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Vantage point – Life for kinase inhibitors in an immuno-oncology world

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At a time when immuno-oncology is all the rage it is tempting to write off small-molecule approaches targeting kinases as yesterday's science. But the funding progress of at least two biotechs suggests that this strategy has plenty of life left in it yet.

Blueprint Medicines and Deciphera were both founded on the promise of kinase inhibition, and have captured investors' imagination, respectively raising $169m in a float and $175m in private money. If the route each group is taking indicates growing complexity, it does at least show a clear rationale for developing a new generation of kinase inhibitors.

Still, the chief executives of both companies accept that immuno-oncology has completely changed the landscape. Blueprint's Jeff Albers, speaking to *EP Vantage* at the recent JP Morgan meeting, said: "We are as enthusiastic about cancer immunotherapy as anybody, but it's also been our unyielding view that there will always be a place for targeted therapies."

"There's room for a lot of different approaches," said Deciphera's Mike Taylor in an earlier interview. "The frontier-breaking technologies are great, but in many ways unproven. But kinase inhibition has proved to be an exceptionally successful approach – it's the backbone of targeted therapies."

Scientifically the idea is simple enough. Many cancers are driven by a kinase that has become faulty or overexpressed by virtue of a genetic mutation – the abnormal overactivity of this enzyme contributes to uncontrolled cell growth, and thus blocking it provides a targeted way of stopping the root cause of the cancer.

But the approach has drawbacks, the most obvious of which is development of mutational resistance. A malfunctioning kinase can only be blocked for a certain time before a new mechanism becomes dominant in driving the tumour, and the patient's cancer relapses, this time driven by a different pathway.

Selectivity

This is where Blueprint comes in. The group's founding principle was to build a library of all kinases and try to understand the underlying biology, aiming to zero in on whatever kinase might be driving tumour growth in a given situation.

"That could differentiate us from other companies – that you understand the biology, and now you have a library that'll give you a fast starting point," said Mr Albers. "We have molecules or starting points for kinases that no one even knows what they do yet."

Blueprint's R&D projects target specific kinase mutations – potentially improving efficacy but surely also limiting the treatable patient population – and beyond target specificity the approach does not differ from, say, Novartis's Gleevec, the kinase inhibitor poster child.

With more than 30 kinase inhibitors approved, and several times that amount in industry pipelines, it is hard to argue that this has not been a successful approach. Gleevec sold $4.6bn in 2015, the last full year before its patent expired.

For now, Blueprint has two clinical-stage compounds: BLU-285 and BLU-554. It is developing BLU-554, an FGFR4 inhibitor, in hepatocellular carcinoma, where around 30% of patients are thought to have an abnormally activated FGFR4 pathway.

Meanwhile BLU-285, a Kit-PDGFRa inhibitor, is being trialled in systemic mastocytosis and two different subtypes of gastrointestinal stromal tumours (GIST): third-line Kit mutation-driven disease, and first-line PDGFRa D842V mutant GIST.

And, beyond that, Mr Albers highlighted the group's ability to move quickly on any targets that might suddenly become interesting, comparing the approach to the ice hockey legend Wayne Gretzky "skating not where the puck is now but where it's going to be – so anticipating where interesting targets may emerge."

Mutation resistance

Deciphera's approach has one key difference from Blueprint's: Deciphera reckons it has been able to rationally design kinase inhibitors that could actually resist mutation. "We're able to inhibit not only wild-type kinase, or some specific mutations – but all the mutations," said Mr Taylor.

On the face of it, of course, Deciphera's lead candidate, DCC-2618, looks like a straight Kit-PDGFRa kinase inhibitor, competing mechanistically with BLU-285.

However, Mr Taylor draws a key distinction versus Gleevec, which binds when a kinase is in its "off" state, and prevents the enzyme from becoming activated. In contrast, Deciphera's molecules have been designed to bind in the kinase's "switch pocket", preventing this region from locking the enzyme into its "on" state.

"This produces a very potent binding … and robustly inhibits activation; it directly leads to our ability to control mutant forms of the kinase," said Mr Taylor. To circumvent this the kinase would have to mutate in such a way that the inhibitor could no longer bind, but that the switch would still work.

"That seems to be a Venn diagram with no overlaps," he stated; modelling suggests that all such mutations would be non-functional, a fact that if true could allow DCC-2618 to inhibit all known forms of Kit kinase.

This switch pocket-targeting has not been attempted by anybody else, he said: "It's a simple but elegant approach; I call it artisanal." And the potential is clear, not only in different patients with different Kit mutations, but also single patients each harbouring multiple mutations.

A late-breaker at last year's Triple meeting (EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics) in Munich showed early hints of efficacy with DCC-2618 in a first-in-human dose-escalation trial in Kit-mutant GIST patients, some of whom had established resistance mutations.

An entirely separate Deciphera approach came about serendipitously when rebastinib, a molecule being tested for Bcr-abl inhibition that failed in leukaemia. The discovery that this asset was a potent inhibitor of Tie2 led to continued study based on the belief that Tie2 is a macrophage target involved in damping down immune response in the tumour microenvironment.

This shows yet another novel way in which kinases are involved in cancer, and another means by which hitting this tried and tested enzyme class can yield novel results.

Companion diagnostic?

Blueprint's idea to cut the patient population into ever finer subgroups based on the specific kinase involvement raises a separate question – that of genetic testing, though Mr Albers reckons only BLU-285 will need a companion diagnostic, and only in PDGFRa D842V mutant GIST.

This is because PDGFRa-driven GIST only accounts for 5-7% of front-line disease; Blueprint is already developing such a test with Qiagen. In contrast, in advanced systemic mastocytosis a single driver, D816V, is present in 90% of patients, while refractory Kit-driven GIST involves upwards of 95% of patients having a Kit exon 17 mutation by third line.

This targeted approach has not put off investors: Blueprint's 2015 IPO came at a time when it had only preclinical assets, and it raised another $134.5m in December on the back of early phase I data presented at Ash and the Triple meeting.

That IPO came a little after two other kinase-focused biotechs, Loxo Oncology and Ignyta, completed respective $77m and $119m floats. These groups are focused specifically on neurotrophic tyrosine receptor kinase (NTRK) gene fusions – a rare oncogenic driver that occurs across a range of cancers.

Selection of novel kinase inhibitors				
Project	**Company**	**Mechanism**	**Indication(s)**	**Status**
Entrectinib	Ignyta	Pan-TRK, ALK & ROS1 inhibitor	Solid tumours	Phase II
LOXO-101	Loxo	Selective TRK inhibitor	Solid tumours	Phase II
BLU-285	Blueprint	Kit PDGFRa inhibitor	Systemic mastocytosis, GIST	Phase I
BLU-554	Blueprint	FGFR4 inhibitor	Hepatocellular carcinoma	Phase I
DCC-2618	Deciphera	Kit PDGFRa inhibitor	Systemic mastocytosis, GIST, GBM	Phase I
Rebastinib	Deciphera	Tie2 inhibitor	Solid tumours	Phase I
DCC-3014	Deciphera	CSF1R inhibitor	Solid tumours	IND approved
BLU-667	Blueprint	RET inhibitor	NSCLC, thyroid cancer	IND accepted

Blueprint also has another asset, BLU-667, that should go into phase I this year, plus partnerships with Alexion and Roche, though details are hard to come by. The Roche deal covers up to five undisclosed targets in cancer immunotherapy, and could see resulting molecules combined with Roche's checkpoint inhibitor Tecentriq – potentially making the hot immuno-oncology combo space more personalised.

Still, it has not all been plain sailing: Mr Albers admits that Blueprint halted four programmes "based on progress we've seen other companies make". This includes stopping a project targeting NTRK gene fusions, perhaps after seeing Loxo and Ignyta's work with LOXO-101 and entrectinib respectively (*AACR – Loxo and Ignyta clash on novel kinase mechanism, April 18, 2016*).

Deciphera, too, has been active in this space: altiratinib acts on the Met/NTRK pathway, which Mr Taylor accepts is a rare oncogenic driver. "We're completing the phase I and evaluating the profile in light of the competitive situation," he stated in November, but this asset no longer appears in the R&D pipeline, suggesting that Deciphera followed in Blueprint's footsteps and canned it.

If competition is a problem now, pricing could be longer term: if a broad-patient approach like Deciphera's might fit a typical model, one with very low patient numbers like Blueprint's could necessitate premium pricing to be viable. Mr Albers is keeping his cards close to his chest, saying: "It's early days. I think we'll let the efficacy and safety profile dictate the value."

Another factor to consider is the potential entrance of generic competition; while monoclonal antibodies are still relatively resistant to biosimilar competition, a small-molecule approach naturally entails the risk of generic entry as soon as the original patent goes.

When asked how Blueprint stacks up against competitors like Deciphera, Mr Albers said: "How we think we're differentiated is maybe the breadth of our portfolio. But the notion of developing targeted therapies – we're not unique in that."

And while Mr Taylor acknowledges Blueprint as a competitor in the Kit inhibitor space he is at pains to stress the difference between his opponent's emphasis on specificity and Deciphera's "breadth of control over all resistant mutants ... rather than just selectivity".

Clearly interest in kinase inhibition is not about to abate – something that will only give rise to more competition.