we view the future of cancer drugs as being curative or in some sense being able to make cancer like a lifestyle drug, right? If you can just prevent the tumors from growing and going into the rest of the body and proliferating, you know, then it could be a disease that isn't gonna kill the patient that they can manage for the rest of their life with, you know, a small molecule taking a pill every day. Um, and there are some drugs that we've been able to bring to the market where, you know, patients have now been on these drugs for 10 years, 15 years, um, and are still continuing to respond to those drugs.

RAVEN: Now to be clear, it's still going to be a while before tons of patients are using these new types of drugs.

RON: Bruh…

RAVEN: But the good news is that the scientists we heard from in this episode are working every day to inch us closer to that goal. And we *are* getting closer. And it's Jennifer LaFontaine's job at Pfizer to track that progress and push her team forward whenever they find molecular glues that look promising for therapeutics.

Jen: Our goal is really to identify glues that are more specific and more efficacious, right? So they're more intentionally designed against a target rather than a serendipitous finding from decades ago. We want to design glues that hit a very specific and important protein, and that's what we're starting to do and bring forward to the clinic. So I think the next generation of drugs, just like the next generation of inhibitors, is showing itself to be more efficacious and safe. I think you'll see the same thing emerging in the molecular glue space where you'll start to see compounds emerging from the clinic that look very efficacious and safe.

We are very excited right now about the potential for progress and it's moving faster than I think we even thought it could.

RON: Honestly, it's pretty amazing that researchers have been able to figure *any* of this out.

RAVEN: Totally. Especially since the big breakthroughs that laid the groundwork for scientists to understand molecular glues only happened in the last decade or so. But scientists like Jillian are not resting on their laurels.

Jillian: We are doing things in drug discovery now that 20 years ago would've been unimaginable. So it's hard to imagine like what the field will be like in 10 to 15 years, but I hope it's at a stage where cancer has become either a curable or a lifestyle management disease, and that we're able to target, the vast majority of cancer types. Cancer is such a heterogeneous disease. No two patients have the same exact cancer. Even two patients that have breast cancer, like their tumors can be very different. So imagining that we can have drugs that treat the vast majority of those patients, that would be a huge, huge breakthrough in the field.

RAVEN: There's even potential for the power of molecular glues to be used *beyond* cancer treatment. Today, we've mostly talked about protein *degradation*. And how molecular glues can tag cancer-causing proteins for the cell's garbage disposal system. But like we said earlier, lots of bodily processes come from protein-protein interactions. Which means there's potential beyond what molecular glue *degraders* can do for cancer patients.

Jillian: Oncology is often the sandbox for new ideas and new fields in drug discovery. So things break through in oncology first, but then see examples of those, new ways of drugging proteins show up in other, you know, treating autoimmune disease or, you know, other very deadly diseases.

RON: So moral of the story: there's a lot of exciting stuff on the horizon.

RAVEN: Exactly. As long as we remain patient and persistent in reaching those big goals—we'll get there someday.

Jen: I think so much of what we do in society is actually framed around science, whether we realize it or not, when you think about healthcare, um, the advancement of science has advanced our healthcare and is so fundamental to

how we live. And I think society falls apart without it, without people realizing how important it is. Um, I think it, it actually changes our lives every day.

RAVEN: Well, like I said, I could talk about molecular glues until my voice is GONE. And it's just about gone. [laughs] And I just love how much potential there is in this field. I definitely get excited about it. But I feel like we covered some cool stuff today, right? Even though we didn't cover *everything…*we still got to some really cool stuff.

RON: You had me hooked all the way. I learned so much about molecular glues. Like…what were those??

RAVEN: Now you know! Now, I'm super sad say goodbye to our molecular glue episode, but as sad as I am to say goodbye, I'm just as excited and pumped for our next week…but then again I'm really sad because it's our last episode of the season! So bittersweet!

RON: Next week, in our final episode, we're diving deep into the field of antibody-drug conjugates. And we're talking to researchers and patients about how this revolutionary modality could get us even *closer* to a future with better cancer treatments. And I AM READY!

RAVEN: I'm so glad you're ready, Ron! Because *I'm* ready. Next episode is gonna be amazing. Season finale, here we come! [laughs] Until then, bye y'all!

RON: See ya!

RAVEN: Science Will Win is produced by Acast Creative Studios and hosted by me, Dr. Raven Baxter—

RON: And me! Dr. Ron Gamble. Please take a minute to rate, review and follow Science Will Win wherever you get your podcasts. It helps new listeners to find the show.

RAVEN: Special thanks to all of our guests and the Pfizer research & development teams. And thank you for listening!