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00:05 Sarah Crespi: Welcome the Science Podcast for November 20th, 2020. I'm Sarah Crespi. Each week, we feature the most interesting news and research published in Science and the sister journals. First up, I talk with staff writer, Erik Stokstad about fish farming's future. From giant offshore farms to breeding boneless fish. I also talk with researcher Jan Claesen about skin microbes that use their own antibiotic to fight off harmful bacteria. Finally, we have a sponsored segment from MilliporeSigma and our custom publishing group. The director and senior editor of custom publishing, Sean Sanders interviews chemical synthesis and data science researcher Timothy Cernak on the topic of retrosynthesis.

00:48 SC: Now we have staff writer, Erik Stokstad. He wrote a feature on the modernization of fish breeding in this week's issue. Hi, Erik.

00:55 Erik Stokstad: Hey, great to be back, Sarah.

00:57 SC: Great to have you. So fish farming is modernizing and on the rise. What's the big picture here?

01:05 ES: The big picture. If you go back to 1950 and you compare what's happened over the last 70 years, you can see with wild-caught fish, the overall harvests, they've flattened off in the last couple of decades, but aquaculture is continuing to rise that production of farmed seafood. Nearly half the protein that we eat from aquatic organisms is grown on farms. Most of it is fresh water, and in Asia, most of the farm fish in the world are coming from the land. These are ponds with carp in them, grass carp, silver carp, common carp, tilapia, trout, catfish. There are a lot of these aquaculture species that are being grown on land.

01:50 SC: I was surprised to learn that fish are behind the times. Humans have been keeping fish to eat or at least to look at for thousands of years, but as you point out in your story, fish haven't been altered through breeding like other livestock. How have things been different?

02:06 ES: The big difference is that most of the seafood that we're eating, it is closer to being wild than the terrestrial livestock.

02:16 SC: Do you think it's just because the people who did this intensive breeding, the people who were interested in tracing lineages of animals and getting the best from their cows, they just weren't that interested in fish farming or in seafood? Is it just a coincidence of history that the focus of all this intensive breeding has been terrestrial animals?

02:36 ES: If you're talking about the last century or the last 150 years, or if you're talking about thousands of years.

02:43 SC: I'm talking about thousands of years.

02:45 ES: So thousands of years. So over 10,000 years where humans first domesticated sheep,

goats, cows, and then lived with them, and over that time, picked the ones that had the traits that they like. They gave more milk, they had more meat on the bone, that's been happening for a longer time. We've had a longer stable relationship for the most part, there's some exceptions here. For the most part, a longer relationship with those animals that walk around than with the ones especially from the sea. And the other is that over those thousands of years, the terrestrial livestock went through population bottlenecks that reduced their genetic diversity.

03:25 SC: It's like when you bring a few parrots or cows to a continent, but nobody is bringing around a pond full of fish, right?

03:32 ES: That's a great point. It is harder to bring those with you as you're trucking across the continent. There is some archeological evidence for aquaculture. There's a lot of, I think, inference there. There's evidence that in Australia, aboriginal people 6000 years ago were building ponds to keep eels. Who knows to what extent they were selecting. If you can control the life cycle, that's really the key thing with domestication and being able to have it reproduce in captivity, and then you really can pick the ones that you like and selectively breed those for continued improvements.

04:11 SC: Now, researchers are jumping way ahead, skipping centuries of painstaking documentation, breeding line analysis and using modern technologies to get what they want from fish. Well, what do we want from fish, Erik?

04:27 ES: It depends on who you are. On the one hand, if you're a fish farmer, there are key things that you want, the first one is fish that grow well, or not just fish, I guess I'll probably say fish a lot, but we're really talking about a huge range of organisms, fish, crustaceans, mollusks, really hugely different organisms. But no matter what you're growing, you want creatures that grow well. They have a lot of protein that you can sell to the grocery stores and to the consumers. You want bigger, fatter, oysters, and you want large fillets, you want them coming from animals that grow quickly, so maybe you can do more generations, like more cycles per year. So that's the first thing you want. The second thing you want is hardy animals, healthy animals, ones that resist disease. And this is... It's a huge issue in aquaculture. Outbreaks of disease can really hamper an operation. In shrimp farms, you could lose 40% or your entire crop. In all of those cases, having disease-resistant animals is a real benefit.

05:35 SC: Fast and good growers, disease-resistant in animals. Anything else that you want out of your domesticated livestock?

05:42 ES: Once you've made progress with that, breeders will turn to traits like, what does that fillet look like? With salmon, consumers really like reddish, pink fillets, so you can breed salmon to have a naturally redder flesh color. A rounder fish rather than a longer fish. Or color, apparently in Japan, trout with a bluer color and fewer spots or spots just in the right place on the outside of the fish, that's desirable. So Chilean breeders have optimized their trout that they export for those qualities.

06:17 SC: Well, what technologies are fish farmers, livestock breeders using to achieve these goals?

06:25 ES: So what you need to do as a breeder is you need to be able to pick the fish that you wanna propagate. So for a faster growing fish that's not hard, you just need a ruler and a scale. You can... And when salmon breeding got under way in the late '60s, early '70s, they were getting gains in growth rate of 10% to 15% per generation.

06:51 SC: Wow.

06:52 ES: Wow. And put that into context, if you're a poultry breeder, a few percent is a really good thing.

06:57 SC: Yeah.

06:58 ES: So you can measure that, but it's not always that simple. If you wanna measure the color of the fillet, obviously you need to sacrifice the fish. So you can't use that fish for a hatchery 'cause it's dead. So what the breeders have done is they use something called a family-based approach, where they have crosses between two parents and then the offspring, hundreds, thousands in a tank and they can test some of those, but they'd have to use the siblings for the actual production of the fish that go off to the farms.

07:35 SC: How do they know which sibling, which family members carry those desirable traits?

07:41 ES: So the way technology comes into this is using genetic markers where you can look for little changes in the genome that reveal whether a favorable allele of a gene is present. You just take a little clip of the fin if it's a fish, and you can sequence that tissue for the genetic markers that are in it. So that allows you to really get a much more accurate selection of fish for the next generation.

08:12 SC: We've been talking about fish for a while here. Let's move to some of these invertebrates. You talked a little bit about oysters, triploid oysters. What is that and what does that accomplish?

08:23 ES: Oysters in the wild, they've got, like us, two copies of each chromosome, so you call them diploid. If you took a human and you added an extra copy of every chromosome, they wouldn't survive that. Oysters are... I was talking with one oyster breeder who... I asked him, "Why did you get interested... You've trained as a geneticist, why did you get interested in oysters?" And he said, "They're so tolerant of genetic abuse. You can really manipulate their genes and they'll survive." So it's...

08:54 SC: Like you can give them a whole half extra genome and they're fine?

09:00 ES: Or double it. You can make them tetraploid and it really has a tremendous impact for improving the production of the oysters. If you make a triploid oyster, it becomes sterile. It's healthy. It's normal. It might be hardier, more disease resistant, so they mature faster, you harvest them sooner and in some places, that means you pull them out of the water before the disease outbreaks in the hotter, warmer conditions. And there's another advantage of triploid oysters, is that

because they're sterile, they're not putting much energy into reproducing. Why bother? So they don't develop the same mass of sperm or eggs that a fertile oyster does. There's more meat on them, so there are real advantages to making a triploid oyster.

09:52 SC: I see in your story that there are things like boneless or low-bone fish that might be on the market. Can you talk a little bit about that?

10:00 ES: There are a lot of reasons why people love salmon. One of those reasons is you can get a nice big fillet of salmon and you eat it and you hardly ever find a bone in it. But if you eat a carp, it's just full of bones. But carp is the number one aquaculture species in terms of volume, either you cook the whole fish and you pick the bones out of it or sometimes they process it by chopping it up so the bones are all tiny. What if you could breed a carp that didn't have those little fillet bones in it? You could feed carp to your babies and you could feed...

[chuckle]

10:35 SC: No.

10:36 ES: And not worry about them choking. There would be a lot of advantages to doing that. Now, there's work done, just with traditional breeding to see, can we select fish that have smaller fillet bones or fewer fillet bones? Because people find these mutants in the brood stock on the farms? But the other thing is to find the genes that are involved and people are identifying those. You knock them out with gene editing and you can create wanton sea bream with fewer of these bones. This is still in the lab and it will take years, but that kind of gives you an idea that there's a lot you could do. If you understand the genetics and the biology of these organisms better, you really could create new traits that would be really valuable, that would help provide more healthy protein for people.

11:28 SC: What does a low-bone fish look like? How does it function?

11:32 ES: They're called intermuscular bones and the fish can be healthy without them. If you look at the incredible diversity of finfish, some have them, some don't.

11:44 SC: Are there advances in how fish are housed and kept? There's this giant fish farm you talked about called Ocean Farm 1 that is pretty far offshore. Why would fish farms go farther away from land?

11:58 ES: I love that question because it sounds like it's more work. You have to take a boat out there, 5 kilometers offshore. You have to anchor this thing to the sea floor and this thing is 110 meters wide, that's a football field wide. This is a trend that some of these higher value species, they're being farmed offshore with the goal of eventually moving them into the open ocean. One motivation is just space. There's only so many fjords to put your coastal pens in. Aquaculture is looking to expand, and the open ocean, there's a lot of it. Now, the other advantage is the temperature is actually better, more stable and better further offshore for salmon, and then there's the waste issue. We really haven't talked about that. In a coastal environment, you're feeding the

fish, the fish are pooping. Nutrients is coming out of these fish farms that can cause some problems. There's the issue of sea lice for salmon, that's one of the biggest problems salmon farms have. These parasites that latch onto the salmon and weaken them, injure them. If you're further offshore, there are fewer of these sea lice.

13:10 SC: If we're talking about fish farming on the coast versus the open ocean and increased popularity of fish farming, is there a lot of concern about the environmental effects of fish farming on those environments? To me, it sounds like you go from wild-caught fish to farming fish. It sounds like a good deal for the environment.

13:33 ES: It depends on what species you're talking about. Shrimp, it's a high value species. Over the years, a lot of coastal mangroves were destroyed to create shrimp ponds. That's a problem because mangroves have a lot of ecological benefits. They reduce storm impacts, so you really wanna keep your mangroves. There are several issues with farm salmon, one of them is the sea lice. Not only are sea lice a problem for farm salmon, they're a problem for the wild salmon. If you have a fish farm that's near a place where wild salmon are swimming by, the lice can move from the fish farms on to the wild salmon. There's also the risk with salmon and some other farm species that they escape from the farms, and if they escape from the farms and they breed with the wild relatives, that can cause some problems, especially if the wild species is endangered. There are salmon populations that are in real trouble. So if they interbreed with farm salmon, first of all, you'll lose some genetic diversity in the wild stock and you can, and the offspring can be less adapted. It can impact the populations of the wild salmon, so you really want to avoid the escaping, which is why they create sterile salmon as well.

14:55 SC: What about not catching fish anymore though?

14:58 ES: Right. There's a reason we don't farm wolves.

15:05 SC: [chuckle] So true.

15:06 ES: The reason is if you wanna farm wolves, you have to catch a lot of rabbits or farm a lot of sheep to feed the wolves. There's the same issue if you are farming carnivores. If you're farming a predatory fish like salmon, they have to eat fish, so you have to catch other fish, smaller fish, you're catching the anchovetas, other predators in the ocean have less to eat, so that's an impact. Now, there's a lot of work been going on to modify salmon diets, to feed them soybeans or plants as a greater part of their diet, figure out an optimal diet that has less fish in it, and then also to breed salmon that better tolerate that new diet.

15:51 SC: Alright. Thank you so much, Erik.

15:53 ES: Really nice talking with you, Sarah.

15:54 SC: Erik Stokstad is a Staff Writer at Science. You can find a link to his fish feature at sciencemag.org/podcast. Stay tuned for an interview with Jan Claesen about how microbes compete for space on our face.

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16:14 SC: Over the past decade, we've learned more and more about the bacteria in our guts, the way they help digest food, interact with our immune system and other important functions, but what about all the other bacteria living on us and in us? What are they up to? Jan Claesen and colleagues published a paper on skin bacteria this week in Science Translational Medicine, and he's here to talk to us about it. Hi Jan.

16:36 Jan Claesen: Hi, Sarah. Nice to meet you.

16:36 SC: Yeah, nice to meet you. You found a skin-dwelling microbe that produces an antibiotic that kills other skin-dwelling microbes. Were you looking to find out more about microbes on the skin, or were you looking for antibiotics or something else?

16:53 JC: A little bit of both actually. So we were looking for specifically how microbes can colonize and establish themselves in a specific niche in the skin. And from my backgrounds in antibiotic research and soil organisms, I was particularly interested in finding these types of antibiotic molecules that's being produced by skin microbes.

17:13 SC: The bacteria that you looked at, are they specific to certain parts of the skin?

17:18 JC: The bacteria that we looked at are Cutibacterium acnes and they're actually present all over everyone's skin, so they're part of the healthy microbiota. But the bacteria that make this particular antibiotic called Cutimycin are not as widely distributed.

17:34 SC: One thing I noticed in your paper was that you distinguished between microbes that like dry, microbes that like moist, and microbes that like oily, which one is this?

17:43 JC: Cutibacterium itself is a bacterium which mainly likes more oily type skin, so it's actually living more inside of the hair follicles. It's an anaerobic bacterium, so it means that it doesn't really like oxygen much. It burrows more deeply into your hair follicles, and actually it uses your sebum, so the lipid-rich secretion of your sebaceous glands sort of as its food.

18:05 SC: And so this oily skin loving bacteria creates a molecule called Cutimycin, and it's an antibiotic, and this antibiotic doesn't kill the bacteria that makes it. What does it target?

18:16 JC: It turns out that this antibiotic doesn't kill cutibacterium as much as it does, for example, staphylococcus species that live in your skin.

18:24 SC: Now, how did you narrow in on this particular bacteria? Did you know ahead of time that it was making this or what was the selection process like?

18:31 JC: We didn't know that this bacterium was actually making the molecule, but we used a genomics-guided search to find this particular antibiotic biosynthetic gene cluster. Bacteria, when

they want to make a specific compound, they have all of the enzymes that are involved in the biosynthetic process clustered in a certain location in their genome, in a biosynthetic gene cluster as we call it, and that actually makes it easy for us to figure out what biosynthetic pathways are present in which bacteria. And so using an in silico approach, we looked for antibiotic biosynthetic gene clusters in the skin microbiota and this one popped out as being a candidate for making a thiopeptide antibiotic. And thiopeptides are pretty potent antibiotics, and then some of them are known to kill staph species. So that's why we initially narrowed down on this.

19:20 SC: So you found that these bacteria were on people's skin and then also that they were making this molecule. What was the effect of the bacteria making this antibiotic on the microbiota, the local microbiota?

19:34 JC: Yes, when we looked at the individual follicle level, it did turn out that the presence of the cutimycin biosynthetic gene cluster correlates with a reduction of the Staph epidermidis colonization in the individual follicles.

19:46 SC: And that's good news, right? Staph can cause problems for the skin.

19:51 JC: Yeah, Staph can definitely cause problems. Usually, it's Staph aureus which has a pretty bad name, but that organism isn't really very abundant in normal skin, but it can flare up in skin conditions. Staph epidermidis though, is closely related to staph aureus and certain conditions can also cause problems.

20:10 SC: Yeah, let's talk about how this relates to skin disease or skin disorders. Is this something... This antibiotic, could you use it to treat certain disorders? Could you apply this bacteria to people if you wanted to help them straighten out a problem with their skin?

20:26 JC: We haven't really explored it that much. It's something that we'd like to do in the future. The idea is to use more natural or naturally occurring compounds and then naturally occurring strains to decolonize or to prevent colonization of invading pathogens or pathobionts. Something that we could explore further is using the cutimycin-producing Cutibacterium to basically ward off Staph aureus or Staph epidermidis strains that might cause trouble in a certain condition.

20:55 SC: You talk about a few clinical possibilities for this new understanding of the production of Cutimycin by this bacteria. One thing you talk about is atopic dermatitis, how would that work?

21:06 JC: So basically, what our strain or the production of cutimycin could mean for conditions like atopic dermatitis is that we could try to restore the balance in the microbiota by colonizing those layers with cutibacterium that produces Cutimycin and thereby reducing the Staph aureus or Staph epidermidis colonization in these areas, thereby, maybe reducing the inflammation.

21:31 SC: The other clinical application you suggested out there in the future might be for acne vulgaris.

21:36 JC: Acne has been linked traditionally over the years to Cutibacterium acnes which used to

be called Propionibacterium acnes.

21:43 SC: So Cutibacteria acnes is the one that you're talking about right now that makes Cutimycin.

21:46 JC: Yes, that's the one. So since everyone has Cutibacterium all over their skin and not inflamed skin and inflamed acne lesions all the time, it means that there's good and bad. There's definitely some involvement. The evidence in literature at the moment suggest that there's a lot of healthy or beneficial Cutibacterium strains that just live happily on your skin without causing any inflammation or any acne-like phenotype, but there's other Cutibacterium isolates that are more associated with inflammatory acne. At the moment, what we're trying to figure out is the molecular mechanisms involved in this process, so how do health-associated Cutibacterium acnes strains differ from acne-associated Cutibacterium acnes strains, and what molecules might be different between those two isolates.

22:34 SC: Could we synthesize or make this antibiotic and then treat people with it or would it be better to give them the bacteria that produce it?

22:43 JC: Cutimycin is actually a pretty complex molecule, so it would be difficult to synthesize it. It is possible though. Another way to obtain it in high quantities might be to use microbial fermentation and then purification or the combination of purification and chemical synthesis. I'm thinking it might not be the best to apply it directly as an antibiotic rather than delivering by the Cutibacterium themselves, so we can just apply strains of Cutibacterium that have the ability to make these compounds, to basically establish themselves in the skin and ward off the colonization by Staphylococcus species. In comparison to continued application that might be more beneficial to have a stable colonizer there that can just produce the antibiotic in situ.

23:28 SC: And as you said, there are many different kinds of... There's different strains of the Cutibacteria, some that are more closely linked with acne, some that produces antibiotic. Do you know anything about the relationship between the ones more closely linked with acne and the ones that produce the antibiotic?

23:45 JC: The Cutibacterium strains that are most closely related with acne, they don't typically produce this antibiotic, but they have other biosynthetic gene clusters in their genomes, and one of these might be involved in causing an inflammatory reaction when they're colonizing the hair follicle. So within the hair follicle, there's a competition going on, of course, between different types of bacteria, different genera. So there's a competition between Cutibacterium and Staph and Corynebacterium, but there's also a competition between different strains of Cutibacterium going on. So if a niche is occupied by one strain, it might not be permissive for colonization by a different strain. So if we can use a specific strain of Cutibacterium acnes, which is health-associated to decolonization or to ward off colonization by the acne-causing Cutibacterium strains, then that might help in the inflammatory acne as well.

24:36 SC: Is applying beneficial bacteria to people's faces a treatment that's already in use?

24:40 JC: It's not widely in use. There's several trials going on in Germany, and there's a couple of companies that are putting either dead or even live Cutibacterium acnes in their skin products. But I don't think it's been done in a very systematic way, yet. I think at this point, it's looking more at do these bacteria colonize, what's the effect, how long do they remain after the initial application.

25:07 SC: With gut bacteria, there are all these mechanisms that people are trying to tap into, feeding them things that might make certain ones to grow better, prebiotics, probiotics, all that kind of stuff. Are there things that people are putting on their skin to feed particular bacteria?

25:24 JC: Yeah. As I mentioned before, there's several companies that are trying to improve your microbiota balance on your skin. You can imagine that if you put a lot of greasy skin cream on your skin, then a fatty-acid-loving bacterium like Cutibacterium might like this and start growing better and blooming. So there's an interest in trying to modulate the skin microbiota using prebiotic or molecule that the bacteria can use as food. There's definitely an interest there, but we're not quite as far ahead as the gut microbiota research.

25:53 SC: This is just one bacterium and its product, are you going to keep looking for more products, what's next for this kind of research?

26:02 JC: Yeah, so you're absolutely right. This is just one bacterium and one product, there's plenty more out there. The paper already alludes to that in different isolates of Cutibaterium acnes. There's different types of biosynthetic gene clusters which are predicted to make different compounds. Some of which might also have an antibiotic activity some which might be involved in interaction with the host. In terms of future directions, what we're interested in is, is looking at how these other molecules play a role in niche competition between a different bacteria. We're also interested in other common skin commensals like Corynebacterium species, which are also known to make bio-active compounds that are involved predominantly in the micro-post interaction.

26:45 SC: Okay, thank you so much, Jan.

26:46 JC: Yeah, thanks, Sarah.

26:48 SC: Jan Claesen is an assistant professor at the Lerner Research Institute at the Cleveland Clinic. You can find a link to his Science Translational Medicine paper at sciencemag.org/podcast.

Stay tuned for an interview sponsored by MilliporeSigma, in which Science's is Custom Publishing Director and Senior Editor, Sean Sanders talks with Timothy Cernak on Retrosynthesis.

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27:15 Sean Sanders: Hello, everyone, and welcome to the sponsored interview from the Science/AAAS custom publishing office, brought to you by MilliporeSigma. The Life Sciences Business of Merck KGaA Darmstadt, Germany operates as MilliporeSigma in the US and Canada. I'm Sean Sanders, Director and Senior Editor for custom publishing at Science. And I'm talking today with Dr. Timothy Cernak, Assistant Professor of Medicinal Chemistry at the University of

Michigan. Tim's work is focused on studying the interface of chemical synthesis and data science, and I'm going to spend the next few minutes mining Tim's extensive knowledge of retrosynthesis, particularly as it relates to recent advances and ongoing challenges. Tim, welcome, and thank you so much for talking with me today.

27:57 Timothy Cernak: Hey, thanks. Thanks very much for having me.

28:00 SS: So Tim, let's start off with an easy one for you. I think briefly, could you tell us what retrosynthesis is and how it is currently applied?

28:09 TC: We have molecules all around us in our lives, medicines and agro-chemicals and materials, and so someone's gotta make those. And you need to have the recipe that you're gonna use to make those molecules. So retrosynthesis is this idea of going backwards that I have this final product that I need to make, and then I have all the pieces that I can buy. And retrosynthesis is the logic that we use to break that final product into its pieces.

28:37 SS: Tim, could you step us through a typical retrosynthesis project? Where do you start and how do you proceed?

28:44 TC: Yeah, sure. So let's start with the target, the molecule we wanna make. We know its structure, we know what it looks like, we don't know how to make it, and we're gonna start breaking it down into pieces. And ultimately, we need to arrive at pieces we can get, pieces we can buy, and hopefully, pieces we can buy cheaply. Now, what we have to build the thing is reactions. We invent chemical reactions all day, every day. There's this huge lexicon of available reactions to us, but these reactions have rules and we have to follow the rules. You're not allowed to run certain reactions at a certain temperature, or you're not allowed to run certain reactions in the presence of other functional groups, that's gonna shut the reaction down. So there's this set of rules we have to follow, and our objective is to get to this final product, starting from the cheapest starting materials that we can get. And then so it's a sequence of moves, much like chess, and we have to follow these rules and find our way through. But there's this infinite number of possible moves or combinations of moves that would give us the recipe to make our target molecule.

29:44 TC: The fun part is that all of this was laid out as a logic in the '60s by EJ Corey, who won the Nobel Prize for this logic, and even tried to feed it into the computer in those days. And while it was successful, but you can imagine then in the late '60s computers were not what they are today. So today, we have these awesome commercial platforms, Cynthia is one that we use, and it is powered by a database of all of these rules and all of these reactions. And so you give it a target, and it knows the rules of chemistry, and it knows significant number of the reactions of chemistry, and it also knows the prices of starting materials. It navigates through this combinatorial explosion of possible moves to get us to our target, and then it still requires human intuition though. It doesn't... You were not yet at the stage where you hit a button and you get an answer, you get a very satisfying answer that is, at once, efficient and what we like to call elegant. The chemist needs to sit down and look at all of these possible routes the computer proposes as ones that will work, and then decide among a highly truncated list which ones would be the best to move forward with.

30:53 SS: Tim, what are some of the challenges that are as yet unsolved in the space?

31:00 TC: So we still can't make a complex molecule easily. It still takes years, typically. Sometimes, many, many years. And if you look at the medicines that we need, they're becoming increasingly complex, they're more difficult to make, that makes drugs expensive. But it's because society is asking us for more sophisticated molecules. We want molecules that are long-acting, that are non-toxic, if we're talking about medicines. And so our ability to design those molecules has improved significantly, but that makes these molecules a lot more tricky to make. And so, we're still at a stage where... I think you can make any molecule, but if you can make any molecule given enough time and resources, and that time and resources aspect of it is still expensive and long, and so we would like to make it... That you can have any molecule right away.

31:50 SS: In the midst of the Coronavirus pandemic, there's obviously a frantic search for small molecules that can be used as therapeutics against SARS-CoV-2. How is retrosynthesis being used right now to drive this research?

32:05 TC: What is clear is that medicine is gonna be needed to get us out of this pandemic, whether it's a vaccine or a small molecule. I think that the life sciences and chemists are gonna be true heroes of this scenario. And there's a couple of ways that retrosynthesis is helping out. So one is that there's supply chain issues with a lot of the medicines that are out there. We are gonna run out of a lot of the most important medicines given the scale of this pandemic. We're not talking about thousands of doses that are needed for these molecules, we're talking about millions, maybe billions of doses that may one day be needed. So we need new ways to make these molecules because we're gonna run out of the existing supplies, so retrosynthesis has been really engaged in that area of research. Another area is that we may need new drugs like very specific COVID-19 drugs that have yet to be invented and so the modern power of retrosynthesis allows us to imagine more complicated molecules that have more sophisticated functions for tackling COVID-19. So it's like the ability to make new molecules influences the design of the molecules that you make and so we can design more sophisticated molecules because we can use these more advanced retrosynthetic tools to make them.

33:22 SS: What do these advances mean for the production of generic drugs which manufacturers hope, obviously, to make as cheaply as possible?

33:29 TC: In all likelihood, there's gonna be this continued decreasing cost as we get better and better at making molecules, so there's been automation of this retrosynthetic process. This is one of the main developments in recent years, is that we have commercially available softwares or open-source softwares that allow us to perform these automated retrosynthetic experiments that couldn't be... The technology wasn't accessible to anything but the most expert groups earlier. As these are now available to us, we are exploring ways that we can make these drugs cheaper and faster and better. So with generic drugs, if you look at a lot of the generic drugs that we currently have in our arsenal, they're largely simple molecules. Some of them are complex structurally, but they're naturally derived like morphine and codeine, so nature makes those for us, we don't need to synthetically make those.

34:29 TC: But what is coming our way is a wave of complex molecules. The ones that come to mind for me are the HCV drugs that are currently on brand and they're not generically available, but these are devilishly complex molecules. They really speak to the advances in chemical synthesis that we can even dream of having these molecules as a product and indeed, they are made but because they're so complex, they're really difficult to make and when they become generic, I think that there's gonna be... Companies are gonna be able to use their synthetic prowess to win in the market, whereas I think that historically, it's been a lot around the design of the molecule. This new wave of generic drugs coming have really sophisticated structures, they have chirality, they have unique functional groups and lots of little rings and heterocycles that make them difficult to make, but also make them have very specific or very powerful functions. With HCV, as I've been talking about here, this class of molecules, this disease has been all but eradicated because these molecules are so good at what they do.

35:39 SS: Looking ahead, what possibilities do you see in the future in the space that you get excited about?

35:47 TC: The thing that excites me the most is this idea of a robo-chemist, that we might have a system where you hit a button and you get a molecule that does something for you, and so thinking out into the kinda Star Trek future, there might be... Maybe you have symptoms of a disease and you hit a button, and the molecule gets designed and made for you right there.

36:06 SS: It sounds like what you're talking about is truly personalized medicine on a scale that I've never really heard of before.

36:13 TC: Absolutely. Yeah. I think that the biology behind personalized medicine is advancing rapidly so that we can understand... If you have this mutation in this enzyme, then that's gonna give you this type of cancer. So if we know that, then we, in theory, know what a molecule needs to do to hit just that mutated form of that enzyme, but then you've gotta make it. You've gotta think about what tools do I have to actually make the thing and that's going to influence your design. You're not gonna design something that you can't make quickly and so as retrosynthetic logic and strategy has evolved significantly, we look at molecules that were once too complex to even consider making and today, we would say, "Yeah, I'll make that." And so I'm super excited about this idea that, one day, we could push a button and get a molecule that does whatever you want. As well, I'm very excited about what's happening in education that I think that, right now, organic chemists are becoming a lot more data savvy. I think that maybe the lockdown of coronavirus has maybe forced us all into our computers and we've become a lot more data-centric as organic chemists in the past nine months, particularly. But right now, there's very much a movement to harness all of the data and digest it into new objectives in organic chemistry and I'm super excited about this.

37:37 SS: Tim, thank you so much for your time. It's been a really enjoyable as well as informative conversation and I appreciate the opportunity to pick your brain.

37:44 TC: It's my great pleasure, thank you so much.

37:45 SS: And our thanks to MilliporeSigma for making this conversation possible and to the

Science Podcast audience for your interest and attention. Until next time.

[music]

37:57 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions for the show, write to us at sciencePodcast@aaas.org. You can listen to the show on the Science website at sciencemag.org/podcasts. On the site, you'll find links to the research and news discussed in the episode. And of course, you can subscribe anywhere you get your podcast. The show was edited and produced by Sarah Crespi with production help from Podigy, Meagan Cantwell and Joel Goldberg. Jeffrey Cook composed the music. On behalf of Science Magazine and it's publisher, AAAS, thanks for joining us.