Steve Lewis 00:09
Welcome to Speaking of Mol Bio, a Thermo Fisher Scientific podcast series about molecular biology and its trending applications in life sciences. I'm Steve Lewis, and I'm delighted to welcome you all to season three of our show. We have a fabulous slate of guests coming up to discuss a broad diversity of topics in molecular biology, from biosecurity to epitranscriptomics. I've learned so much from scientists on the cutting edge of our field, and I can't wait to share with you all this season. Today, we kick things off with Dr. Giles Yeo, a professor of molecular neuroendocrinology at the University of Cambridge's MRC metabolic diseases unit. Giles has studied food intake and the genetics of obesity for over 20 years. We begin by asking Giles about his academic background and how he found his way to Cambridge and his current position.

Giles Yeo, PhD 01:07
I'm a transplanted Californian. I did my undergrad at Cal Berkeley, University of California at Berkeley, where I did molecular and cell biology. Then I specialized in genetics in my senior year, and really got hooked on that, and so ended up in Cambridge doing a PhD in molecular genetics of Japanese puffer fish. So I worked in the lab of Sydney Brenner for my PhD, though, and he's obviously one of the fathers of molecular biology. He won a Nobel Prize in 2002. It is one of these things where I didn't think that the molecular evolution of Japanese puffer fish was going to pay my mortgage. And so I went. My wife is English, so I met her at the time. I wanted to stick around Cambridge, and so ended up in a lab studying the genetics of severe obesity. And so that was my in and then from then on, I then started doing the genetics of obesity, molecularly characterizing mutations that we found in genes that caused obesity, initially in children and now, really throughout the body weight range.

Steve Lewis 02:07
Now you are the honorary president of the British Dietetic Association. Can you tell me a little bit about that as well?

Giles Yeo, PhD 02:14
So the British Dietetic Association, or the BDA, is two things. It's the union, actually, of all the dieticians in the UK, so there's over 10,000 members in it. But it also forms their professional organization. It's chaired by a dietician and run by dieticians. Obviously, it's a professional organization, but they needed someone as an honorary president, so it's a titular role, shall we say, who is sort of like field adjacent, who could bring something else to the table. And so obviously I study obesity, and I study food intake, and so that's obviously related to dietetics, but I also have, at least within here the UK, some form of a platform. And so I could bang a pail, shall we say. And so if they needed me to front something, if they have a new campaign that they wanted to then they can utilize me to actually go and front things for them in. But I'm not a dietician, just before people thought to ask.

Steve Lewis 03:10
I want to take a moment to highlight the fantastic passion you have, very clearly for scientific communication. And I do really appreciate kind of the story that you told, and how important it is to really take that moment, to take your technical expertise and bring it out into the world in a very unabashed and very educational way.

Giles Yeo, PhD 03:35
I guess it's twofold. I had a pre-pandemic view, and the pre-pandemic view was, well, first of all, why are we having this weight stigma? That was one, but actually that most of us are taxpayer paid. So while 0.0001% of those people might understand what I do, 99.9% don't, and I feel that there was a duty to let them know what we were doing. So that was that. Then the pandemic hit. And what have we known, seen over, over the last few years of pandemic? Well, I think we've seen some wonderful examples of science communication. We've also seen some god awful examples of science communication. And I think what I would hope that people now understand, you know, in a post pandemic, whatever you want to call it, world, that bad science communication within a viral pandemic kills people. But this is also true for most things that we study. I study obesity and nutrition; bad science communication will kill you over a different temporal rhythm. It doesn't kill you like at the same speed, but it will. Same thing for cancer, same thing for most things that you study, bad science communication tends to eventually kill someone sooner than they could. So for those two reasons, I remain passionate, and I think it's not just something nice to have. I think it's one of my duties as a scientist.

Steve Lewis 04:57
Let's, uh, let's dive a little bit into your science. Why don't you tell me a bit about what your lab does and maybe what you're working on today?

Giles Yeo, PhD 05:05
Put simply, I'm interested in how hormones south of the neck communicate at the molecular level to the brain. That's pretty much what I study in the context of body weight. Okay, and so, in all contexts, I'm interested in how these new drugs, Ozempic, Mounjaro, how they function within the brain, for example. And so there's two elements to what I do on a day-to-day basis. We use the prism of genetics in order to point us to the molecules and genes to study. So in other words, we look at any number of different approaches prior to the whole next generation sequencing thing, we use candidate gene approaches in order to identify mutations in genes, and that was interesting, and that was obviously a bit of a gamble. And then next generation sequencing occurred, and now we have too much information rather than too little information, but we then tracked down genes that are that may or may not be associated with body weight changes, and then molecularly try and characterize them. I'm not a mouse physiologist per se, so I tend to use it in as much a human context as possible. So we tend to use stem cells, you know, and edit mutations into stem cells and then functionally characterize what happens. So that's one element of it. The second element of it is the circuit mapping in the brain. So we now know that the genetics of body weight, of which obesity just happens to sit at one end of the spectrum, is, by its definition, the genetics of how our brain influences our feeding behavior. Okay, so in other words, the genetics of body weight equals the genetics of eating. So what we try and do is look at circuits within the brain, because it's a brain control, but it's pretty difficult to look at it in humans for obvious reasons. So most of our circuit mapping have come from mice, but now with the technologies that have emerged, a single cell, single cell genomics, spatial genomics, together with access to brain donor samples, the largest part of my funding at the moment is in using spatial and single cell genomics to map circuits within the human brain. So we're working on a hypothalamus. So people don't know where

the hypothalamus is, the bridge of the nose, base of the brain, sitting right above the pituitary. Within the context of body weight it acts as a fuel sensor to them. And so we're mapping that area. Just got a paper. It's just in press at the moment, we've got a 3D map of it, and then we're also doing the hindbrain. Now, the hindbrain is where the vagal nerves come and feed into where the gut hormones, where a lot of things, and we're mapping there as well. So that is my day-to-day job is looking at genetics of body weight changes and looking at what those mutations may or may not be doing and then using single cell genomics and spatial transcriptomics in order to try and map the feeding circuitry within the human brain.

Steve Lewis 07:48
There's a lot of different directions we can go with that. Starting at the high level, I don't think I can turn on the television without seeing four or five GLP-1 promotional commercials. So what do you think about that?

Giles Yeo, PhD 08:03
It's a crazy time to be within the field of obesity. You know, I've been in the field now nearly 30 years, and we have never had such effective and, broadly speaking, safe tools in order to treat obesity. For your listeners who don't know exactly what they are. they are, in effect, modified gut hormones. They're naturally occurring hormones that in that are secreted by the gut after you eat. Every mouthful of food that we eat, and it moves through the esophagus, the stomach out the other side, hormones are released. And there are over 20 different gut hormones that we know about that are released by the gastrointestinal tract. Most of them make you feel full. GLP-1 is one of these hormones that go up and Ozempic slash Wegovy, semaglutide is the chemical name of it, is a modified version of GLP-1. Something like Mounjaro and Zepbound is a modified version of two, GLP-1 and GIP. And so they are incredibly powerful. They signal peripherally, so to the pancreas, to enhance insulin secretion. And actually that was their initial role as a Type 2 diabetes drug. The side effect, however, was weight loss. So that was the initial thing, the side effects. So people are going, “Ooh, look at all this weight loss.” And so they all the major companies out there, then re-trialed their incretin-based therapies. These are incretins because they enhance insulin secretion and retrial them for obesity and now crazy, crazy stuff. The interesting thing, as I'm beginning to find out, is that aside from semaglutide, which is a single GLP- 1 signaling to GLP-1 receptor modified version, all of the other drugs that are based on multiple hormones, most of these companies don't actually know how they work functionally, and so I'm working with a couple of the companies to try and understand how they work. We're mapping the receptors for the various drugs within the parts of the brain that matter when it comes to food intake. That's what we're doing within the space. But it is a really interesting time, and it's exciting to see that so many people are going to be helped by these drugs.

Steve Lewis 10:15
One of the things I'm struck by in this conversation is your vast knowledge of physiology, just how the different components of the human systems work together. And I know that's your research focuses on the influence of genes on feeding behavior and body weight. Specifically, why don't you talk a little bit about maybe the neuro aspect, and how you came to that area.

Giles Yeo, PhD 10:44

Entirely by chance. So I'm an accidental neuroscientist. When we first started in this business, we were looking for mutations that caused severe obesity rather than normal distribution, and the mutations we found sat within the fact sensing pathway of the brain. So your brain needs to know two pieces of information to regulate your food intake. It needs to know how much fat you have, because how much fat you have, the long-term energy stores, how long you would last in the wild without any food, put simply. It also, however, needs to know what you're currently eating and what you've just eaten. So these are going to be your short-term energy stores, and they're going to come from your gastrointestinal tract, your GI tract. All of these are hormonal. Your fat hormones and your gut hormones circulate and signal to the brain. Now these mutations that we have found happen pretty much all within this fat sensing pathway. And so we sort of like it was like pulling a thread where we found, you know, another receptor, then another gene, then another enzyme, then another receptor, and then before we knew it, you know, aside from the long-term signals, from fat or the hormones, everything we found was within the brain. And so since this happened, then you said, I suddenly needed to know something about the brain. And this happened, you know, two or three years into my job, and so since then, I've had to be a neuroscientist. So if I didn't do any professional neuroscience training, it's not like I didn't have a degree in it. I sort of, then you just learned on the job about neuroscience. So that's the neuro, that's really is the neuro element to it, where, let's put it this way, a lot of people, their brain is less sensitive to these circulating hormones. So say you're carrying 20 kilos of fat, 40-50 pounds of fat, or whatever. It doesn't really matter, but if your brain is only sensing if you have 10 kilos, but your brain is only sensing 8 kilos of fat. Just as an example, okay, it's going to say "Eight, eight. I thought we had 10," and it's going to try and drive you to eat more to get you to 10 kilos, but you're already at 10 kilos of fat, which means that you gain weight, which means somebody can be heavier than someone else in the same environment. Then if you had, I don't know, 1,000 calories for lunch, just as an example, but your brain only sensed that you ate 800 calories for lunch, you see where I'm going with this. So then if your brain is less sensitive to it, it said, "I need to eat more food," which is why two different people sat across the table from each other ordering exactly the same meal. Someone can feel fuller than someone else after they've had exactly the same meal, even though someone is roughly speaking the same size. That's, those are not only where the genes sit, but those are some of the, you know, some of the molecules that are actually involved in why somebody might eat more than someone else and therefore be heavier than someone else.

Steve Lewis 13:31
That's really interesting to think about from a systems biology perspective. And you know, you have the compound neuro endocrinology, as two combine cross disciplinary approaches to both your area of expertise and also your title. Are you going to see more of that convergence, do you think, as we advance technology?

Giles Yeo, PhD 13:56
It's never been more relevant now because of these new drugs. Because ultimately, that's what, that's by definition, is what you're studying, right, how the drug signaling, signals to the brain. It's interesting in terms of drugs for obesity, it's not like people haven't tried for a long time. There were a lot of other drugs that were small molecule drugs, and the main issue with those drugs is, while they were effective for weight loss, they had too many side effects and so were always withdrawn. The difference between modifying a native hormone is they self-home to the correct area of the brain, and that's crucial, right.

So you modify it so that you don't you don't mess about with what it signals to, otherwise then you start to create problems. But what you do is you modify its half-life. You do things like that, but ultimately it still will only bind to the receptor it was evolved to bind to. And so I do think that this is a good way of trying to tackle drugs. Some drugs do require small molecules. I'm not saying that that's the only way to do things, but if you're dealing with the brain, and if you're trying to use a systems physiology approach to try and treat a disease of the brain then it is always, to my mind, a better place to start. If you start with a native hormone, which you know will target correctly, and start from there and then maybe there's new biology that actually emerges.

Steve Lewis 15:21
We hope you're enjoying this episode of Speaking of Mol Bio. We wanted to take a quick moment to remind you about the Invitrogen School of Molecular Biology. It's a great educational hub for molecular biology with rich and reliable technical content designed for new and experienced molecular biologists alike. Check it out today at thermofisher.com forward slash ISMB (thermofisher.com/ismb). And now back to the episode.

Steve Lewis 15:53
Moving into a little bit deeper of the of the science I'm interested in hearing, can you tell us a bit about the molecular biology techniques that you use on the day to day?

Giles Yeo, PhD 16:03
It's interesting, right. So we have to do the genetics, and that tends to come either from standard old-school Sanger sequencing, but that only tends to be when we're now confirming, you know, that something we've cloned is correct, or confirming the mutation runs within a specific family. You know to be to in order to try and understand that whether or not this gene is associated with body weight within this family, etc, etc, we will use Sanger sequencing. But the primary genetic approach is now the next, next general, high throughput sequencing, where that comes in. And so we do a lot of high throughput sequencing, for example, if a family comes in with a condition, and then we may very well do whole exome sequencing, for example, or now whole genome sequencing, because it's because the price, the price between exome and genome is starting to get closer to each other. Then we have to do gene editing. And so we obviously have to use CRISPR Cas and other similar approaches to then knock these mutations into various cell lines that we work with. Then there's a whole series of approaches that require molecular approaches that need to go and need to transfect in the various plasmids. You need to be able to do stuff with it. Then there's, well, what happens after that? Right? So you either do transcriptomics, in other words, you do RNA Seq, or you do qRT-PCR, so quantitative RT-PCR, just to find out whether or not specific targets are up or down. And then after that, you then have to take the protein approaches. I mean, has the gene, has the protein been knocked down? What happens to, is there something that has happened if you're studying a receptor, does it actually interfere? Does the mutation interfere with transport from the nucleus to the cell membrane? And so we have a whole suite of tools as well, which are able to track these molecules running, running through cells. That's pretty much all the molecular approaches that we do, which is quite a lot.

Steve Lewis 17:58
What's the time horizon for going through the full pipeline?

Giles Yeo, PhD 18:01
A long time, actually. So in other words, if we take one gene identified in a human being and then take it all the way to molecules. Now it depends on how easy it is to get a functioning thing, but say it's a GPCR and we have a ligand, okay, so now we know. I would say, from first identification of mutation to some functional work, if we have all our ducks in a row, I would hope six months to a cell line with the mutations knocked in and some idea of what might be happening, and then so six months to nine months, I would say, if we were working on that one target, all the way all the way through.

Steve Lewis 18:38
Wow! That's actually a lot faster than I was anticipating.

Giles Yeo, PhD 18:42
Not publication. Now, when we then write the paper, blah, blah, blah, that's a very different story.

Steve Lewis 18:47
When I was in grad school, G-coupled protein receptors, just because you brought it up, was, in a way, wild west when you're evaluating kind of ligands and GPC, GPCR. So I'm curious, from your perspective, how you have seen those molecular techniques, related to signal transduction pathways, how they have developed over, let's call it 10 years, and then even the last two years.

Giles Yeo, PhD 19:17
Okay, so I can. When we first started working on, because the very first mutation that I found, this was now 26 years ago now. Mutations, the very first one I identified that caused obesity is called the melanocortin bore receptor, or MC4 receptor. It was a G protein coupled receptor. And we did, fortunately, know what the ligand was, which meant that we had an assay. And we started by doing, I mean the most. I mean it was effective, just a reporter, luciferase reporter assay, right. So it's a G it's a GQ-couple. So you add it as cyclic AMP goes up. Okay, and then you just have a cyclic AMP luciferase reporter assay. So when cyclic, and you put in, in all the plasmids, so that when cyclic AMP goes up, luciferase gets turned on, you measure the luciferase, and so you get some kind of action. Okay, and then you can see, “Oh, in the mutation luciferase is down.” And so that's what I did. Now, oh, my God, I don't think I qualify now to actually run some of the assays, because now we have, you know, each of the G proteins have different colors. You know, we have live cell imaging techniques that are now available to actually not only just measure the luciferase going up, we will still do the luciferase to make sure whether or not is well worth doing everything else. But if we know it's dysfunctional, the why is it dysfunctional now is so, so much more sophisticated. I would say, over the past three, four years even. Oh, my Lord, you look at it and you're going, Wow. You can now see the little receptor going to the cell membrane. You can see it going down. There are ways now of labeling the stuff and then releasing it from the ER, right at the right time. It is that the sophistication is now incredible.

Steve Lewis 20:59

What role does de novo technologies play? Maybe, like de novo gene synthesis in plasmid creation things like that.

Giles Yeo, PhD 21:09
I think de novo peptide synthesis is useful so, so for example, if you have a mutation in the gene, and it's a peptide, and it's a and it's a ligand, and you're trying to understand whether or not it signals and it actually is causing, it's causing an issue. Sometimes it is better just to make the protein, make the peptide, particularly this. So you just go. So that's a classic example of that, of that happening there. And that's what we have, we have previously done. I don't tend to work with de novo genes. I know people, colleagues of mine, you know, at the MRC Laboratory of Molecular Biology here in Cambridge, and they do a lot of synthetic genomes and things, and too smart for me. I'm asking more fundamental, more fundamental questions. So I don't tend to make de novo genes. I tend to, if I need them I set and go them. the only time we actually make proteins are when we're trying to test whether they're not a mutated ligand is functioning or not.

Steve Lewis 22:08
So you're really focused on the knockins and knockouts and more of the the CRISPR approach?

Giles Yeo, PhD 22:15
So with the rise of CRISPR, definitely with the CRISPR approach. And so what we, because, for any of you listening who's ever done a transient transfection, it's fine, it's quick, and you can do this stuff. But you really have very little control, and you tend to use a HEK cell or a HeLa cell or something, something very, very removed, particularly if you're studying, for example, neuronal-based gene. And so what gene editing has allowed us to do is to find different cell lines, and we now know they express most of the genes we're interested in, for example, and to be able then to knock in the mutation, which means you get endogenous levels of the mutation. Then you can also have the cell line in heterozygous form, depending on what you found, right. It could be a dominant mutation, and so then you have an heterozygous form. We could have found it in a consanguineous, one of these isolated consanguineous populations, so it's a homozygous mutation. Then you can create that in a cell line as well. It's still a cell. I don't want to use the word physiological, but I do think it is more physiological, at least. We're working within a, within the correct cellular human context, when we are asking the question whether a mutation is dysfunctional or not.

Steve Lewis 23:29
What role does the digital components play in your ability to explore these different areas? Maybe system software, AI?

Giles Yeo, PhD 23:42
We would not be able to, in fact, the only way to extract 65 individuals from half a million people from whole exome and whole genome sequencing, and then do the statistical genetics necessary for it, you need to be computationally trained within, within that scenario. And then then you end up with a situation, and I've been speaking to people where actually, well, what happens if you have mutations, say, within a cell? Okay, let's just think of a cell, and you signal to a G protein-coupled receptor and a

cascade happens. Well, what happens if you have a mutation in one part of the gene versus another part of the gene. How does that influence the cascade of everything else? Now that is where you begin to use so, so what just won the Nobel Prize, in fact, it was a, it was an AI year, right. You have Google AlphaFold. One, so it's sort of like using an AlphaFold based thing, where it predicts the actual change. But now it also predicts, using AI, the cascade changes that actually happens as well. And so that will be very, very, because then it allows us to point this at, which assay should I use? Do we find more mutations in those in those genes? So the actual computational side of things, the AI side of things, is going to, as long as you ask it the right question, I think it's going to make a huge difference in the way we think about signaling cascades. There is a huge temptation, because that's the way we function, when we identify a mutation in a gene, that we just study the gene in isolation, when this is not how it works. It's not how it works. Okay. It's, and it's also not the only variation within the body, right. It may be a big change, but if you look at someone's whole exome sequencing, the number of mutations that I find in myself, for example, I'm amazed I still have a nose and then it hasn't dropped off. The number of mutations that are actually flying around my body, right, which are clearly not biologically relevant to me, but the number of mutations that are there are just, are just amazing to be found. So to be able to predict, to be able to do these things, is going to be amazing.

Steve Lewis 25:53
What is five years out look like?

Giles Yeo, PhD 25:55
A couple of things. Certainly here in the UK, every child that ends up in neonatal intensive care will now have their whole genome sequenced. I think we're probably within five to 10 years of having every baby done. For good or for worse, okay, for better or for worse, I'm not proffering any philosophical or ethical things, for good or for worse. But I think it's going to happen. Now, the moment that happens, and we have all the genes, you can do bad, you can do good. But I think that we can really be able to approach pharmacogenomics properly. So if everyone that partakes in a drug trial, of any variety of anything has their whole genome sequence, and we're able to then begin to predict who has these side effects and who doesn't, you reduce the you begin to save money for everybody and keep drugs that are functional, because then you can prevent the people from going to get the side effects, to stop doing that. So that's, that's number one. I think number two, I think then you begin, even leaving the drugs aside, then you can begin to tackle nutrigenomics, all of these personalized care, and I know it's very buzzy, and I know it's, but that's where we got to get to, right. I mean, at least close to it, we got to be able to get to some kind of personalized medicine. And so I think we are really a lot closer, at least now, to generating the data we need to see if what can be personalized and what can't be personalized.

Steve Lewis 27:00
This is such a fantastic conversation, because it's a real, tangible phenotype that you can speak to, but you're doing the genetics.

Giles Yeo, PhD 27:31
And obviously I study, look, I'm a body weight person. That's why I focused on it. This is why it's so body weight focused. But all of the approaches I take, all of the cohorts and genetics that I take, it can be applied to anything, right to any, any given trait that is out there. So I do think that we are now in an

era where genetics has been democratized. I think it has. Ill of my students now and postdocs, I'm not going to call them computational scientists, but they all know how to code to some degree so that they can handle big data. Now there's still a lot of them are still wet. They're still molecular biologists. We're here to talk about molecular biology, but all of them also have some experience in computational science, because that is where we're at. We need to be able to mine the huge amounts of sequencing data, and then there's, then there's expression data, human cell atlas will suddenly appear, you know, in things, we need to be able to mine and understand and look at this data in order to, I think, in order to move forward. I'm a dinosaur, di-no-saur, you know, and, and that is just the way It is.

Steve Lewis 28:39
That's fantastic. This has been an awesome conversation, and as we come to the end of it, my last question is, what are the keys to your success?

Giles Yeo, PhD 28:48
Luck. Okay, I think I have, now, clearly, I think that I've been able to, I've put myself in a position so I could maximize my opportunities when luck came. But look, I the first gene that I identified, I started in the lab of Steve O'Rahilly, who's used to the head of department, and that's the obesity guy. And he literally said, "This is a new gene we're interested in, screen it," and I found a mutation. So if I ended up in some other lab, somebody's, I didn't know what from Adam, what have you. It was luck that someone found me, hired me, and gave me anything in order to do that. The second thing is one thing which I gave, as I if I might answer, sort of like as a piece of advice. And so it's what I, it's how I run my life. I was dropping my son off a few years ago at college. I took him to college, and I felt, as a dad, that that you needed to, I felt is this, this is the kind of time I have to impart some kind of wisdom. Right. As I was saying, “Bye, bye, hug, hug,” Oh God, I'm going to say and so I said, "be more of a pain in the backside to replace than to keep." And that is what I've done through my life. Through my life, I've had areas, moments of success, less success, you know. And your career does this as it kind of moves up and around and sideways. And when I've hit issues and hit problems, funding didn't come through because I've had my technical niche, but particularly around single, well at the time, microarrays and then RNAseq and single cell genomics. If someone had let me go, who the hell was going to do it? And then so people, people kept me around and for that. And so that is the ethos I've always been. So, be useful. So then when push comes to shove, if suddenly funding runs dry, when we work within academia, so funding can run dry, someone will make the effort to keep you.

Steve Lewis 30:45
That was Dr. Giles Yeo, Professor of molecular neuroendocrinology at the University of Cambridge's MRC metabolic diseases unit. In addition to his faculty appointment, Giles is also an author and broadcaster. His podcast is called *Dr. Giles Yeo Chews the Fat*. Up next is our first ever Mol Bio Minutes episode, which should drop in about two weeks. I think you'll like what we're doing this year with these new additions to our season. The next full interview episode will still come next month, but until then, cheers and good science. Speaking of Mol Bio is produced by Matt Ferris, Sarah Briganti and Matthew Stock.