NEWS maker

Mission Therapeutics

Synthetic lethality pioneers spin out an oncology company targeting DNA repair through interruption of ubiquitin pathways.

Steve Jackson, Mission Therapeutics co-founder.

Scientists who first validated synthetic lethality as a tumor-killing strategy have been buoyed by a cash injection for their new spinout Mission Therapeutics. Established in June 2011, Mission received £6 ($9.5) million in Series A financing in August from a venture capital syndicate led by Sofinnova Partners, Paris, and including London-based GlaxoSmithKline's corporate venture fund SR One, Roche Venture Fund of Basel and London-based Imperial Innovations. Investor interest was piqued by the company's synthetic lethality anticancer approach and insider knowledge of ubiquitination pathway target biology.

In 1997, when Cambridge University biochemist Stephen Jackson founded his first company, KuDOS Pharmaceuticals, synthetic lethality—killing cells by combining two individually harmless mutations—was an obscure concept in yeast genetics that few were considering for cancer. Funding was initially hard to come by. Then in 2005 KuDOS, together with biochemist Alan Ashworth at the Institute of Cancer Research in London, validated the concept using the company's small-molecule poly-ADP-ribose polymerase (PARP) inhibitor olaparib in mice with *BRCA1,2*-deficient tumors (*Nature* **434**, 917–921 2005). KuDOS showed that combining base-excision repair defects (instigated by PARP inhibitors) with homologous recombination defects in DNA (*BRCA1,2* deficiency) could block tumor formation. With the approach validated, KuDOS aroused pharma's interest and, in 2006, the biotech was bought by London-based AstraZeneca for $210 million.

Besides Jackson, Mission Therapeutics founders include KuDOS veterans Niall Martin, Xavier Jacq and Keith Menear. Mission employs 13 at the Babraham Research Campus in Cambridge, UK, including 6 scientists from KuDOS.

But Mission is now one of many companies exploring synthetic lethality in cancer, and enters a more crowded, more competitive landscape than existed when KuDOS was founded. The company's advantage, says Jackson, lies in its choice of targets and in its careful development of biochemical assays. Although other companies target PARP or kinases, Mission has chosen to concentrate on blocking ubiquitination (and related processes) in DNA repair pathways.

Interest in ubiquitination and its role in promoting DNA repair has boomed since 2004, prompted by an explosion in research, much of it from Jackson's laboratory. Ubiquitin targeting of proteins for proteasomal degradation is one aspect, because to perform DNA repair in a dense chromatin environment it may be necessary to degrade one set of proteins to allow others to enter, according to Wade Harper, a cell biologist at Harvard Medical School, in an e-mail. Furthermore, he says that monoubiquitination and lysine 63 polyubiquitination, which regulate signaling and recruitment of proteins to DNA damage repair sites, are also important.

Mission's COO Niall Martin says the company is focused on about a dozen proteins in these pathways. Among these are E2-conjugating enzymes. E2s form a complex with an E3 ligase and a protein substrate to transfer ubiquitin to the substrate. Other preferred targets are the deubiquitinating enzymes (DUBs), proteases that remove ubiquitin from modified substrates and also have ubiquitin editing and proofreading functions. Although E2s and DUBs are less specific than E3s, E3s are more difficult as drug targets. Jackson believes E2 and DUB inhibitors should have effects specific enough to fight cancer, either through synthetic lethality or by taking advantage of replicative stress in cancer cells during the cell cycle. The DUBs USP1, USP3, USP7, USP28 and BRCC36 have been linked to DNA repair in recent years. Martin says a few of these are on the company's target list.

E2s are not classically druggable enzymes and most DUBs are cysteine proteases, which are also difficult to inhibit. One major concern with Mission's approach, says Harper, is that individual DUBs can have multiple functions, some of which favor cancer cells and others not. Figuring out the net effect on cancer cells must be done on a case-by-case basis, using tool compounds. And many DUB and E2 substrates remain unknown or their functions unstudied, according to Ivan Dikic, scientific director for the Frankfort Institute for Molecular Life Sciences in Germany, so drug side effects are a concern.

Mission's Martin says that their scientists have been doing extensive biochemistry, for over a year, pulling full-length target proteins from mammalian cells along with associated scaffold proteins to create assays that are physiologically relevant—work that larger companies often neglect, he says. Besides clarifying the biology, these assays should help Mission find active lead compounds, a process that will gear up in 2012.

Jackson serves as part-time CSO for Mission, but the company relies heavily on Jackson's own research at the Gurdon Institute, in Cambridge, UK, where he heads the Cancer Research UK laboratories. Through agreements with Cancer Research UK and the University of Cambridge, Mission has access to intellectual property (IP) from Jackson's laboratory, and first option on future IP for a limited number of years.

Elsewhere, Hybrigenics of Paris (in partnership with French big pharma Servier of Suresnes) as well as Genentech of S. San Francisco, California, also have DUB programs, according to Harper. Mission's strengths are its biochemistry focus and its access to the Jackson laboratory IP. Jackson's second company is starting faster than his first, but Mission will have to advance its programs rapidly to outcompete more established rivals.

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