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Merck & Co gives epigenetics a boost

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Not only is Merck & Co's $110m buyout of OncoEthix a rewarding exit for the private Swiss company's backers, it also broadly endorses epigenetics – an anticancer approach that has so far failed to live up to its initial promise.

OncoEthix, basically a one-project bet on bromodomain inhibition for treating haematological and solid tumours, is not alone in this space. GlaxoSmithKline and Roche pose formidable competition, and the Merck deal could throw the spotlight on other small players like Constellation Pharmaceuticals, Tensha Therapeutics and 4SC.

Of course, competition is no longer much of a concern to Index Ventures, SV Life Sciences, Endeavour Vision and Edmond de Rothschild, which had pumped $30m into OncoEthix since its formation just five years ago. In addition to the $110m purchase fee they could make $265m from Merck if future milestones are met.

Yesterday's takeout was likely triggered by the presentation at April's AACR meeting of phase I data backing the mechanism behind OncoEthix's sole clinical asset, OTX015. The data showed good tolerability, and set the stage for single-agent phase I/II studies in glioblastoma and combo trials in acute myeloid leukaemia, which are set to start dosing imminently.

OTX015 is a small molecule that inhibits the binding of BET bromodomain proteins 2, 3 and 4 to acetylated histones – the structures around which DNA is wound in a cell's nucleus. This binding is thought to downregulate Myc transcription, switching off Myc-dependent target genes.

OncoEthix thus has a clear focus on epigenetics, which can be defined as the study of molecular mechanisms that influence gene expression. The thinking is that small molecules, which are cheap to manufacture and easy to administer, might directly influence the way particular genes are expressed (*Early success with novel leukaemia drug points to epigenetic progress, October 7, 2011*).

No stranger

Merck is no stranger here, having developed Zolinza, an inhibitor of histone deacetylase (HDAC), an enzyme that affects the tightness with which DNA is wrapped around histones.

However, Zolinza has failed to make an impression in its approved indication, non-Hodgkin's lymphoma. Beleodaq, a Spectrum Pharmaceuticals HDAC inhibitor approved this year, is not expected to become a big seller either.

Thus, while HDAC inhibition might not now provide the leap forward, for epigenetics in general Merck's endorsement of OncoEthix keeps hopes alive.

A related approach to affecting gene expression involves the inhibition of histone methyltransferases like DOT1L and EZH2, and is being pursued by Epizyme, Eisai and GlaxoSmithKline.

The UK firm already has one of industry's most advanced bromodomain inhibitors, GSK525762, and is thus an important epigenetics player. Closely behind it is Roche, which has an option over CPI-0610, a phase I project belonging to the private firm Constellation.

Selected bromodomain protein inhibitors in oncology		
Project	**Company**	**Trial ID**
Phase I		
GSK525762	GlaxoSmithKline	NCT01587703 NCT01943851
OTX015	OncoEthix/Mitsubishi Tanabe	NCT02303782 NCT02296476
CPI-0610	Roche/Constellation	NCT02158858 NCT02157636
TEN-010	Tensha Therapeutics	NCT01987362 NCT02308761
Preclinical		
Bet Bromodomain inhibitors	Orion/Dr Reddy's	–
Bromodomain Inhibitor Research Project	Medivation/OncoFusion Therapeutics	–
ZEN-3365	Zenith Epigenetics	–
4SC/Crelux Epigenetic Cancer Project	4SC	–
KM601	Kainos Medicine	–

Another private US biotech, Tensha, recently started a phase I study of TEN-010 in acute myeloid leukaemia and myelodysplastic syndromes. Germany's 4SC, meanwhile, has done early work on bromodomain proteins, and its lead project is resminostat, a phase II HDAC inhibitor.

Canada's Resverlogix appears to be focusing on non-oncology applications of bromodomain inhibition, and in 2013 it spun out a preclinical oncology project, ZEN-3365, into Zenith Epigenetics, a Canadian biotech.

And Merck is not the only large player to have signalled continued interest in the bromodomain approach this year; back in April Medivation struck a joint research collaboration with OncoFusion Therapeutics covering compounds targeting these proteins.

It must be stressed that all this work is early, and much remains to be proved about the applicability of epigenetics as a realistic therapeutic approach; for one thing, the downregulation of genes that affect other cellular functions leaves significant potential for off-target effects.

That said, backers of Tensha, Constellation and OncoFusion will take heart in the fact that Merck and others are still prepared to give it a shot.

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