Frogs Help Fred Hutch Cancer Center Find the Shape of Small Things

Yasuhiro Arimura, PhD, brings frogs back to Fred Hutch to study the structure of DNA-linked molecular complexes.

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In the summer of 2024, cardboard shipping boxes containing 30 live African clawed frogs packed in damp wood shavings arrived at Fred Hutch Cancer Center.

The amphibians were delivered to the new frog room in the Basic Sciences Division and transferred into long white-framed water tanks stacked on blue racks like bunk beds.

After recovering from their journey, the mottled, greenish-brown frogs settled into their new homes, hiding in plastic tubes placed in the tanks or floating among lily pads, arms and legs splayed like babies at their first swim lessons.

Structural biologist Yasuhiro Arimura, PhD, had spent the first months since his hire at Fred Hutch in early 2024 preparing the frog room, tinkering with the settings on a complex bank of humming machinery and filtration pumps that maintain proper pH levels and precise air and water temperatures.

Now the first of his frogs had arrived, and he was eager to get started.

In the video below: Watch Fred Hutch senior multimedia producer Robert Hood and Fred Hutch News science writer John Higgins talk about how frogs help Fred Hutch researchers understand fundamental biology.

Why frogs at Fred Hutch?

Our genetics overlap so much with the frogs that exposure to a human hormone produced during pregnancy can trigger female frogs to release eggs the next day. That makes this species — Xenopus laevis — a versatile model organism to understand cells and embryonic development.

Frogs have made significant contributions to Fred Hutch science over the years, but Xenopus has been absent from the menagerie for about two decades. For various reasons, researchers moved

on to biological questions best answered by working with other model organisms such as baker's yeast, tiny worms, fruit flies, zebrafish and mice.

Arimura has brought Xenopus back to Fred Hutch for a new era of science because their eggs provide the molecular materials that he needs to make chromosomes in a test tube that look and behave like chromosomes formed naturally within a cell.

He uses the frog-made materials to figure out the structure of protein complexes that interact with DNA to form chromatin — the mixture of DNA and DNA-packaging proteins that cells use to choose which genes are activated and to make exact copies of themselves.

Mutations to those complexes play a role in cancer and other diseases, so Arimura wants to understand how chromatin structures regulate cellular differentiation, diseases and clinical treatments.

Finding the three-dimensional shapes of chromatin's protein complexes matters because the way the proteins fold determines their function. For example, if you open a spring-driven watch and observe the shapes of the parts inside, you can infer how each part works.

Those functions change at different stages of the cell cycle, working one way when cells are growing and another way when cells are preparing to divide.

But figuring out the shape of these protein complexes at different stages of the cell cycle presents many obstacles. They're tiny and not abundant enough when extracted from frog eggs to generate clear images using standard electron microscopy techniques.

However, Arimura brought more than a new generation of frogs to Fred Hutch.

He also brought a new method he invented that overcomes those obstacles, which advances the field of structural biology and creates new opportunities for collaboration.

The strange biomedical career of Xenopus

The story of how frogs became a model species for biology traces back to a British scientist who discovered in the 1930s that Xenopus, which dwells in the stagnant pools and quiet streams of sub-Saharan Africa, could be induced to release their eggs when exposed to a human pregnancy hormone.

That realization led to a living pregnancy test that replaced the infamous "rabbit test."

Doctors injected their patients' urine under the skin of a female frog and if the frogs released a puddle of tiny black-and-white eggs the next day, the patient was pregnant.

"And so it was that tens of thousands of frogs were infused with human urine between the 1940s

and 1960s," according to science writer Ed Yong.

By the 1960s, frogs were replaced by chemical tests that directly measure human chorionic gonadotropin, the hormone that triggers the egg-laying. But biologists found that the frogs were ideal for studying a range of fundamental processes including cell cycle, DNA repair and embryonic development.

Writing for The Atlantic, Yong told the strange and fascinating tale of a scientific journey that sent frogs to space and led to a Nobel prize when Xenopus became one of the first back-boned animals to be cloned.

Frogs also played an important role in early research at Fred Hutch.

The first generation of Fred Hutch frogs

One of the pioneers of the Basic Sciences Division, Harold Weintraub, MD, PhD, studied frog embryos to understand the structure of DNA and the proteins that influence how muscles form, which led to foundational discoveries.

Stephen Tapscott, MD, PhD, helped in that work as a postdoctoral researcher and later worked with frogs in his own lab at Fred Hutch.

Retired staff scientist Lauren Snider, PhD, worked with frogs in both Weintraub's lab and then in Tapscott's lab.

"A major interest in both groups was how cells acquire their differentiated functions during development," Snider said. "You go from a single egg that has no special functions to a full-blown organism that can do all sorts of things. There was a great deal of interest in understanding the gene activation that drove that."

She observed many frog embryos develop from fertilized eggs in a tissue culture dish to study what would happen if a gene was manipulated to become either overactive or silenced.

"I carried the project with me when I moved to Stephen's lab and we continued doing that together," Snider said.

In the mid-2000s, the Tapscott Lab moved on to other projects and stopped keeping frogs around.

Another Basic Sciences founder, Ron Reeder, PhD, spent his career studying frogs to understand the cellular machinery that transcribes DNA into RNA, a fundamental step in the process that makes all the proteins that do the cells' work.

His work focused on RNA polymerase I, the enzyme that synthesizes ribosomal RNA, which is the principal component of ribosomes, the cell's protein factories.

Reeder retired in 2002, and the lab was disbanded, ending the tenure of Xenopus at Fred Hutch.

Except for one frog named Fluffy, who had become a lab pet.

Last of the Fred Hutch frogs

Fluffy's precise genetic provenance couldn't be verified — he was Xenopus, but it was unknown whether his species was laevis, borealis or a possibly a mix of the two.

Though the uncertainty meant that Fluffy couldn't be used in experiments, the Reeder Lab kept him around anyway.

"Fluffy joined the Hutch in 1987 as the result of a slightly confused in vitro fertilization experiment in the Reeder lab," according to a caption of a black and white photo of Fluffy. "He lives very well in his water tub on Judy's bench [Judy Roan, Reeder's wife and longtime research colleague], eating kibble daily with a bath twice a week. He used to sing but has not done so for the last several years, perhaps having given up hope of luring any lady toads to his tub."

How exactly Fluffy got his name cannot be recalled, though one legend has it that Fluffy escaped his tank one day, visited some nearby lab rabbits and came back with fur.

In any event, when the Reeder lab disbanded, Linda Warfield, a research technician in the lab of Steven Hahn, PhD, took him in.

She situated him in a 10-gallon tank on a shelf above her work area. She furnished the tank with some rocks for Fluffy to rest on out of water and fed him his fishy-smelling frog chow every morning.

A sign wishing Fluffy a happy birthday — updated for his 22nd, 23rd, 24th and 25th birthdays — was posted near his tank as well as his official Basic Sciences ID badge with his picture and the words: "I'm hungry."

"I would come in the mornings, and he would see me and get very animated waiting for his food pellets," Warfield said. "When I would clean his tank, I would transfer him to a beaker, and I had to keep it covered because he would jump out."

Fluffy lived for several years in the Hahn Lab under Warfield's care.

Then one May morning in 2013, Warfield discovered that Fluffy, the last of the Fred Hutch frogs, had died.

She converted a sturdy, lidded cardboard shipping box for lab chemicals into a proper frog coffin and took Fluffy's earthly remains home.

"He's buried in my backyard under the dogwood tree," Warfield said.

A new generation of Fred Hutch frogs arrives

Arimura wanted to launch his career as a principal investigator at Fred Hutch because of its international reputation for expertise in chromatin, pioneered by Deputy Director Emeritus Mark Groudine, MD, PhD, who retired in 2023, and many others whose names Arimura recognized as leading researchers in the field.

When Arimura interviewed for the job, he brought a bowl of multicolored jellybeans tangled in string to illustrate one of the problems he hopes to solve.

Each string in his bowl represents a strand of DNA and each jellybean represents a nucleosome, a key component of chromatin that helps pack some six feet of DNA strands into the nucleus of a cell.

If Arimura wants to study the structure of a small subset of nucleosomes, say just a handful of the red jellybeans, it's hard to isolate that sample from the rest in the bowl, and even harder to get enough of that sample in one place to discover its structure using electron microscopes.

The conventional way researchers study how proteins interact with DNA is to make chromatin in a test tube component by component, like building a structure with Lego bricks one at a time.

That approach works for studying specific interactions and mechanisms such as how a protein binds DNA or changes its shape.

"That's what I did during my PhD work, and it was very useful," Arimura said. "But it doesn't fully reflect the situation that is happening."

Just because the Lego bricks can be assembled in a certain way in a test tube doesn't necessarily mean the cell builds it the same way in its native environment.

In real life, proteins are modified by lots of things that happen after proteins are made that change their shape and function.

"You cannot make it properly in a test tube," Arimura said. "That's why we need to have an approach to get the real structure happening in the cell."

That's where the frogs come in.

Rather than build chromatin step by step from purified components in the lab, it's more accurate to use frog eggs, because that's what nature designed them to do.

When an egg is fertilized, it takes DNA from frog sperm and quickly organizes it into chromosomes. During early development, when cells are dividing rapidly, eggs are especially good at replicating chromosomes fast and efficiently.

Arimura extracts from the frog eggs all the proteins required for chromosome assembly and cell division, and then chemically induces them to assemble into chromatin in a lab dish just as they would within a cell.

Frog-made chromatin

Here's how it works:

Arimura injects a female frog with pure hormone, not urine, and then places the frog in a bucket with water overnight. The next day he collects the unfertilized eggs she has released and returns the frog to her tank.

Next, the eggs are crushed and centrifuged to make an extract containing the molecular machinery needed to assemble chromatin outside of the cell's walls where it's easier to isolate for microscopy.

When he adds DNA from frog sperm to the extract, the DNA triggers the assembly of chromatin, just like it would in a real egg.

During interphase (when a cell is growing and functioning), DNA strands are loosely packed in a round nucleus and available to enzymes that turn on genes and initiate transcription, the first step in making that gene's relevant proteins.

By adding calcium, Arimura can push the egg extract into interphase to figure out the shape of the protein complexes at this stage.

He can also see how that structure changes in M phase, or mitotic phase, as the cell prepares to divide and the chromatin is tightly packed into visible bar-shape chromosomes, which compacts the DNA for cell division.

Cancer cells often have the incorrect numbers of chromosomes, which is the result of failed cell division. Many proteins must stop or switch their roles in M phase to focus on evenly dividing chromosomes into daughter cells. The protein complexes Arimura wants to study change their structure and function during different phases of the cell cycle.

Arimura is interested in the relationship between the shape and function of the complexes involved in the formation of two distinct parts of the chromosome during M phase called telomeres and centromeres.

Telomeres protect the tips of chromosomes during cell division like those tiny plastic tubes, or aglets, that keep the ends of our shoelaces from fraying.

Centromeres are like a waistband on chromosomes where a big protein complex called a kinetochore assembles during cell division to ensure that each resulting daughter cell gets a

complete set of chromosomes once division is completed.

Now a new generation of Fred Hutch frogs gives him a steady supply of chromatin to solve that problem.

But that leads to a different problem: It's difficult to concentrate enough of the frog-made sample to meet the requirements of cryogenic electron microscopy, or cryo-EM, one of the most powerful tools scientists use to find the structure of biological molecules.

Molecules too few and far between for standard cryo-EM

Cryo-EM suspends purified and concentrated molecules in a super thin layer of water on a metal mesh grid that is frozen so fast in liquid nitrogen that it resembles glass because crystals don't have time to form.

A machine shoots an electron beam through the frozen sample to a detector that creates millions of two-dimensional images of the proteins captured from many different angles. A series of computer programs averages and sharpens all those snapshots to generate a three-dimensional image of the protein with near atomic-level resolution.

Early pioneers of cryo-EM won the Nobel Prize in chemistry in 2017, and Fred Hutch installed its own $4 million system in 2021.

To prepare a sample for cryo-EM, researchers must generate a lot of the protein they want to study, typically by growing it up in another living system such as bacteria, yeast, insect cells or mammalian cells.

They need a highly purified and concentrated sample because the blotting paper used to ensure the liquid layer is thin enough for the electron beam to pass through it soaks up most of the sample. Whatever liquid remains after blotting must contain enough concentrated protein to get an accurate image.

But the protein complexes Arimura derives from frog-generated chromatin are so few and far between that after blotting, the remaining sample is too diluted — by orders of magnitude — for standard cryo-EM algorithms to reconstruct the 3-D structure.

"I need to significantly reduce the sample size requirement to see the structure of the native chromatin," Arimura said.

Solving that problem takes some magic — or rather, a tool Arimura invented called MagIC-cryo-EM, which makes it possible to study macromolecules in concentrations that are hundreds of times smaller than the thresholds typically required.

New methods make the most of tiny samples

At his previous job at Rockefeller University in New York, Arimura and his colleagues invented a new way to make the most of a small sample using nanobeads that are roughly 1,600 to 2,000 times smaller than the width of a human hair.

The nanobeads are linked to the protein complexes they want to study by a chain of molecules with intriguing names such as SPYcatcher and SPYtag.

The chain includes a spacer molecule that keeps a bit of distance between the nanobead and the target protein complex to make sure the cryo-EM gets distinct images uncluttered by the beads.

To prepare a sample for cryo-EM, Arimura mixes a solution with the nanobeads, tether molecules and frog-made chromatin, which grabs the protein complexes he wants to study and tethers them to the beads.

The next trick is to tow the tethered sample into position on the cryo-EM grid, the part that the electron beams shoot through to get the image.

The grid is a fine gold mesh, about 3 millimeters in diameter, with about 100,000 holes where the sample is captured in a layer of thin ice.

Arimura holds this little gold grid with special long tweezers, drops some of his solution on it, and then suspends the square over powerful neodymium magnets for five minutes as if he were roasting marshmallows over a campfire.

Yasuhiro Arimura holds grid with long tweezers to prepare a sample for Cryo-EM.Courtesy of Fred Hutch News Service/Robert Hood

The nanobeads respond to the magnetic field, which pulls the beads — and their tethered cargo — out of the solution and onto the grid, even though the grid itself isn't magnetic.

Think of it like a magnet under a table moving a paper clip on top of the table even though the table itself isn't magnetic.

Once the nanobeads reach the grid with the sample in tow, other molecules coating the nanobead

help it bind to the grid's surface.

Arimura pulls about 250,000 magnetized nanobeads onto that tiny disk, which fill the holes of the grid with many more of his targeted protein complexes than would typically land there using conventional techniques.

The increased efficiency compensates for the wasted portion soaked up by the blotting paper.

Using the MagIC-cryo-EM method allows Arimura to use concentrations of target molecules that are 100 to 1,000 times smaller than the concentrations typically required for cryo-EM.

Arimura and his Rockefeller colleagues tested the system out on a particular set of red jellybeans they wanted to pull out of the bowl: a protein complex called a linker histone that helps organize the packaging of DNA.

Deep dives into the structure of small things

DNA strands wrap around histones, which are clustered into eight-histone balls called nucleosomes that are threaded like beads on a string into fibers that are further intertwined to form chromosomes.

A linker histone acts like a clamp that holds the string in place and tightens the wrapping.

Arimura and his colleagues used the MagIC-cryo-EM method to find the 3-D structure of a particular linker histone, H1.8, at two different points in the cell cycle of frog-made chromatin.

Arimura, Hironori Funabiki, PhD, and Hide Konishi, PhD, a postdoctoral researcher in Funabiki's lab, described the results in a study recently published in the journal eLife.

They also solved another problem that arises during the computational averaging of millions of snapshots of a scarce and tiny molecule — some of those snapshots include extraneous particles that mask the target.

Arimura invented a method that excludes those fuzzy snapshots from the image the computer generates called Duplicated Selection To Exclude Rubbish particles, or DuSTER.

When they cleaned up the image with DuSTER, they revealed for the first time the structure of NPM2, a chaperone protein that helps H1.8 do its job of organizing chromatin during cell division as well as regulating the cell cycle and gene expression.

"This is an important new tool in the arsenal of single molecule biologists, permitting a deep dive into structure of native complexes," according to an eLife assessment accompanying the study. "This work will be of high interest to a broad swathe of scientists studying native macromolecules present at low concentrations in cells."

It's also of high interest to Arimura's colleagues at Fred Hutch, who are eager to collaborate.

"[Arimura's] expertise is to look at things at the atomic level, but he was not satisfied with the standard method," said Toshio Tsukiyama, PhD, DVM, one of Arimura's fellow chromatin experts in the Basic Sciences Division. "The thing about Yasu's method, it's not limited to chromatin proteins. Anyone who wants to know the structure of stuff will benefit."

Starting something new

Last year, Arimura hired two recent college graduates — Jacob Martin and Priya Digumarti — from Fred Hutch's Postbaccalaureate Scholar Program to help launch his lab.

Martin has continued with the Arimura Lab this year, joined by a graduate student, Juliana Young.

Martin and Matthew Ross, scientific communications liaison for Basic Sciences, used the division's 3-D printer to make a resting stand for the long tweezers used during the marshmallow-roasting part of the process. The stand makes it easier to suspend the cryo-EM grid over the magnet.

Meanwhile, 200 frogs are now settled into their homes (there's room for up to 400) and they have few duties other than laying eggs about every four months.

Arimura expects the frogs will live as many as 10 years and maybe more, which is a good thing because he needs their help to answer many questions about the protein complexes interacting with DNA that change shape and function in different phases of a cell's life cycle.

By dramatically reducing the samples size and amount required for leading-edge electron microscopy, Arimura's MagIC-cryo-EM method opens many new possibilities for discovering the structure and function of protein complexes in what amounts to an authentic, living system.

It may be possible to use human cells from cancer patients, for example, instead of frog-extract, to better understand how mutations can cause strange molecular complexes that affect DNA at different stages of cell division.

"Now we can target so many native things," Arimura said.

And just as collaboration marked the early years of frog research at Fred Hutch, Arimura's methods will help anyone trying to learn the shape of any molecule that has been too small and sparse to study until now.

"This idea has inspired people to start something new," Arimura said.

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