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Vantage point – Going small to hit it big

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On paper it looks like an intriguing proposition: you take a blockbuster cell-surface protein target currently addressable only with antibodies, hit it with a small-molecule drug, and reap the benefits of improved dosing convenience and lower cost of goods.

The opportunity is even greater now that a new generation of drugs – checkpoint-blocking antibodies like Opdivo and Keytruda – have quickly rewritten the rulebook on treating cancer, offering certain patients nothing short of a cure. So just how difficult is it to block these same protein-protein interactions using a small molecule, and why are so few companies going down this route?

The answer to the first question is that it is very difficult, which likely explains the second point, too. Still, just because something is tough never stopped pharma from trying it – look at the repeated attempts to crack Alzheimer's disease. So the fact that immuno-oncology is the domain of antibodies, and that no big pharma groups are openly trying the small-molecule approach, should give pause.

Serendipity

Ali Fattaey, chief executive of the biotech Curis, puts it down to luck; antibodies were first to be shown to work, so this is what pharma picked up.

"When two immunologists, one working for Ono, and another working for Organon – a company looking at hormonal treatment of gynaecological disorders – began working [on checkpoint-blocking MAbs] it came totally from left field," he tells *EP Vantage*.

But this work would later, in the hands of Bristol-Myers Squibb and Merck & Co, give rise to Opdivo and Keytruda respectively. Yet none of these big players was "even touching [immuno-oncology] until it was shown that it could have a benefit", he states. "Then they rushed in."

Of course, it is in Mr Fattaey's interest to play up the similarities. Curis is perhaps the only industry player trying to hit immune checkpoints with small molecules, courtesy of a deal Mr Fattaey struck last year with the Dr Reddy's subsidiary Aurigene (*Curis's turn with the immuno-oncology buzzword, January 22, 2015*).

But he insists that the serendipity of where Curis and Aurigene find themselves now is not unlike those early days at Ono and Organon. After all, he says: "It was only one [Aurigene] chemist who said, 'the structure of PD-L1/PD-1 is out, I'm looking at it and I think this is addressable by small molecules'."

Andy Smith, a UK portfolio manager who most recently worked as chief investment officer at Mann Bioinvest, agrees that luck plays a big part, and that there is no reason why Aurigene, part of an Indian generics company, should not have discovered something relevant.

But he makes no bones about how tough this is to achieve. "Two soluble proteins have different conformational structures versus when they bind together," he says.

"That final tertiary structure may depend on other charges close to one or both of the individual proteins, and all of that is very difficult to replicate *in vitro*. Trying to get small-molecule inhibition of a specific protein-protein complex that only assumes this conformation once the two proteins are complexed and active is very difficult."

Cracking the puzzle

Curis and Aurigene make up one team trying to crack this puzzle. Another is an early-stage academic effort at University of Alberta spearheaded by Dr Khaled Barakat, assistant professor at the faculty of pharmacy and pharmaceutical sciences, focused specifically on small molecules to hit T-cell targets and thus replace existing antibodies.

Dr Barakat has met the Curis/Aurigene group, but says he is taking a different approach – for one thing he is targeting the PD-1 receptor rather than its ligand PD-L1. "We use computer simulations to model protein-protein interactions. We don't do it in a blind way, we do it in a rationally designed way," he tells *EP Vantage*.

This is done specifically to model the conformational changes in the proteins under physiological conditions, and takes months of calculations using supercomputers. “We simulate how the atoms interact together... We access binding sites that are not available in any crystal binding structure.”

“Once we identify the changes we think how to fill them with a small molecule that can block the interaction rationally,” he says, underlining that he really is trying to design molecules from scratch.

On the other hand, Curis/Aurigene initially approached the problem a different way, starting with the PD-L1 protein, cutting it into peptides and identifying those that were able to compete with the whole ligand for the PD-1 receptor.

They then cleaved the promising peptides further, until they arrived at a small molecule that was still able to block this interaction. “I think they have very good data on PD-L1 and Vista,” says Dr Barakat.

“The proteins are very dynamic,” he adds. “A key point in discovering small molecules is understanding [their] flexibility and rigidity.” Last year his work attracted funding of C$3m ($2.2m) from the Li Ka Shing Institute of Applied Virology and C$2.4m from the Alberta Cancer Foundation.

At present Dr Barakat’s group has just generated lead structures, but he says: “We are looking for partners to work with us to develop these compounds into a clinical lead.” He expects to have a lead in the clinic by the beginning of 2018.

B7 family

Curis’s strategy is to go after the B7 family of membrane proteins, which includes PD-L1, Vista and Tim3, and its clinical efforts initially focus on two small molecules: CA-170, against PD-L1 and Vista, and CA-327, which Mr Fattaey says blocks PD-L1 and Tim3.

The chief executive accepts that protein-protein interactions are “difficult places to try and address” with small molecules, but argues that the problems are insurmountable only when trying to break up the tightest interactions, like those between preformed, intracellular protein complexes.

It is a different story for membrane-anchored complexes like PD-1 and PD-L1, which by definition have weak binding affinity because regulation of T cells through them must be transient. “Small molecules can actually affect that interaction, as long as the molecules can bind to the correct regions,” he says.

The discovery of a series that allowed T cells to remain active in the presence of PD-L1 led to CA-170, and direct binding of the small molecule to the protein has been measured in biochemical assays. “We also have co-crystal structure of these molecules with several B7 family members, [which] allows us to do structure-based design.”

Indeed, the fact that the crystal structure of PD-1 and PD-L1 was solved as early as 2008 made these checkpoints the natural first target. But then, Mr Fattaey says, an intriguing discovery was made: “It appeared that the interaction hotspots – including PD-L1, Vista and Tim3 – have quite a bit of similarity in terms of structure.”

After that, identifying the binding sites that B7 proteins share, and trying to hit them with the same molecule, was a no-brainer.

Mr Fattaey also insists that Curis was not a late, opportunistic convert to this approach, having tried some years ago to develop CUDC-427/GDC-0917, an inhibitor of the IAP protein. And the first thing the chief executive worked on after entering the industry 24 years ago was protein-protein interactions with a dimerising transcription factor. Talks with Aurigene first took place three years ago.

Invoking Venclexta

Others’ success with the Bcl2 protein, which in the small-molecule Roche/Abbvie drug Venclexta has clear evidence that it is “druggable”, has spurred Curis on, and it is Venclexta that Mr Fattaey often invokes to back up his case.

But Mr Smith is not so sure, again arguing serendipity: “Rational design *in silico* with supercomputing power could have been the start of [Venclexta’s] discovery but in any event, to get an efficacious small-molecule inhibitor of *in situ* Bcl2, you've got to have been very lucky.”

Michael Gladstone, principal at Atlas Venture, agrees. “Venclexta is a fantastic success, but the decades of R&D that went into discovering and developing Bcl2 inhibitors speak to how challenging these types of projects are,” he tells *EP Vantage*.

“Drugging protein-protein interactions with small molecules may be possible for certain targets, but it has historically been very hard to find compounds that do this that are drug-like in terms of oral bioavailability, pharmacokinetics and specificity. It’s been hard reliably and repeatedly to achieve a combination of MAb-like

potency and drug-like properties."

Surprisingly, Mr Gladstone is also sceptical about the potential benefits that small molecules could bring in areas where a highly effective antibody is already available.

"It's unclear whether the convenience of an oral molecule is a major advantage in oncology, where there is comfort with bi or tri-weekly infusions, and many therapeutic regimens include a combination of agents, with one or more that are infused," he says, stressing that his criticism is not aimed at any company in particular.

Naturally, both Mr Fattaey and Dr Barakat argue that oral exposure and bioavailability are key benefits. "The big difference apart from cost is untethering a patient from a chair psychologically and from a convenience perspective, because a patient doesn't really need to come in every two weeks. Patients in our phase I trial go home with a bottle of capsules," says the Curis chief.

Another benefit is pharmacological, since an antibody tends to be given in a massive dose sufficient to hit its target over several weeks. Considering that immune checkpoint therapy is not about directly inhibiting cancer cells but about stimulating an immune response, with the concomitant toxicity worries, there are additional considerations.

"A small molecule has a half-life of six to eight hours, and it's very cheap to make compared with antibodies," says Dr Barakat. "You can titrate with a small molecule; you can't with an antibody. If you have a side effect you can stop the treatment. This is how small molecules will change the game."

Finally, small molecules might access locations in the body that are not accessible to some antibodies, such as the brain, and with other agents in the right setting could be given as an all-oral combo.

Dr Barakat and Mr Fattaey also do not foresee any difficulties targeting a small molecule to a tumour site, though Mr Gladstone points out that making molecules that are sufficiently cell-permeable is another problem when trying to target intracellular protein-protein interactions.

The godfather

If any of these arguments is persuasive about PD-1/PD-L1 at least having a chance of being "druggable" with a small molecule, how about targets beyond the B7 family?

Professor Frédéric Triebel should know. He is now chief scientific officer of Prima Biomed, but is more famous for having discovered, back in 1990, the immune checkpoint Lag3. Perhaps unsurprisingly he is sceptical.

"It's very difficult to drug such large hydrophobic surfaces contacting each other, and a lot of the difficulty of Lag3 is that the 3D structure is not known, while for PD-L1 and PD-1 it is known," he tells *EP Vantage*.

"There are of course small molecules blocking smaller protein interactions [like with Venclexta], and it's even much easier if you have a cleft – if it's an enzyme, for instance. But it remains to be seen if this is feasible for Lag3 and PD-1."

Professor Triebel also confirms that the lack of big pharma activity here is purely down to the difficulty. Dr Barakat reckons a few big groups have looked at this space, but says it is very hard to identify any binding locations in the proteins' crystal structures, which have traditionally been the starting point.

"If you look at the crystal structures by themselves these are very shallow surfaces," he says. "Designing antibodies is easier." Mr Fattaey, however, says he knows from patent filings that Bristol-Myers Squibb has carried out early work on the small-molecule approach.

If Bristol and others have been reluctant to follow through on these early efforts, Mr Fattaey remains optimistic: "Let's wait until we show some responses in patients, and let's see how fast they come back in."

Bristol-Myers Squibb did not respond to requests to comment on the issues discussed in this feature.