UC San Diego
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By Mario C. Aguilera Jul 02, 2020

Historical Disease Meets Modern Biology in New Faculty Member Cressida Madigan's Lab

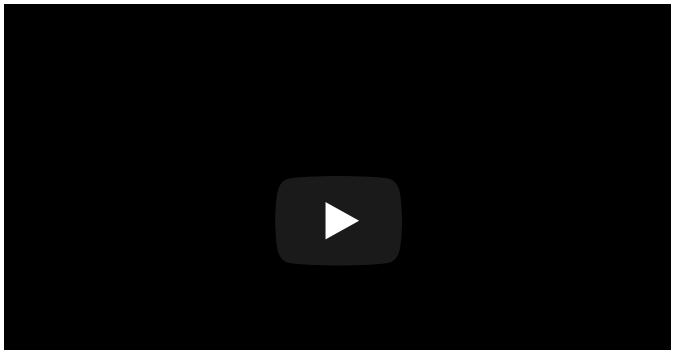
New Biological Sciences faculty member Cressida Madigan doesn't mind if an ancient disease such as leprosy is not something we think about every day.

Influenced by her art historian parents and diseases that changed the course of world history, Madigan works at the crossroads of microbiology, neurobiology and infectious disease research. Using modern biological tools, including a see-through fish that reveals infection pathways, Madigan believes exotic infectious diseases may hold clues to more modern afflictions such as Alzheimer's and Parkinson's.

In this new faculty profile, she discusses her scientific interests, European art history influences and the fascinating connections between her research and the COVID-19 pandemic.

Q. Broadly speaking, what are your research interests?

A. My lab is interested in understanding how microbes are controlling the functions of our nervous system. Biologists have only recently come to understand that this is happening in many different environments, every day. Often *how*microbes like bacteria or viruses are changing the way our nervous system works is not really well understood. My lab is interested in understanding how, but also *why*. Why would a microbe want to change the way we make a memory or our perception of pain or inflammation in the brain? What's the benefit to the microbe of doing that? Essentially, I'm studying a three-way interaction between microbes, the immune system and the nervous system.



Q. Describe the targets of your research.

A. The primary questions that my lab is investigating address two examples of different neurological infections. I work on leprosy, which is a bacterial infection of our nerves. Leprosy does something very unusual to our nerves. It stops them from working. It stops us from being able to sense pain in our skin. How that happens

[redacted] is almost completely not understood but we know it involves the immune system. What I'm trying to figure out is how does leprosy take our immune system and cause it to attack our nervous system? And can we use this microbe to learn how interactions between the immune system and the nervous system are occurring in lots of other diseases? The other half of my lab works on mycobacterial infections of the brain—tuberculosis (TB) meningitis is the most common of those. In each disease, we are interested in understanding how the microbe regulates inflammation within the nervous system and then how that inflammation destroys the cells of the nervous system and changes their function.

One of the really fascinating things we are finding about these exotic infectious diseases is that they activate the same inflammatory pathways that are activated in the brain of someone who has Alzheimer's, Parkinson's disease or multiple sclerosis. The way that inflammation works in the nervous system seems to be similar between these infections and these common neurodegenerative conditions of humans. So, what we learn from studying these infections is going to be, we think, broadly applicable to understanding many neuro-inflammatory conditions of humans.

Q. What parallels do you draw from the current COVID-19 pandemic and your research?

A. There are so many fascinating connections between SARS-CoV2 and the infections I study! In terms of the basic biology, some COVID patients have neurological symptoms (for example, loss of smell and taste). And some children with COVID have suffered from vascular inflammation that resembles Kawasaki Disease, which is another interest in my lab. There's also overlap with the vascular inflammation that occurs in bacterial meningitis, another focus of our work. It seems likely that we will pursue one of these COVID projects at some point.

From a public health perspective, I'm sorry to say that COVID-19 is impacting the same patient populations that suffer most from TB: people living in poverty. To understand this, I'm working right now with historians to compare COVID-19 with epidemics of the past. Remarkably, we're finding that the bad human behavior we're seeing during COVID-19 (racism, xenophobia, violence, food shortages, misinformation campaigns) is not new! Rather, humans have had these same responses to epidemics, going back to the very first recorded outbreaks. I find that both comforting and profoundly disappointing. This research will be a focus of an undergraduate course I'll be teaching on plagues (BILD 30) in Spring 2021.

Q. Describe your scientific interest origin story.

A. I got into science strangely enough through my parents. They're both art historians, so growing up I spent a lot of time in Europe with them, hearing about the various plagues that would come through Europe and wipe out huge percentages of the population. They were interested in how that affected

the art. I was more interested in: How does an infection kill a third of Europe? It's amazing that's even possible and that's what really stuck with me.

I love infectious diseases that have a historical context to them and have been important throughout human history. Leprosy is a great example, also tuberculosis. These are some of the earliest known infectious diseases of humans. So, there is a lot of evidence that they changed the way that humans have evolved in terms of our DNA, certainly, but for me I'm also interested in how they've changed the way our culture has developed.

When these epidemics of TB or leprosy and other infectious diseases came through Europe, they changed everything about European society and history. They changed the outcomes of wars, the kind of art people were making and the kind of music that was being written. With examples like the plague, they reduced the population density in Europe by huge amounts. So some of these diseases had a huge impact on the way human history played out.

Q. Many people don't realize that leprosy is still actively afflicting people in many places around the world.

A. Today, leprosy is not going to be a concern for most Americans. There are about 200,000 new cases every year, but they primarily occur in South America and Southeast Asia. So, this disease is not by any means gone from the world, but it has decreased in frequency a lot. So, why am I interested in a disease that's on its way out?

There is fascinating biology going on with leprosy. This is an organism that is one of the oldest infections of humans. It has been co-evolving with our immune system for tens of thousands of years. So, if you want to understand how your immune system works, what better teacher could you have than an organism that's been engaged in this very high level chess game, essentially, with our immune system, for as long as we have been Homo sapiens.

Leprosy is not an infection that Americans would typically have any experience with, but I really think we live in a global community, a global village. So, the infections that I might run into are not any more important than the infections that someone living in poverty in Peru, for example, might run into. Yet there is not as much funding that goes toward those infections and diseases of poverty. I'd like to be a small part of the solution to that. I want to make sure that the money that is being spent on infectious disease research is not being disproportionately put toward things that are important to Americans, affluent Americans. I think that diseases of poverty are a worthy place to spend that money.

Q. How do you study these diseases?

A. The model organism that we use is zebrafish. As adults, they are about an inch and a half long but the larvae are only about a millimeter or two long and one of the really remarkable things about them is that they are completely optically transparent, sort of like glass. So, that means that we can do really

nice subcellular confocal imaging of microbes interacting with the nervous system or with the immune system at any site within the animal while it's alive. We can take these really lovely time-lapse movies of microbes infecting the brain and changing the function of different cells within the brain.

Zebrafish have been used in neuroscience for decades and there's an increasing use of them in immunology, but no one has really brought together the neuroscience tools in zebrafish and the immunology tools in zebrafish. I'm basically combining those two toolsets in the context of infection. So the combination of genetics and imaging give us this unprecedented view of neurological infections that is not available in any other model organism.

Q. Why did you choose to come to UC San Diego?

A. UC San Diego I think is one of the most exciting places to be working on microbiology and neurobiology. The research that's done here is very cutting edge and really pushes the envelope. But they support scientists in doing that kind of research. My research is a little unusual. When I went on the job market I was worried that, would anyone want to employ someone who works on leprosy?

Luckily, people did. But I think one of the things I was looking for is an institution that was willing to take the plunge with me and pursue some of these questions that other people weren't pursuing in the microbiology field. One hundred percent I know I made the right choice. My time here has been amazing. I'm really happy with the support from the institution, with the students and with the academic environment at UC San Diego. I couldn't be any more happy with the way my research has been playing out in terms of the academic environment here.

Madigan earned her Ph.D. in microbiology and molecular genetics at Harvard Medical School and completed postdoctoral positions at the University of Washington and UCLA. She joined the Division of Biological Sciences' Section of Molecular Biology in 2018.