AN AUDIENCE WITH…

Michael Hanson

Around 40% of drugs target G protein-coupled receptors (GPCRs), membrane-bound signalling receptors with diverse physiological roles. And yet, drug companies have successfully explored only a small fraction of GPCR space. This is in part because researchers have solved the structures of only a subset of GPCRs, limiting their ability to rationally design selective and potent small-molecule modulators. To boost the tractability of this important drug class, Michael Hanson and colleagues launched the GPCR Consortium in 2014 to solve more GPCR structures. Now, nine pharmaceutical partners and three academic centres are on board. Hanson, president of the GPCR Consortium, told **Asher Mullard** about their successes to date and the technological advances that will continue to open up GPCR space.

What did you achieve and learn in your first year of the GPCR Consortium?

One of our main achievements was simply getting individuals from disparate institutions — academia and industry — together in the same room to combine resources, knowledge and ideas towards the same goal. It is one of those rare times when you can have all of these top scientists from all of these really large pharma companies together in one room brainstorming on the problems at hand.

Most of the lessons we learned have come from having to accommodate the diversity of ways in which our members handle their information and intellectual property. Our industry partners have had different perspectives on what they are willing to share with the consortium and under what circumstances. For example, most companies were happy to share compounds that can help stabilize GPCRs, a key step in crystallization, but were reluctant to share the specific structures of the compounds they were contributing. We realized that for the initial rounds of research there is really no need to know what the structures are; only once a GPCR structure is solved do the academic partners need to know which structure is in the binding pocket. Getting everybody comfortable with this model has helped the consortium move smoothly.

How many GPCR structures are you working on solving?

So far we have progressed eight GPCRs to the crystallization stage. And some of these have already yielded diffraction data. All of the structures will be published in due course, and translation of these results into drug discovery and drug development programmes has likely started already at the industry member sites.

To put this in context, only 33 GPCR structures have been solved to date. One of our successes is that we were able to progress eight GPCRs to crystallization trials so quickly. Five years ago we expected that a GPCR structure would take two to four years to solve. Now it's not unreasonable for us to expect to get it done within one to two years. And hopefully the pace will increase over the next four years.

Your initial focus was on GPCRs that are involved in diabetes, cancer and mental disorders. Is that still the case?

That initial focus was mainly driven by what areas our members were interested in when we launched. We've been able to expand our membership since that time, and because each company gets to nominate GPCRs our indications are now all over the map in terms of therapeutic areas. There was surprisingly little overlap in terms of the initial nominations from the companies.

What technologies are improving your ability to solve GPCR structures?

One of the most exciting new technologies being deployed is the free electron laser (FEL). One of the issues that we used to run into with crystallography projects is the need to grow large crystals. The FEL allows us to do crystallography with dramatically smaller crystals, short-circuiting our need to extensively optimize crystallization conditions. It also operates at room temperature, rather than at the temperature of liquid nitrogen, providing us with more physiologically relevant structures.

We are also seeing great progress in terms of using NMR to characterize GPCRs. NMR will allow us to start looking at the dynamics of GPCRs rather than simply at their static structures. We will eventually be able to see differences in the conformational states between agonist-bound and antagonist-bound GPCRs, for example. And by understanding the different conformations of the GPCR we'll be able to understand the unique pharmacology of different compounds. This is kind of the missing piece of the puzzle, especially given how conformationally dynamic GPCRs are.

We are currently at the point where we can use NMR to start to understand some of the dynamics with selective probes. In the next 10 years we will see entire structures being determined with NMR.

Do you think that the proportion of drugs that target GPCRs is changing over time?

The frequently cited 40% estimate comes from a paper that is 14 years old by now. I think that it has probably dropped a bit since then, especially with antibody therapies coming onto the market. Antibodies can address targets that small molecules couldn't, and have struggled to target GPCRs very well. But based on the interest we are seeing from pharma in developing drugs against previously unknown or 'undruggable' GPCR targets, I think the ratio will increase again over time.