Host: Robert Frederick
Hello and welcome to The Conjectural — an experiment to figure out a better way to decide what science news is, and how we should talk about science. The data for this experiment? Your feedback to TheConjectural.com. I'm Robert Frederick. In this episode, a story about what just might be the most important part of the human genome.

It takes just three little words to change a life. Three words to inspire someone. Three words that can cause another's heart to race. Three words that can set in motion the most wonderful events. Perhaps because of the power of these three words, it can often take great courage to say them. And it can take a lifetime to get comfortable with the sentiment that's behind them.

The three words are "I don't know." Okay, so you might argue that's two words and a contraction, but still. Among scientists, "I don't know" is often more exciting than "Eureka!" The blissful highs and devastating lows that go along with "I don't know" can last a long time.

For Ting Wu, a genetics professor at Harvard Medical School, it's been over a decade.

Speaker: Ting Wu
In my lab, it's understood anyone who wants to work on this project, I bring them into my office and we have a conversation and I always tell them that the only way they can work on this project is if they are willing to wake up every morning ready to know that they are completely wrong. And that's the only way we can go forward. So I could be wrong completely tomorrow.

Host: Robert Frederick
Wu was speaking in front of a large group of science writers, like me, at the 2015 ScienceWriters meeting, which was held earlier this month in Cambridge, Massachusetts. At the end of her talk, time for questions. I asked one.

Interviewer: Robert Frederick
You mentioned early on in your talk that everything that you know now — today — could be wrong tomorrow — I don't know if that timeline is hyperbole or not — but what would be a piece of information that would throw you off or lack of information — an experiment that you might do that would say 'Oops…'

Interviewee: Ting Wu
We're on the wrong track.

Interviewer: Robert Frederick
We're on the wrong track.

Interviewee: Ting Wu
That's a great question. So, I'll tell you a story. I thought our model was going to last for two weeks….

Host: Robert Frederick
Wu then told a couple of stories about her team's model — her understanding of what just might be the most important part of the human genome — might be wrong and all the ways they tried to show that her team's model was wrong. But they kept failing to do so. Of course, failing to show something is wrong is not enough to show that something is right.

Interviewee: Ting Wu
I think the thing, well, you know, this is… what would make me feel like we were completely wrong?

Interviewer: Robert Frederick
Sorry.

Interviewee: Ting Wu
It is definitely one of these ethical things about being a scientist, right? You come up with data, can you come up with a model?

Host: Robert Frederick
But even for all the stumbling it caused her, Wu actually loved the question. She concluded by giving me a big smile, and said this:

Interviewee: Ting Wu
You know, I, let me think about that as I…. You caught me. I'm going to, I'm going to have to think about this. I'm going to answer some more before this session ends.

Host: Robert Frederick
And after her talk, I went up to her and the first thing she said to me was:

Interviewee: Ting Wu
I loved your question!

Interviewer: Robert Frederick
Thank you! Thank you! Have you thought about it any further?

Interviewee: Ting Wu
I have been thinking about it, and I think that… we were — actually, I have to tell you — stunned every… I thought this model was going to die in two weeks. It's been 10 years.

Host: Robert Frederick
What Wu has been studying in the genome for all that time is what are called "ultraconserved elements." They are parts of the genome that just don't change. From her talk, Wu explains:

Speaker: Ting Wu
Alright, where are they? They are scattered across the entire genome….

Host: Robert Frederick
And now the really amazing part:

Speaker: Ting Wu
They're 100% identical between human, mouse, and rat….

Host: Robert Frederick
Now, a mouse and a rat may look somewhat alike, but from a genetics standpoint, mice and rats are very, very different from one another. So the fact that there are parts of our genome that are 100% the same as mice and rats' genomes means that for tens of millions of years those parts of

our genomes have been conserved: they've remained unchanged. It turns out, though, ultraconserved elements in our genome have been frozen in time for a lot longer than that.

Speaker: Ting Wu
They have been conserved for between 300 and 500 million years — way before the dinosaurs. Something happened, we think, in the common ancestors between mammals, reptiles, and birds that froze the molecular clock for these sequences…. They are all unique…. Alright, here's the puzzle. We have no idea what they do. We have no idea why they've been so conserved…. ….And here's the problem. In general computational biology believes is the higher the conservation, the more important the function. So basically what this is saying is the most important parts of our genome — we have no idea about the most important parts of our genome.

Host: Robert Frederick
And that's what Wu has been trying to figure out for more than a decade. That's the "I don't know" that she is willing to wake up for every morning — ready to find out on any day that she is completely wrong.

Interviewee: Ting Wu
They are, I think some people say, "The most mysterious thing to come from the genome" because they are so puzzling.

Host: Robert Frederick
Again, speaking to her one-on-one after her talk she speculates about what these ultraconserved elements in our genome might be for.

Interviewee: Ting Wu
I think these elements represent a new kind of genetic element, a new kind of function, and it's function is simply not to change. Unlike promoters and transcription units that make a product or embody an activity, I think the function of these elements is to not change. And I think that it would be just so much fun to have that kind of element.

Host: Robert Frederick
What would an unchanging element in a genome be useful for? Wu says you might think of the ultraconserved elements as fences around playgrounds. Inside the playground, the genome can play — evolve, or change. But beyond the fence, outside the playground, no playing allowed.

Speaker: Ting Wu
So they basically keep certain parts of our genome intact while letting other parts of our genome become malleable.

Host: Robert Frederick
And let creatures evolve into different things, like mice, or rats, or us. But again, no one really knows yet. As it happens, in one of the many experiments Wu and her colleagues did to try to prove themselves wrong, they removed the fence: they removed four of the ultraconserved elements from the genomes of mice. In doing so, the researchers thought, if these elements of the genome are so important to have been conserved for hundreds of millions of years, removing them should mean the mice would die, or maybe, if they live, they'll be unable to have baby mice.

Speaker: Ting Wu
And amazingly these mice were completely viable and fertile. This was a shock, even to us. What it says is that these elements, which have remained unchanged for over 300 million years, or change extremely slowly, they're actually completely dispensable for viability….
It's at this point that I have to tell you I have no idea this model is right. I also need to tell you that it is not a very popular model in the field. The most popular models have to do with ultraconserved elements regulating very important genes. So, this model — for which there, at the time we proposed it, there was no evidence — could explain ultraconservation, but did not fit with what we knew about biology.

Host: Robert Frederick
And in the 10 years since Wu and her colleagues proposed their model, what's changed? Well, scientists have learned a lot more about biology, and Wu has continued to experiment and search for evidence that would make her to say "Oops."

Interviewee: Ting Wu
We're on the wrong track.

Interviewer: Robert Frederick
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Host: Robert Frederick
At the end of my interview, Wu still isn't sure what that evidence might be. So I unplug my microphone, put away my recorder, and she starts talking to someone else. But then she finishes up and turns my way and smiles. I turn my recorder back on. She walks briskly over but before she speaks, I see she's positively bubbling and can hardly wait to say what she wants to tell me. Scientists often talk about how exciting it is to make a discovery, to be the first person in the history of the world to know something new. Eureka! I've found it! And I get the sense that it's that kind of excitement Ting Wu has at this moment, too. But, in this case, is it because she's quite possibly the first person in the world to know something new that we don't know — and that there just might be another way to disprove her own understanding of ultraconserved elements? Is this really what she's so excited to tell me — that she's thought of a way, an experiment to run, that could disprove something she's been working on for 10 years? Now I've been the one stumbling, but finally, I get the microphone plugged in and she leans in and says:

Interviewee: Ting Wu
I have thought of one thing, and probably more, too.

Host: Robert Frederick
You've been listening to The Conjectural. Thanks to Ting Wu of Harvard Medical School, the National Association of Science Writers, and the Council for the Advancement of Science Writing for hosting and participating in ScienceWriters 2015. You can find us online at TheConjectural.com where you can give feedback and support, download a transcript, and subscribe to the show. Follow me on Twitter @TheConjectural. I'm Robert Frederick. Thanks for joining us!