Evaluate Vantage

September 23, 2019

As the heat rises, Clovis turns to radionuclides

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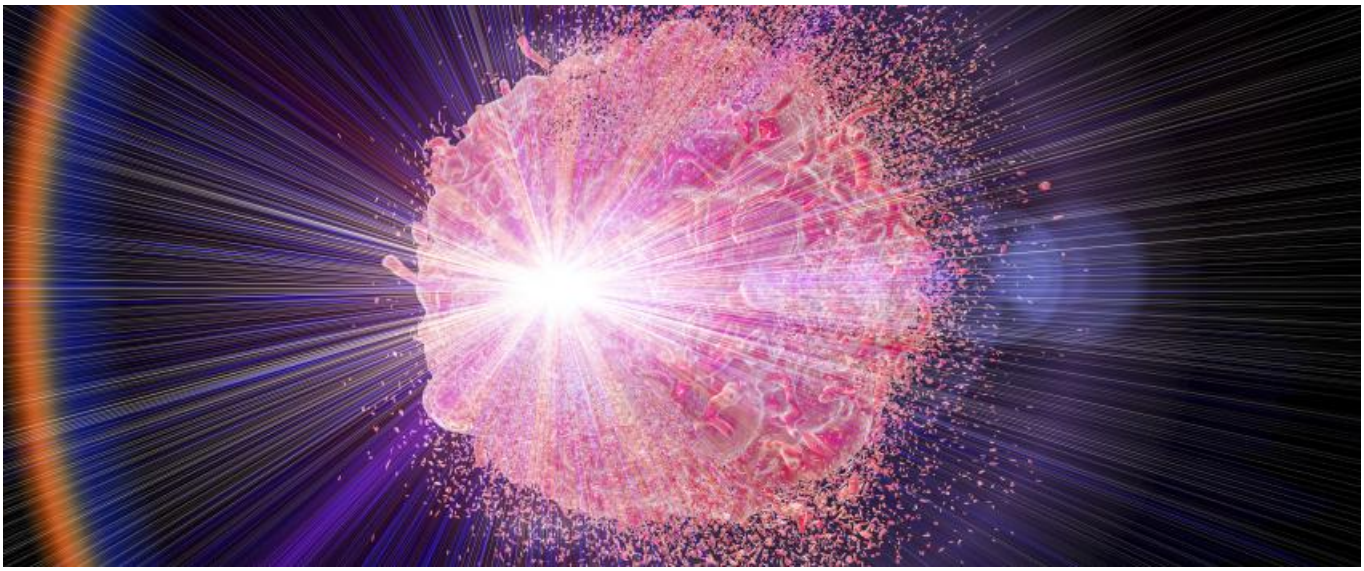

The beleaguered drug maker has licensed a preclinical FAP-directed radiopharmaceutical, a target that has made little progress.

Clovis Oncology's Parp inhibitor Rubraca has long struggled against the competition, and concerns about the company's future have prompted investors to flee, with the stock losing 93% of its value since the beginning of 2018. Today's licensing deal, featuring a preclinical radiopharmaceutical that targets a common tumour marker, is unlikely to prove much of a panacea.

At least the transaction did not cost Clovis much: 3B Pharmaceuticals, a private German biotech, will receive $12m up front for worldwide rights, ex-Europe, to a fibroblast activation protein-targeted agent that could enter the clinic in late 2020. A discovery programme directed at three additional targets for radionuclide therapy is also covered.

A quick look at what else is happening in FAP-targeting throws up very few pharmaceutical projects, though imaging agents targeting the molecule are also being explored. No commercial companies seem to be using it in the radiopharmaceutical space.

Still, Novartis's moves in this broader field – spending $6bn on Endocyte and Advanced Accelerator Applications – show that there is certainly value in this technology.

Targeting fibroblast activation protein: a thin field			
Project	**Mechanism**	**Company**	**Notes**
BXCL701 (talabostat)	DPP VIII & IX & FAP inhibitor	Bioxcel Therapeutics	Phase II trial ongoing
RG7461	Anti-FAP MAb-IL2 fusion protein	Roche	Four large phase II trials recruiting.
NG-641	Oncolytic adenoviral vector, coding for FAP	Psioxus Therapeutics	Phase II trial ready to start
RG7827	Anti-FAP 4-1BBL MAb	Roche	No active trials - abandoned?
BIBH1 (sibrotuzumab)	Anti-FAP MAb-iodine I-131 conjugate	Boehringer Ingelheim	Abandoned in phase II
RG7386	Anti-FAP-DR5 bispecific	Roche	Presumed abandoned in phase I
Source: EvaluatePharma.			

A recap of the development history of other FAP-based agents suggests that, rather than direct inhibition, the protein's use for targeting might well be the best way forward.

FAP alpha is highly expressed on cancer-associated fibroblasts, which play an important role in tumour proliferation. Numerous attempts have been made to target FAP to block growth signals, with little success: the most advanced project, Bioxcell's talabostat, has been in the clinic for over a decade.

The failure of a phase III lung cancer trial back in 2007 spelled the end for talabostat's then-owner, Point Therapeutics. Bioxcell is pursuing a combination strategy to tease out the agent's potential: a phase II study in small cell neuroendocrine prostate cancers, on top of Keytruda, should yield data before the end of the year.

Bioxcell is also gearing up to start a triple-combo study in pancreatic cancer that would see Nektar's cytokine NKTR-214 and Merck KGaA/Pfizer's anti-PD-L1 agent, Bavencio, added to the mix.

As well as hitting FAP, talabostat targets DPP 8/9; Bioxcell describes the latter as an immune checkpoint, and it is hard to know whether one mechanism is more important than the other here. But the long history of disappointment with talabostat, and concerns about projects that fail to show single-agent activity, mean that Bioxcell will need to provide unequivocal evidence of talabostat's contribution to any positive findings before hopes can be rebuilt for this project.

Elsewhere

Roche is also pursuing a combination strategy of sorts with RG7461, an engineered variant of IL-2 fused to an anti-FAP antibody. Encouraging data in melanoma patients were presented at last year's Esmo, though presumably the role of the anti-FAP mechanism here is limited to targeting the cytokine to the site of the tumour.

The Swiss pharma giant also lists RG7827 in its pipeline, describing it as having an antibody-like structure, with one arm binding to FAP and the other carrying the signalling molecule 4-1BBL. No active trials appear to be under way, however, and this project could well be heading the same way as RG7386, a FAP-DR5 bispecific, which seems to have been abandoned.

Psioxus is taking another approach entirely with NG-641. This is an oncolytic adenoviral vector that encodes for four separate genes, one of which is a FAP-targeting bispecific T-cell activator, plus three additional genes to recruit and activate those T-cells. A phase I study is poised to start.

Work elsewhere is preclinical, or already consigned to the scrapheap. Boehringer Ingelheim's sibrotuzumab, for example, failed a mid-stage colorectal cancer trial in 2003 and the company does not seem to have retained interest in the mechanism.

By using FAP to direct a potent radiopharmaceutical to the site of tumours, Clovis could have found a viable way forward here. However, work is very early, and it will take success elsewhere – probably from the remaining Roche asset – to build hopes in these efforts.

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