A year in the life of the mouse lemur

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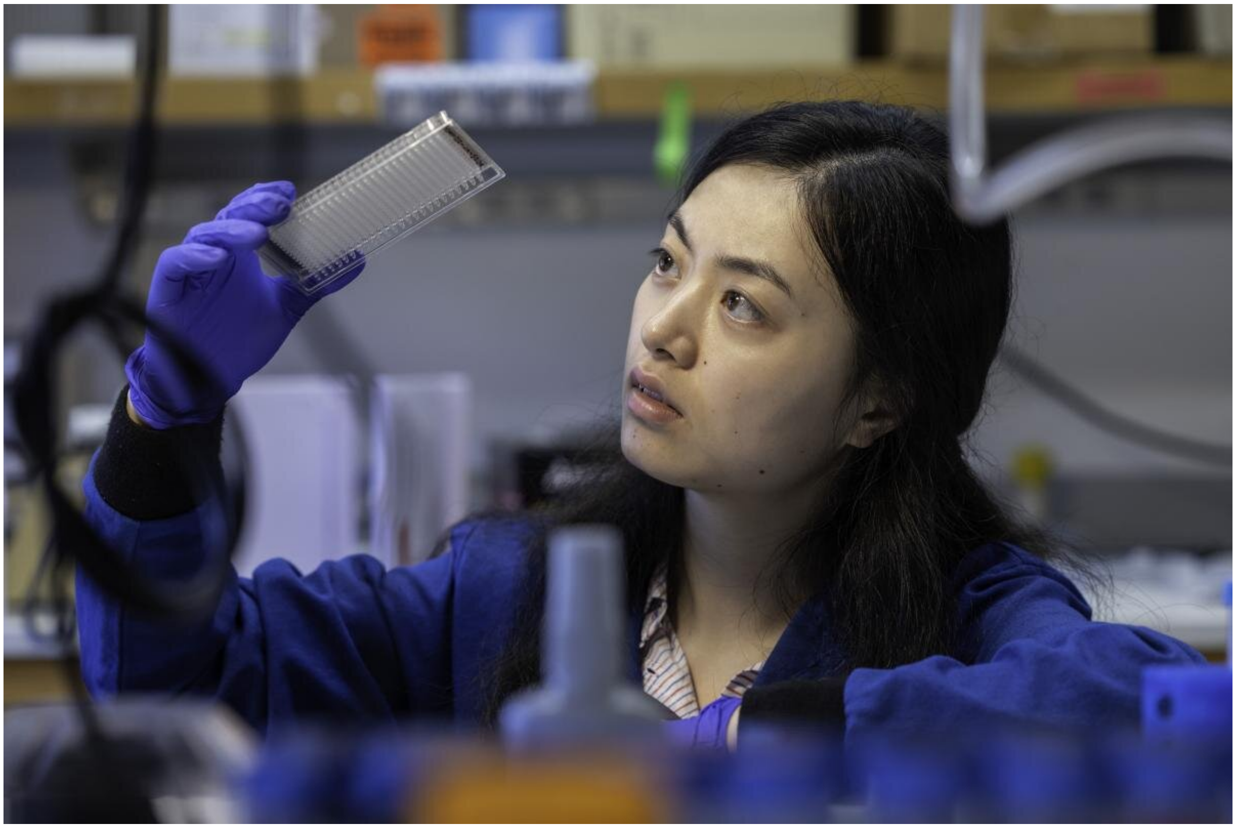
Mouse Lemur, Ranomafana, Madagascar. Credit: Francesco Veronesi from

Animals in the wild may not have an annual planner to keep track of the year, but they nonetheless manage to keep to a strict calendar—for example knowing just what time of the year to breed and when to hibernate. Research into the circadian clocks that regulate our 24-hour cycles led to a recent Nobel Prize, but very little is known about how animals maintain much longer-term seasonal rhythms.

Shixuan Liu aims to tackle this thorny question using her deep expertise in quantitative biology. The Wu Tsai Neurosciences Institute Interdisciplinary Postdoctoral Scholar has previously used systems biology approaches to study molecular oscillations in cells and quantitative imaging to explore the dynamics of cell division that operate on a timescale of hours. But now she is taking a leap across biological and temporal scales—applying her quantitative know-how to understand year-long oscillatory patterns across an entire organism.

To study these long-term oscillations, Liu turned to the mouse lemur, a diminutive primate native to Madagascar that exhibits robust seasonal rhythms—breeding during the summer and hibernating during the winter. There is a great deal of excitement about establishing the mouse lemur as a model organism in neuroscience and primate biology as it is genetically more closely related to humans than mice, reproduces fast and is easy to breed in the lab.



Liu has helped lead an international effort to create a molecular cell atlas for the mouse lemur, a public resource which she hopes will advance ability of researchers around the world to use this valuable model organism to better understand the evolution and function of the primate brain. Credit: Steve Fisch

Working in the labs of James Ferrell in the Department of Chemical and Systems Biology and Mark Krasnow in the Department of Biochemistry, Liu is currently leading a massive global effort to build a "molecular cell atlas" of the mouse lemur. With a team of collaborators around the world, she is looking at gene activity simultaneously in hundreds of cells types in different tissues all across the animal during different seasons.

Using this atlas, Liu hopes to uncover the intrinsic "master calendar" that controls seasonal rhythms in the mouse lemur. By understanding the biology behind seasonal rhythms, we may gain insights into important medical mysteries, such as why some psychological disorders and metabolic syndromes display seasonal variations and why globally more people die in winter than any other time of year.

We spoke with Liu about her work in establishing the mouse lemur as a model system to study seasonal rhythms, how hormone regulation may play an important role in this process and how the scientific community at large can benefit from open-access resources her work has created.

Can you tell me about how you ended up studying the mouse lemur?

I have always been interested in quantitative biology. My Ph.D. work focused on understanding molecular pathways that control cell cycle dynamics using quantitative microscopy. For my postdoctoral research, I wanted to apply this systems biology approach to understand molecular interactions at an organismal level. So at the end of my Ph.D., I talked with James Ferrell (Jim), a systems biologist at Stanford who studies the cell cycle oscillator and builds theoretical models of oscillator mechanisms in various biological systems.

Jim was interested in the idea of long-term biological oscillators. He had been talking with Mark Krasnow, who has been doing really exciting work to establish an animal called the mouse lemur as a new primate model organism. This also happens to be an appealing model for studying seasonal rhythms that are widespread in wild animals, yet we do not have a good understanding of how they work. One of the problems is that domesticated animals like laboratory mice have lost seasonal rhythms and hence, are not ideal candidates for the study of seasonal rhythms.

Mouse lemurs are among the smallest primate in size, only about 11 inches long and weighing ~60 grams. They share many logistical advantages of working with mice in the laboratory such as rapid reproduction. At the same time, they are more closely related to humans than mice on the evolutionary tree. As a part of a large international consortium, Mark's lab is doing groundbreaking work to establish useful resources to study this emerging model organism. I was very excited to explore new frontiers in a cutting-edge research area and joined the two labs for my postdoc.

Why are seasonal rhythms so important for animals like the mouse lemur?

Mouse lemurs exhibit striking seasonal changes in body mass and reproduction. During the summer, they have higher metabolic rates and are relatively lean. Summer is also their breeding season. During the winter, however, the animals transition into hibernation or torpor to conserve energy as resources become scarce. Their metabolic rates decrease and they accumulate fat in different body parts, especially the tail.

Of course, many wild animals exhibit seasonal rhythms. For instance, certain Arctic species routinely change the color of their coat to snowy white in winters. This phenomenon called seasonal molting involves the shedding of an external layer of the animal like fur or feathers and provides camouflage in snow.

Do humans have seasonal rhythms?

Humans may not show obvious seasonality, but several reports suggest certain trends. A famous example is the seasonal affective disorder (SAD) where patients face depression in winters and naturally recover in the spring. In addition, more people die during winters than summers. In the northern hemisphere, deaths are higher in December, January and February, while in the southern hemisphere, deaths are higher in corresponding winter months of June and July. In the US alone, death rates are about 10% higher in winter months.

Recently, Michael Snyder's lab at the Department of Genetics identified many blood biomarkers and hormones that show seasonal trends. For example, they found that HbA1c, a common biomarker for type 2 diabetes peaks in summer and declines in winter. Similarly, molecular signatures associated with immune responses, hypertension and cardiovascular diseases also often peak seasonally. Recently, Uri Alon's lab at the Weizmann Institute systematically analyzed millions of blood tests of the Israeli population from the last 15 years and observed seasonal rhythms in many hormones, like peaking of sex hormones in winter and growth hormones in spring. So, if we understand the mechanisms of seasonal rhythms in humans, we can potentially design treatment strategies for season-related illnesses or deaths.

Tell me more about the mouse lemur cell atlas that you created. Why was this an important step for the field?

In order to study a new model organism, it is essential to build a cellular and molecular foundation. The "Molecular Cell Atlas" of the mouse lemur is essentially a detailed catalog of over 750 types of cells and expression levels of proteins in different tissues in the lemur. We built this atlas using a technique called single-cell RNA-sequencing which allows us to measure expression of individual cells in different tissues of the organism.

This project depended on bringing in people from different fields including biologists, pathologists and genomicists as part of the Tabula Microcebus Consortium, which consists of ~150 scientists from over 50 labs at 15 institutions worldwide.

We have created a publicly accessible online portal hosted by The Chan-Zuckerberg Biohub where the scientific community can study cell types of the mouse lemur by tissue, organ and function. The data can be used to compare cell types to each other in different parts of the body and also for comparison across species like human and mouse where similar information is available. We believe the atlas will be useful in understanding not only seasonal rhythms in the mouse lemur but also broader questions in the field of primate biology and evolution. The pipeline can also be used to build similar atlases for emerging new model organisms.

The discovery of genes that control the daily circadian clock led to a Nobel Prize in 2017. Do we know what mechanisms regulate seasonal rhythms?

We know about cells in the hypothalamus that coordinate the 24-hour circadian cycle, but we do not know much about cells or molecules that coordinate the 12-month annual cycle in animals. Fortunately for us, mouse lemurs are ideal animals to study seasonal rhythms. Our collaborators Fabienne Aujard, Martine Perret, Jeremy Terrien and their colleagues at the National Natural History Museum in France have established a large breeding colony of ~500 mouse lemurs and—unlike standard lab animals—they exhibit seasonal rhythms in the lab, including seasonal weight changes, hibernation, and breeding behaviors.

Many animals, including the mouse lemur, can sustain seasonal rhythms even when the length of the day remains constant. This suggests an internal calendar controls these rhythms, independent of environmental cues. The molecular cell atlas of the mouse lemur we created gives us detailed information about what biological markers that are produced in different types of cells across different tissues of the animal. I am now comparing samples collected during summer and winter to create a seasonal version of this atlas. This will allow us to identify factors regulating and driving seasonal rhythms by measuring changes in levels of molecules in different cells of the body in different seasons.

You have a preprint where you used the cell atlas to study hormone signaling in mouse lemurs. What insights do hormones provide about seasonal rhythms?

We think hormone regulation may be vital for seasonal rhythms due to the kind of phenotypic changes observed in different seasons. In our recent preprint, we described 12 hormones that differed in concentration during summer and winter, including testosterone, melatonin, thyroid and several gut hormones. We also found that these hormones target a broad range of cells and tissues. We know about changes in appearances in some tissues during different seasons, for example, increased fat in adipose tissues and decreased size in gonads during winter. Our data suggest that many other cell types likely experience changes in their physiology or function in response to the seasonal hormones. In the future, we may be able to tease apart these mechanisms and compare them to seasonally varying hormones in other organisms like humans to understand season-associated human diseases.

What are your hopes for how the mouse lemur resources you've created will be used by the scientific community?

Traditionally, in order to study a biological process, we have often focused on only one or few molecules and pathways. A molecular cell atlas, on the other hand, provides insights into relationships between different cell types and organs on an organism-wide level. We are now using the atlas to study mouse lemur gene evolution, physiology, and disease with different collaborators. In collaboration with Prof. Peter Perham at the Stanford School of Medicine, we are studying expression levels of immune genes in different cell types. We also have an ongoing collaboration with Prof. Bo Wang at Stanford Bioengineering to study the evolution of gene expression patterns across human, lemur, and mouse. We hope this rich data can be further exploited by the broader research community to better understand primate biology and disease.

All our data and pipelines are publicly accessible. We believe this will be a valuable resource for establishing cell atlases in emerging model organisms. This will also serve as a new way to identify genes and their function by doing organism-wide comparisons and break away from the mold of studying select few genes in only select model organisms.

More information: Shixuan Liu et al, An organism-wide atlas of hormonal signaling based on the mouse lemur single-cell transcriptome (2021). DOI: 10.1101/2021.12.13.472243. On bioRxiv.

Tabula Microcebus: A transcriptomic cell atlas of mouse lemur, an emerging primate model organism (2021). DOI: 10.1101/2021.12.12.469460 On bioRxiv.

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