AN AUDIENCE WITH…

Hal Barron

Credit: GlaxoSmithKline

Hal Barron feels like he has been training his whole life to run R&D at GlaxoSmithKline, even if he didn't know it at the time. His broad set of experiences — including an undergraduate degree in physics, a medical degree in cardiology, a professorship in epidemiology and biostatistics, as well as time spent steering R&D at Genentech and Roche and helping to build the Google-backed biotech Calico from scratch — will come in handy as he tackles the challenges of drug discovery and development at scale, he told **Asher Mullard**. After over a year on the job, he talks about doubling down on genetically validated targets, functional genomics, machine learning, immunology and more.

You left Roche in 2013 to start Calico, working on ageing-related diseases. What brought you back to big pharma in 2017?
The opportunity to provide the leadership that enables a big R&D organization to embrace a new strategy, and deliver things that no biotech could even remotely get close to delivering, is amazing. I'm not saying that always happens. But that's what is so exciting about pharma.

The strategy you've embraced focuses in part on genetically validated targets. How do you see this improving your drug discovery odds at GlaxoSmithKline (GSK)?
As a clinician scientist I've always held several beliefs as sacred. The first — and really what's driving a lot of my interest now — is that the human should be our model organism. Not yeast, and not mice. We're very different from these organisms, and much of the failure of the biotech–pharma model is due to biological mismatch of these organisms, in my opinion.

I've always thought that a very large collection of well-annotated human phenotypic data, integrated with genomics, proteomics and other data sets, could significantly improve our ability to identify targets that are actually causal for diseases. And with this, productivity would improve.

We've shown at GSK that genetically validated targets are twice as likely to succeed in the clinic versus non-genetically validated targets. And that led to our deal with 23 and Me to work together to leverage more of these data. With data on north of 5 million people, there is an enormous number of insights that can be gleaned from 23andMe's data set. And we can also combine it with other orthogonal data sets that maybe don't have the sample size but might have much deeper phenotypic data, such as the UK Biobank, Open Targets and the FinnGen collaboration.

A recent JCI article argued for a reconsideration of the "ongoing obsession with the human genome", because this focus has yet to help improve public health. What do you make of this argument?
As is often the case when significant advances in science and technology are introduced, there are overly optimistic projections regarding their impact, and in particular the speed of this impact on medical practice. That said, we strongly believe that human genetics has and will continue to identify targets with a higher chance of becoming medicines and will help remove targets when the genetics suggest they won't translate into medicines.

When do you expect to see the use of genetically validated targets measurably shifting drug development success rates?
Unfortunately it still takes a decade from the initiation of a drug programme to approval. And the number of genetically validated targets is still small. Frankly, the world hasn't even converged on what it means for a target to be genetically validated. But my guess is that over the next decade we'll see more and more of what I would call robustly genetically validated targets. And the metric I would watch carefully is the probability of success of these targets. I don't know what it will be, but I would bet it will be substantially higher than the current 10%. Even 20% would be transformative.

I also think that the industry will move from most, if not all, of these targets being identified through variants in coding regions, to some of these targets coming from functional genomic analyses of variants in non-coding regions.

How do you see functional genomics bolstering the genetic validation of targets?
In around 90% of the genotype–phenotype associations that we find, it's not really clear what protein we should target because the genetic changes aren't in coding regions. That leads us to functional genomics, in which we can reconstruct and deconstruct the base pair changes that lead to different phenotypes. And with gene-editing tools like TALENs and CRISPR, we can do large-scale gene-mapping exercises, studying gene–gene interactions in mammalian cells to look for synthetic lethality and other gene–gene interactions that can shed light on what is happening in the cell.

There has been a massive transformation in the last 5 years in terms of the ability to do these gene–gene interaction studies. This is not something that people thought was obviously going to happen just 10 years ago. We believe that this field will advance at incredible pace, and we hope to become leaders here at GSK.

Functional genomics studies are making waves in oncology, with synthetic lethal interactions pointing to new cancer targets. What about beyond oncology?
One of the reasons I was so excited about our acquisition of Tesaro last December was because of their PARP inhibitors. These are such a great example of synthetic lethality in the clinic, and I think they are an underappreciated class of drugs.

But I don't think that this type of interaction is limited to PARP. And I don't

even think it's limited to cancer. You can imagine that incomplete penetrance — in which some but not all individuals who carry a genetic variant express an associated trait — might be explained by genetic interactions that are protective. By unravelling those interactions, we might get clues as to what targets to pursue.

Part of the reason why we haven't found these interactions yet is because we need enormous data sets to see epistatic relationships. We tend to focus on the mean and the median of a distribution, but as sample sizes increase we can also look at outliers, individuals who should get a disease but don't. I'm excited about these tails and what they might be able to tell us as sample sizes increase.

Of course, these gene–gene interaction studies will give us millions of data points. And you can look at different phenotypes, in different cell types, generating trillions of data points. So we also believe that machine learning is needed to unmask insights that otherwise are imperceptible.

There's a lot of hype around machine learning. Do you have favourite examples of its application in target identification?

We are beginning to see examples, especially in oncology. But people do certainly throw around the terms machine learning and artificial intelligence a lot.

Having been at Calico, which is a Google company, I did learn a little bit about what kinds of data sets machine learning is most appropriate for though. And my takeaway is that machine learning really only starts to provide value when you get massive data sets with enormous complexity. Those haven't been very common in drug discovery efforts until very recently, even in the past 12 to 24 months. So, examples will be coming soon.

In terms of therapeutic areas, you have refocused GSK on immunology. Why?

There were two main questions that we wanted to address during our strategic review. Could we do anything to increase the probability of drug discovery and development success to something more reasonable? This is where the technologies we've just discussed come in. And one consequence of this solution is that when we find a compelling target through human genetics, we don't want to be constrained by therapeutic areas. We want to be more agnostic about pursuing opportunities.

But a second problem we wanted to address is that when a drug gets approved for its first indication, much of the heavy lifting has been done and there's a real opportunity to find other diseases that it can work in. So we wanted to think about how to take advantage of that opportunity more routinely.

I've worked on several such drugs, including the anti-CD20 drug rituximab. It started out as a lymphoma drug, and now is used in indications with no resemblance to lymphoma. This is because it targets the underlying biology that's critical for the pathophysiology of disease in general. This was a big driver for my belief that we need to focus on the immune system, not just for its role in autoimmune diseases but also because of its role in cancer, neurodegenerative disorders, liver disease, cardiovascular disease and more. So many diseases are now known to be immune mediated, particularly as a function of ageing.

At GSK we already had outstanding scientific focus on the innate and adaptive immune systems. My belief is that this focus will now allow us to find drugs that are sort of pluripotent across multiple diseases.

GSK sold much of its oncology portfolio to Novartis in 2015, and you are now rebuilding this as part of your focus on immuno-oncology. Do you regret that sale?

Maybe this says more about my personality than anything else, but I don't tend to look back. I don't get frustrated about things that I can't fix. The sale clearly had some upsides to it, and may have had some downsides. But to me when I look at where the biology is currently exploding, I thought it made sense to make these investments, especially given our expertise in immunology and the quality of our immuno-oncology group.

I will also say that a lot of the drugs that ended up going to Novartis were kinase inhibitors. And one of the upsides of not having those around anymore is that we don't have to think about maximizing the success of those drugs. Immuno-oncology and cell therapy are very exciting areas, and we can now focus there in a less constrained way.

So maybe there's a silver lining. We went from having 8 assets in the clinic in July to having 15 assets in the clinic at the end of last year. And our GSK3377794, a T cell receptor cell therapy that targets NY-ESO-1, will probably be the first T cell receptor therapy to be approved. That's a disruptive bet we are making: cell therapies might be to medicines what antibodies were to small molecules. It's early days, but cell therapy is looking very promising. And while I don't think I'd want a portfolio that's predominately disruptive, it's nice to have a few disruptive opportunities.

GSK has cut or divested 80 programmes, a third of its portfolio, since the start of 2017. Was it hard to make those cuts?

As a clinician scientist, I am strongly of the view that the patient always comes first. And by that I mean not only that I care deeply about helping patients, but also that I am really driven to achieve the biggest impact at all times. Sometimes that means killing things. When you kill something early, you can put the resources towards things that have the most chance of making a difference.

As an example of that, when I came to GSK our most advanced oncology molecule was the anti-BCMA antibody–drug conjugate GSK2857916, which had completed a phase I trial in around 30 patients. The data this trial generated were very compelling to me, and so we cut several projects from our portfolio to fund an additional nine studies of GSK2857916, including a pivotal study that has already finished recruiting patients.

When you find a programme that's going to really work, it's important not to treat everything equally. You have to be willing to make the courageous decisions to kill things, and the courageous decisions to double down on what you believe has the most potential. You might be wrong, but those are the kinds of bets that can be transformative.

This is the sort of cultural shift we want to make at GSK. This is a risky business, but if we make enough smart decisions we're going to end up winning. We have to be willing to make the difficult decisions and to keep the patient in mind.

Do you think industry is overly averse to such decisions, hedging its bets with broad portfolios?

I do. I'm not sure I'm right, but certainly at GSK I was convinced of that. Some companies are better at focusing than others. But spending a lot more money on a lot fewer assets — to understand how the drugs work, who they will work on and what other diseases they might be used in — can ultimately help a lot more patients.