Science Forward--Drug Discovery

A production of CUNY Advance and Macaulay Honors College
http://cuny.is/scienceforward
License: CC-BY-SA-NC

[music]

Summer Ash: When we look at the fragments of the past, it can be hard to figure out how they all fit together. How can we use the evidence we collect to build a more complete picture, a model, to improve our understanding and ask more informed questions?

[background music]

For example, we know that in the second century the emperor Hadrian built a huge villa in the town of Tivoli, near Rome. But little of that villa remains today. So how can we know what it looked like, or how it was used?

Archaeologist Bernard Frischer and his team are working on this very problem. They're building a virtual 3D model of the villa using data from surveys of the site, documents and artwork of the time, and actual artifacts that survive in museums around the world. They're even using historical, astronomical data from NASA to reveal how Romans aligned certain buildings with the sun and with the planets.

But historians aren't the only ones that have to come up with new solutions to complicated puzzles. Scientists also have to pull together different lines of evidence, see how they connect, and then build models to better understand their data and direct their research.

New discoveries often come from putting together pieces you already have. In this video, we'll talk to scientists who are developing new drugs. We'll hear about their research and some novel approaches and even some venomous snails. Chemical biologist Derek Tan explains how scientists working on new drugs need to bring together a wide range of skills and approaches.

Derek Tan: Some of the specific skills that we use in organic chemistry are a knowledge of the literature, of reactions that are available. Pattern recognition, to know when to apply those reactions, and a deep understanding of reaction mechanisms. A chemist has to integrate that knowledge as well as an ability to view molecules in three dimensions. To consider their conformations and the impacts that that has on reactivity.

Chemical biologists, then, have to take all of that chemical knowledge to be able to apply the chemistry to study and controlling those systems. That's the challenge for us in training the next generation of chemical biologists, and that's one of the things that we do in our tri-institutional PhD program in chemical biology.

Summer Ash: What is rational drug design?

Derek Tan: Rational drug design is one of the major approaches to developing drugs whereby one chooses a target that the biology says is going to be useful for therapeutic indications. We try to develop a molecule to often inhibit the activity of that target, or otherwise interact with it. In our lab, we use both rational therapy approaches and serendipitous approaches to drug discovery.

Summer Ash: This is a very important part of the way scientists and science can work. Using multiple approaches at the same time provides more avenues and more information. It also allows for stronger confirmation and better reliability of results. Laura Juszczak Of Brooklyn College explains.

Why is it important to both study these proteins from an experimental standpoint and from a computer modeling standpoint?

Laura Juszczak: Because one validates the other. One method validates the other. You have the real world, what's happening in the real world. You shine light on these proteins. How do they behave in the real world? Then you have the modeling.

In the laboratory we're exploring different molecular systems and just waiting, or hoping that we'll get some result that will either confirm our hypotheses. But even more significantly and more exciting is when we don't get the results we expect, so there's this real ah-hah and hooray moment when that happens. It's that joy of discovery, of finding something new, that really keeps scientists going.

Summer Ash: Drug discovery, like so much of science, involves moving back and forth between discovery and testing. Finding new questions and using new techniques to answer them. Sometimes new ideas and new solutions begin in very unusual places.

Mandë Holford: We study the evolutionary history of venomous marine snails in order to figure out why it is that these snails have venom to begin with, and also what are the components in their venom that might have therapeutic appeal, or appeal for biomedical research purposes.

Juliette Gorson: We go about finding potential drugs in nature by actually going out into the field and collecting snails. I've been very, very lucky as the biologist in the lab to be able to accompany Mandë Holford in the field. I've been out to Hawaii, I've been to Papua New Guinea twice, and hopefully we'll be going to Abu Dhabi in November to collect.

We're also lucky because these snails have about 500 species in the family, so there are a lot of different bioactive compounds that we can take from these snails.

The family of snails that we work with is the Terebridae family. This is a close relative of the Conoidea family, which are more commonly known as cone snails.

These snails are like any other snail. They crawl along the ground very, very slowly. But the proboscis, so that hunting organ, shoots really quickly. They can shoot their prey in less than a second.

They're really exciting to watch. I've actually, when I was looking at snail-hunting snails, cone snails, they actually both slowly move around the tank. It's a really, really slow game of a predator trying to catch the prey. Eventually, once the cone snail gets close enough to its prey, it's going to stab it quickly and then consume it quickly.

Mandë Holford: There's an arms race happening between the predator and the prey, and so the venom has been evolutionary tested and approved. It's the best FDA in the world, because these compounds have to work.

We combine tools from chemistry and biology in order to investigate and try to figure out what's happening both in the snail, and also to identify novel peptides that can manipulate functioning and cellular physiology. Our biological tools are for the most part based in taxonomy, genetics, and evolution.

More recently, sequencing and bioinformatics. We use those tools because we're trying to identify which species are the ones that seem to be giving us bioactive compounds. We trace the evolutionary history of these venomous snails and we try to identify which lineages are the ones that seem to be doing what we are most interested in.

Once we have that information we then pair it with the chemical side in that we synthesize the peptide synthetically, and that is putting together the amino acids on a chain in a particular order. Then we fold, because peptides are only functional when they're in a folded format.

If you think of a pearl necklace, all those beads on the string, those are different amino acids. But you can't wear the necklace until you clasp it behind your neck. That's what folding is. Until you fold the peptide, it won't be functional.

After that, we then go through a series of biological assays to try to identify, what is the molecular target of this particular peptide? That'll tell us, OK, what we've synthesized is correct, and it seems to be bioactive. It doesn't tell us what the specific target is. It's like a funnel effect. You start very broad, and then you get narrower and narrower with each step.

One of the biggest misconceptions in my field is that discovery research is not relevant. I find that really troubling, because there seems to be this tension between hypothesis-driven work and discovery-driven work. Really, all of it is good work.

When you think that 70 percent of the drugs on the market right now were derived from natural compounds, the only way we're going to find those compounds is if we go out and do discovery work.

There are systematic ways to go about doing discovery work, which is what we hope we're doing by looking at the evolutionary history, identifying species from phylogenetic trees that look promising, and then going out and targeting those species, instead of just going randomly to the beach and picking everything up.

But discovery research is very, very relevant, and it's very important, and it shouldn't be diminished in any way, shape, or form. Because nature has a lot of the answers that we're looking for in science, and if we're learning to listen more and to better identify what those teachings are, then I feel we can make significant advances in science.

Laura Juszczak: The most interesting thing is the possibility that I'll get an unexpected result. That's what's really the driving force, the driving interest in science. Because you always think you're going to get a result, but then nature pulls the rug out from under your feet, and you get something totally unexpected.

Mandë: It's a lot of what we should be doing when we think about science as a whole. No one knows the answers, and if you're so tied to your hypothesis that you don't allow other things or observe other things that happened, then we're in danger and it slows down the rate at which we advance science.

[music]

Transcription by CastingWords