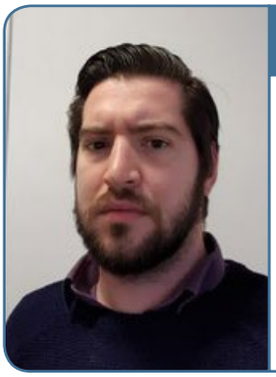
# THE BENEFITS OF USING ALLOSTERIC AND ORTHOSTERIC ANTIBODIES




## MARTIN REDHEAD, Group Leader Molecular Pharmacology, **UCB**


Martin earnt his BSc in Biochemistry from the University of Liverpool followed by a PhD in Pharmacy from the University of Nottingham. He began his career at Sygnature Discovery in Nottingham UK where he developed methods for determining allosteric effects via thermal shift assays. Martin joined the Structural biology at UCB team before transferring to the Primary Pharmacology Group working on small and large molecule discovery projects for a number of target classes including enzymes and PPIs. He currently heads the Molecular Pharmacology group which aims to discover and characterise lead molecules and the systems they interact with. UCB employ a number of novel kinetic and thermodynamic methods which feed data into bespoke systems biology models to improve dose prediction and time to clinic.

**What are your thoughts on the commercial potential of allosteric antibodies?**

I'm not completely convinced they do have commercial potential compared to an orthosteric antibody. They're a lot more difficult to develop, and their effects can be a lot more subtle. They probably only really find niches in a few areas where you were looking for a really tightly-controlled effect, compared to an orthosteric, which could completely knock something out, allosterics tend to be a lot more subtle, so it's often harder to find the niches to put them in.

**Which one appeared first; allosteric or orthosteric?**

99.9% of all commercial antibodies are orthosteric.

**Do you work specifically with allosterics?**

I work with allosterics and orthosterics; allosterics tend to be a lot more interesting from an academical point of view. They do find those niche uses, and they do things that orthosterics can't. It's leveraging them to specific situations which is the difficult part.

**What would you say are the key benefits of using allosteric antibodies?**

You start to see a different part of the protein they're binding to, compared to orthosterics. Orthosterics will see the same binding sites, and that might be shared across a large number of other proteins. You start making it about the selectivity. If you want to limit what the actual effect size you have is, by knocking something out completely, you might get on-target toxicity. By controlling the amount, you limit the effect, and you might be able to avoid things like on-target toxicity.

**What would you say the main challenges that you face in the work that you do?**

If we look at allosterics, their effects aren't as obvious as orthosterics. You need to have the right type of experiment set up. You also need to be prepared to look for things which are sitting just on the outside the noise; a traditional antibody would give very clear results whereas allosterics can be slightly confusing.

**Are there any key technological innovations that have helped you with that?**

We mostly use traditional drug discovery. Function-led assays ahead of just using biophysics binding on its own, for example, really tracking functions are key.

**What would you say will be the top three takeaways from your presentation?**

First one would be: anyone who's discovering antibodies has probably already discovered a lot of allosteric antibodies and has not realized that they're much more common than you think. The second is that you can use them in some fairly unusual ways, which may aid other drug discoveries such as small molecules. The third one is that when they do have an effect, it tends to be different to an orthosteric antibody, so perhaps you can think about situations where you can swap one of these into a drug discovery programme.

**Have you thought about the future of allosteric antibodies?**

I suppose they're always going to be competing against orthosterics, which are like a sledgehammer. Although people may need a sledgehammer to crack a nut, sometimes you're really cracking paving stones. I think they'll always struggle to compete, but as long as we understand when to use them, they're always going to find some use in drug discovery.

**What do you aim to gain from attending congresses such as this one?**

We want to just see what everyone else in the field is up to; see if we're doing things right, or we could do them better? What new technologies are out there? What are other people looking at that we've perhaps not even considered at all? It is useful for networking, and the suppliers are also very useful when you've got a specific project in mind or a specific need. It's good to be able to talk to a lot of them about it and see how they think about solving your problem.