MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

MIGRAINE BIOCHEMISTRY: CGRP & BEYOND

PETER GOADSBY, MD, PhD, FRS
PROFESSOR OF NEUROLOGY & NEUROLOGIST
KING'S COLLEGE, LONDON

Introduction (00:05): But it's certainly true that anyone who's listening to this, unless you're in the PACAP study — that's a small number of people — then you haven't had everything that's been developed under the sun. If nothing else — and it's cold comfort in many ways — but it's important to know that just because the CGRP story has been successful, that hasn't stopped people. In fact, what it's done is told us that you can develop things if you understand enough about the biology. So the next step is to explore that PACAP biology.

Elizabeth DeStefano (00:39): Identification of CGRP's involvement in migraine was a revolutionary pivot point in migraine research, leading to the development of CGRP inhibitors, the monoclonal antibodies, and gepants for use in migraine management. These medications have been absolute game changers for some people living with migraine disease. Yet they're not effective for everyone. To learn why that is and what might be coming next, we're going straight to one of the experts who first explored CGRP's role in migraine, Dr. Peter Goadsby. Dr. Goadsby, we're thrilled to have you. Welcome back to the Migraine World Summit.

Dr. Goadsby (01:13): Thank you. It's kind of you to ask me to speak.

Elizabeth DeStefano (01:17): So to start, what is CGRP, Dr. Goadsby?

Dr. Goadsby (01:21): Well, CGRP stands for calcitonin gene-related peptide. It's a 37-amino acid — for people where that makes any difference — peptide that's found in the brain and in other parts of the body. It's a chemical that the body uses — that the body makes — that it uses to transmit signals between nerves and blood vessels, nerves and other nerves, for example. So, it's called a neurotransmitter. Of its many roles, one is that it's overexpressed in migraine.

Elizabeth DeStefano (02:07): What medications involving the CGRP pathway exist now in migraine management?

Dr. Goadsby (02:14): So, broadly speaking, there are at least three classes of medicines, you might say, that involve CGRP. As we've begun to understand the biology, it's pretty clear that the triptans — sumatriptan, zolmitriptan, rizatriptan, eletriptan, naratriptan, frovatriptan, almotriptan — not to leave anyone out. Among the things they do is they influence CGRP release from nerves. So there was always a CGRP component of what was going on.

Dr. Goadsby (02:45): More recently, as you said in the introduction, we've been able to block CGRP either with monoclonal antibodies or with small molecular, you might say, ordinary tablets called gepants. And the monoclonal antibodies either mop up the CGRP, so they bind to it and stop it having its action, or they jump on the receptor, the lock in the cell, so to speak, that turns activity on. And there [are] four of them. The three that jump on the CGRP are eptinezumab, fremanezumab, and galcanezumab. And the one that sits on the receptor, the CGRP receptor, is called erenumab.

Dr. Goadsby (03:23): The other way of blocking what CGRP does — CGRP interacts with its receptor. So you can block that interaction by competing with the CGRP with something called a CGRP receptor antagonist, or gepant. And instead of the CGRP interacting with the receptor, the gepant interacts with the receptor, and that stops the CGRP having its interaction. And there are several now available: ubrogepant and zavegepant, used exclusively for the acute treatment of migraine (or licensed for that); and rimegepant, which is licensed for both acute and preventive treatment; and atogepant, which is licensed for preventive treatment of migraine. So we have a lot of ways of blocking CGRP.

Elizabeth DeStefano (04:10): Well, what has been their impact in terms of the proportion of those with migraine who have benefited from these medications?

Dr. Goadsby (04:19): I'll first start by saying their impact is not enough. I think they've been useful, and I'll come back and say something specific about that. We've got a long way to go. For the people in whom they're useful, and that's ... one of the great things about the CGRP — the monoclonals or the gepants — is that they tend to have very few side effects. So most people who get a response will get a response without paying a penalty. And those of the listeners who've paid the penalty of drugs in the past, say of propranolol — being tired or having nightmares — or of having amitriptyline — having dry mouth, sleepiness — or of topiramate — having the pins and needles or having cognitive word-finding problems — you know what I'm talking about with paying a penalty.

Dr. Goadsby (05:05): The penalty for the CGRP-targeted medicines is rather minimal. Small number of people have some constipation, which in my experience is not — usually not — enough to want them to stop the medicine. So broadly speaking, a useful step forward. Probably what we saw in the clinical trials is about right. About half the people who have the medicine will have about half of their attacks go away. And about a third will have 75% go away, and maybe in the range of about 15 to 20% will have all of their attacks go away. So for some, a really spectacular benefit, I would say, and for some [a] really good benefit. But it has to be said for about 25% of people, 30%: Useless. So we have more to do.

Elizabeth DeStefano (05:59): Speaking of side effects, given that the CGRP monoclonal antibodies initially were really touted as having potentially fewer side effects — given that they are more specific to certain targets in the body than prior migraine medications — we do, though, in the real world, as you mentioned, hear about some side effects. So why is that? Why are there some side effects when they are targeted so specifically to CGRP?

Dr. Goadsby (06:28): Well, CGRP, for a start, is widely distributed. It's distributed in the brain. It's distributed in the covering of the brain — the dura. It's distributed in hair follicles. It's distributed in the GI [gastrointestinal] system, in the gut. So it's not surprising, perhaps, that a small percentage of people have significant problems with constipation. What's more remarkable in many ways [is that] it's so widely distributed and, relatively speaking, so few people have problems with it given the wide distribution. That's No. 1. No. 2, some of the side effect reporting is probably unrelated to the treatment but related to, well, unrelated to the mechanism but related to the treatment.

Dr. Goadsby (07:13): Let me give you an example. If you control most aspects of a migraine but not all aspects of a migraine, then the aspect you don't control will become more noticeable. Let's say, for example, you're a person with migraine that has vertigo, that also has, so what's sometimes described as vestibular migraine. If your migraine days reduce and your headache reduces but you get less impact on the vertigo, you might think, "Well, actually, my vertigo is worse." I'm not saying the vertigo doesn't feel worse, but if everything goes away and that's all that's left, sometimes I think side effects are about beginning to notice what doesn't get fixed. I'm not saying that as a panacea. There are clearly side effects that occur with these CGRP drugs.

Dr. Goadsby (08:05): We're in early days. It's relatively few years that these things have been used, and I think over time we'll begin to understand the way they interact with the body and the way changing the disease changes the perception of what's happening, which is not to diminish the side effects. I'm sure there are side effects. The other thing, of course, is that there

are idiosyncratic things that happen that are individual to the person's biology. It's complex and it'll take us a long time, I think, to bottom it all out.

Elizabeth DeStefano (08:39): You mentioned that while so many people have been incredibly helped, there are certainly nonresponders. And one of our viewers, Jeanne-Marie, voiced thoughts on this on behalf of many who are frustrated after they had hope. And she noted that she was thrilled when the anti-CGRP medications came on the scene, and they seemed to be life-changing medications that we've been hoping to find for so long. And Jeanne-Marie says: “But when I tried one, then another, and another, I found that they did not prevent or reduce my intractable migraine. I was beyond disappointed. I had to think, why do these drugs work for so many people but not for me? What's wrong with me? Why is it that CGRP-targeted treatments don't help everyone with migraine?”

Dr. Goadsby (09:26): I mean, because CGRP is not important in everyone's migraine. I mean, I don't want to sound trivial about it or trivial about the person who doesn't respond. You might expect that the more focused the treatment, the less people will respond, but the less side effects they'll get. So the ones who are happy are truly happy. Like the CGRP clinics are, they're sort of "Kleenex clinics," and — I mean that in the tissue paper sense — in that there are people who cry because they're so happy they're well. And there are people who cry, just like the person you mentioned, because they're very disappointed, and I understand entirely why they're disappointed. I think that as we pursue further targets in this area, what we'll do is we will slowly but definitely capture most people by understanding what's important in their biology, individualizing things, you might say.

Dr. Goadsby (10:28): And in many ways, you could iron out migraine quite easily, relatively speaking, but you'd probably have to anesthetize people. So it's not really practical. So put that down for a minute, because that's more troublesome than the disability of the disease.

Dr. Goadsby (10:45): So, what we're looking for in the future — as with the CGRP story — [is] doing spectacularly well for the people who get a response and establishing other targets for those who don't. And as disappointing as the CGRP story is, the upside is it shows you that if you actually understand individual parts of the biology that are important and you target them, you'll get people who will respond. They'll respond very well, and they'll get good tolerability. So I think it's a call — the nonresponders are a call to double down on our efforts on the research side.

Elizabeth DeStefano (11:23): So this really speaks to what's happened here with CGRP for some people — how incredibly complex migraine is, right? That one person's migraine is not like another. And also, what is possible when we match what's happening for one particular person with a specific approach.

Dr. Goadsby (11:42): Yes, completely. And as we understand that better, the disappointments will be less. But we're in relatively early days. Modern era of research and migraine is maybe 40 years old at best. When you look at other central nervous system conditions — and I'm not making an excuse for the people who aren't responding; I'm not trying to sop it at all — but we've done all right with a really atrociously minimal standard of support in terms of research. We've carved it out pretty well, and we will do better. We will double down, and there are new things coming.

Elizabeth DeStefano (12:21): In contrast to complete responders versus complete nonresponders, what does it mean if CGRP meds help somewhat but not significantly or completely with someone's migraine condition?

Dr. Goadsby (12:36): I think in [people with migraine] who find their condition somewhat affected, one's interested in what that means. So for frequency, say for preventive, if it means that you lose half the attacks and you've still got half them, well, it tells you that you need — there are other targets that are involved. If you're talking about the acute attack, what it means is the medicine is unpredictable. So it treats 2 out of 3, but leaves you one with your pants down, so to speak, in a very metaphorical sense. Then that almost certainly means that there's probably a delivery … there's some sort of what's called a pharmacokinetic problem — how the drug is getting there. Or maybe the attacks are changing, as well. If you're a person who has an acute treatment that works partially, then it says to me that there are other transmitters involved. And I think what we'll end up doing, there'll come a time when there'll be a smorgasbord. And there'll be a range of choices, and we'll need to try and work out how to pick from the smorgasbord for the individual to get reliability, to get excellent tolerability. I think that's a little way off, but it's not so long off that we won't see it. Well, I hope to see it, see something of it in my lifetime, let me put it that way — and I'm no spring chicken.

Elizabeth DeStefano (14:01): Well, that really may answer one of our next viewer, Wendy's, question who asked: Well, why do the oral small-molecule CGRPs seem to work so inconsistently? And you've, I think, answered that in part to say that may have to do — that unreliability — may have to do with something about deliverability. Is that right? Also wondering: Could that have to do with different biochemistry from one attack to another? Is that possible?

Dr. Goadsby (14:32): Yes, attacks can vary. [People with migraine] will tell you that some attacks are worse than others. They'll tell you that sometimes different parts of the attack are more focused — perhaps the light, or the sound, or "head boom" — that things change. So that's not changing by magic. It's changing, as you say, because the chemistry is changing. And so, you might predict if the attack changes, that we need a different approach for individual attacks.

Elizabeth DeStefano (15:00): Not just different approaches from person to person, but different approaches for each person, as well.

Dr. Goadsby (15:06): Yes, I think we would like to end up with a toolbox, so to speak. No one doing any DIY activity at home just has one thing: one screwdriver. And migraine's not a carpentry problem, but the principle being that you need enough tools to deal with the range of attacks. I'm sure there are people who are listening who find some of their attacks dealt with — maybe not many people listening — but some people with migraine will find many of the attacks dealt with reasonably well by simple things — some simple nonsteroidals (NSAIDs), for example. And then an attack will come along, and they can take the nonsteroidals until they're blue in the face, and it doesn't make a blind bit of difference. So we need tools, and we also need ways of predicting which thing to take. It's no good waiting until the horse has bolted to decide that you needed to have, on day two, to decide you should have taken the medicine in the first two hours on day one.

Elizabeth DeStefano (16:07): Well now we've begun to hear about another neuropeptide — PACAP. What is PACAP, and how is it of interest to migraine treatment?

Dr. Goadsby (16:16): PACAP is pituitary adenylate cyclase-activating polypeptide. It's almost cruel, isn't it? That the more the new things that we have just feel the need to be … the names need to be longer. What can you do? So it's a polypeptide like CGRP. It's released from the important nerves and in important places in the brain that we know are involved in migraine.

Dr. Goadsby (16:40): And we have the initial data from the first study presented at the International Headache Society meeting in Seoul to show that blocking PACAP with an antibody, another monoclonal antibody, to the actual PACAP can reduce [the] frequency of migraine. So we have another target moving forward, which is quite clear. Will it be another CGRP? Will it have the same effect? We don't know, in the sense that it'll be the same patients; we don't know. Will it be different people? Will it be people who don't respond to CGRP? Will we need to combine the two things together? Will we need [to] use one or the other? These are all the questions that we're going to have to answer over the next five years or so, as this medicine is developed.

Dr. Goadsby (17:27): But it's certainly true that anyone who's listening to this, unless you're in the PACAP study — that's a small number of people — then you haven't had everything that's being developed under the sun. If nothing else — and it's cold comfort in many ways — but it's important to know that just because the CGRP story has been successful, that hasn't stopped people. In fact, what it's done is told us that you can develop things if you understand enough about the biology. So the next step is to explore that PACAP biology.

Elizabeth DeStefano (18:01): So is it far too early to have any ideas about how much potential this has, if it has as much potential to help as many people as CGRP-focused treatments did, and what type of potential side effects it could involve?

Dr. Goadsby (18:19): Oh yeah. We're a little bit early on deciding where to go. It's back where the CGRPs were, maybe, what 10 years ago, there and thereabouts, because the first study showed that it worked. But you don't pick up all the side effects — we didn't even pick up really all the side effects in the clinical trials and understand everything fully. And you never really understand a medicine until it starts, when the rubber hits the road in clinical practice. So I think we're a long way off. The fact that it works, however, and no serious adverse events occurred — that's a pretty good marker because people don't often talk about it. But there were a dozen or so medicines that were being tested in various ways in migraine that didn't work, and we never talk about them. It's not easy to develop these things.

Dr. Goadsby (19:08): The good thing is that when something's — in migraine, when something has failed — good is maybe the wrong word to use, but reliable. When something failed every time it was tried, it just failed, and that was the end of that. And everything that's worked in one well-designed study has continued to work and to be useful. So I think one could be reasonably optimistic if what we've done in the past is any indicator at all of what will happen in the future.

Elizabeth DeStefano (19:32): Reportedly, in clinical trials, administration of PACAP triggered not only those primary migraine attack pain symptoms as with the CGRP trials but also some premonitory symptoms.

Dr. Goadsby (19:45): Indeed.

Elizabeth DeStefano (19:45): What does that potentially mean, clinically, for treatment if this pathway pans out?

Dr. Goadsby (19:53): Well, if you think about the premonitory symptomatology, what the premonitory symptomatology is doing is warning you of the earliest part of the attack. If PACAP is involved more significantly in the early part of the attack, then you might predict that it's going to be a, broadly speaking, more effective preventive. That is, more people will get a response because literally the attack starts with these premonitory or prodromal symptoms.

Dr. Goadsby (20:23): Now we know that CGRP is involved because there's a good study that was presented at the American Academy of Neurology this year with ubrogepant, showing — placebo-controlled, double-blind, crossover study — showing that you could use 100 milligrams [mg] of ubrogepant in the premonitory phase and stop headache coming against placebo. So there is a CGRP effect in that phase, and that's what you'd expect given that the CGRP mechanism is preventive. It's not as obvious when you do the CGRP infusions.

Dr. Goadsby (20:51): With a PACAP infusion, as you say, it's more obvious. And if you had to adduce anything, you might adduce that that would predict it to be really quite a good preventive. And so one can have reasonable hope that there will be people who don't respond preventatively to the CGRP class and will respond to this PACAP treatments. As I say, we're fairly early days. There's maybe not more than 250 people there and thereabouts in the study, in that first study that was reported. Nevertheless, very exciting.

Elizabeth DeStefano (21:30): Now I'm understanding from what you're saying that we can reasonably expect that there are multiple pathways involved for many people with migraine. So is it possible that some people's migraine involves processes in both the CGRP and PACAP pathways, not to mention potentially others yet undiscovered, and therefore could end up being best managed with drugs that address both?

Dr. Goadsby (21:56): Yes, yes, and yes. And in fact, the antibody people have already thought about developing something called bispecific antibodies that actually can mop up both. That technology's available. This is going to just be unrecognizable in five to six years, as we've started to understand this. And as you say, there are other options. PACAP is not the only player in town in terms of the possibilities.

Elizabeth DeStefano (22:27): What other targets are currently being researched that you are excited about?

Dr. Goadsby (22:33): I think that one of the targets that's been difficult and has been looked at over quite a period of time now is glutamate. So, glutamate is a chemical the brain uses to turn things on. It's called excitatory. Now obviously, you can't block all glutamate because otherwise you'd be asleep and worse. And glutamate has a number of receptors, two classes: one that talks to so-called channels, and another one that talks to what are called metabotropic receptors — two classes, let's say it that way. Quick things in the nervous system rely on this ion channel glutamate transmission. And when you block that, and that's been tried, quite significant side effects occur. So we might put that down for a moment, but these other receptors act over a longer period of time, you might say. They're more modulatory, and you can change them with drugs that are aimed to subtly alter the receptor, called allosteric modulators. That sort of turn it down, you might say.

Dr. Goadsby (23:34): And that's a different target entirely. And it strikes me as a way, and there is work that's gone on in this area, a way to get out to a whole other group of people where these peptides aren't as important as this small molecule called glutamate is important. As an

example, we just saw a new target being discussed again at the International Headache Society — the protease-activated receptor 2 or PAR2, which Dr. Dussor talked about and is involved in inflammation.

Dr. Goadsby (24:09): We've seen Dr. Pradhan — Amynah Pradhan — talk about the delta-opioid agonist as a way forward in these models. We ourselves have looked at one of these glutamate receptors drugs, called [mGluRs, metabotropic glutamate receptors], and we've been interested in a chemical in the body called orexin, which is involved in pain and sleep — which is in the right places in the brain. These targets are all sitting there and thereabouts. The problem, in many ways, is not finding the targets in the biology in the lab but is to develop safe drugs that you can use to manipulate those without side effects in humans. There's quite a bit of work, and the chemists have a lot to do. And the chemists have done a great job getting us the gepants, and the ditans, and the triptans. And I have no doubt the chemists will get us other medicines that we need.

Elizabeth DeStefano (25:11): We'll continue to be deeply grateful to them and everyone involved.

Dr. Goadsby (25:16): There are many unsung people in this. The chemists — if it wasn't for the chemists, we wouldn't have the molecules to study. There are the patients who go in the studies. You are asking people effectively to have an extra migraine for the team because — half of them get the placebo — they take a hit for the team. And we should. Everyone who's using a monoclonal should not forget that there's someone out there that has had extra attacks so they could have less attacks. I think it's important to recognize it's a team effort, from the chemist through to the patients. Regulators: Sometimes they get a bad time, but regulators are there to make sure that no one gets hurt by any of these medicines. There's a whole range of things. Everyone sort of thinks that everyone's in the way, but I don't think so. I think everyone's working to make sure that you can take a medicine and be pretty sure that your feet aren't going to fall off, so to speak.

Elizabeth DeStefano (26:10): An added bonus while you're better managing migraine in your life.

Dr. Goadsby (26:15): You've got enough going on if you've got migraine. You don't need more problems.

Elizabeth DeStefano (26:18): Right, right. Big picture, how can learning which types of medications — meaning those that target different pathways, those that we know about, those that are still to be explored — how can that teach us more and more about different manifestations of migraine in meaningful ways?

Dr. Goadsby (26:36): An example of this is this study I mentioned from the American Academy [of Neurology]: the gepants study in the premonitory phase, so-called prodrome study. What it teaches us is that you don't have to have headache necessarily, even if the attack is started. I think we've more or less thought that headache is sort of center of things. And once you get it, if you're going to get it, you're going to get it. It's inevitable. It's not. So the idea that you could develop treatments so that you never had to have pain — that might sound crazy. And maybe six months ago, it would've been crazy. Although I've always been happy to say something slightly crazy because if you're not sort of thinking out of the box, you're not really looking at the

future. But all of a sudden, after that prodrome study, that's not crazy anymore. That's actually a thing.

Dr. Goadsby (27:34): If we got it right, we may not get a cure to start with, but if we got it right well enough, we would understand how to really offer people, offer sufferers the opportunity just not to have pain, not to have the bad part of the attack. And I think the fact that we're able to get on top of it that well tells you there is, there's really substantial hope in the research world.

Elizabeth DeStefano (28:02): What final thoughts would you like to share, Dr. Goadsby, about this idea of CGRP and beyond with the audience?

Dr. Goadsby (28:11): Well, CGRP was the first — I'm a bit of a *Star Trek* fan — so it was the first movie. Well, actually, I'd like to think the triptans were the first movie. I like to think that CGRP was the second one, because I rather like *Wrath of Khan*, if I had to — I'm sorry, I'll just say that. But there's a whole series afterward, and if you're a bit of a Trekkie, you always look forward to the next series. And it really — the CGRP story has lifted the field to understand that yes, we can do it. And no, we are not satisfied with things as they currently are. So the CGRP story is one of hope. It's one of delivery, and it's one of promise.

Elizabeth DeStefano (28:55): Thank you so much Dr. Goadsby for being here with us. We greatly appreciate you.

Dr. Goadsby (29:00): My pleasure and thank you.