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Science-Business eXchange

Scots aggregate a ligase platform

By Tim Fulmer, Senior Writer

For the past three years, **Scottish Enterprise** has been working with multiple international academic and commercial labs to investigate therapeutic targets that were regarded as too challenging by many drug development companies. Now, the Scottish government's economic development agency has lifted the curtain on its most advanced life science program—small molecule modulators of E3 ubiquitin ligase proteins.

The ubiquitin-proteasome system contains the cell's chief machinery for breaking down proteins and is dysfunctional in a variety of cancers, including lymphomas and prostate, bladder and breast cancer.

The one marketed drug that targets the system—proteasome inhibitor Velcade bortezomib—leaves room for improvement, as the drug is poorly selective for tumor cells over normal cells and can have off-target toxicity.

Nevertheless, Velcade posted global sales of $1.4 billion in 2009. It is marketed in the U.S. by **Takeda Pharmaceutical Co. Ltd.**'s **Millennium Pharmaceuticals Inc.** subsidiary to treat multiple myeloma (MM) and mantle cell myeloma. **Johnson & Johnson** has rights outside the U.S.

The E3 ubiquitin ligase protein complex is immediately upstream of the proteasome. Unlike the proteasome, the E3 ubiquitin ligase family is diverse. Thus, targeting a specific E3 ligase complex associated with a particular cancer might decrease the likelihood of off-target toxicity.

However, given the intricacy of the E3 ubiquitin ligase complex and the protein-protein interactions involved, the open question has been whether selective ligase-targeting compounds can be identified or designed.

In 2008, Scottish Enterprise decided the answer was "yes" after an in-house review of the field.

"Initial surveys of IP filings and peer-reviewed publications on the ubiquitin-proteasome system, followed by extensive discussions with key global opinion leaders, made it clear there were multiple targets in this area that had extensive therapeutic potential but were underexploited in company R&D programs," said program manager Neil Wilkie. "Notable among those were the E3 ubiquitin ligases."

"Based on the surveys and discussions, we put together a preclinical work plan for developing platform technologies that allowed the identification of compounds that target specific E3 ligases implicated in disease. We then fielded applicants throughout the world who worked in this area, making offers to 10 labs, inviting them to participate in a collaborative research program to identify and design E3 ligase–targeting compounds," said Wilkie.

The result was a 3-year, $15 million program awarded to a team of 32 researchers from 8 labs at **The University of Edinburgh**, the **University of Glasgow**, the **University of Strathclyde**, the **University of Toronto** and Millipore Corp., which was acquired by **Merck KGaA** in 2010.

Funding for the program came from Scottish Enterprise's Intermediary Technology Institute (ITI), which exists to commission development of technology platforms that can be licensed to create high-value companies in Scotland, according to Wilkie.

The resulting team "combines expertise in cell biology, cancer biology, peptide biochemistry, high throughput assays, X-ray crystallography and computational modeling. As a result, we believe the program provides an excellent example of a drug design and *in vitro* screening platform that can be applied broadly to the entire E3 ligase family," said Mike Tyers, a principal investigator on the program and professor of systems biology at the University of Edinburgh.

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> ***—Neil Wilkie, Scottish Enterprise***

Wilkie told *SciBX* that the team's lead small molecule peptidomimetic is "an inhibitor of low nanomolar potency that specifically targets the oncogenic βTrCP1 E3 ligase. Behind that lead, we have also identified small molecule modulators with micromolar potency against two additional E3 ligases that we are continuing to optimize."

The next step is to begin testing the E3 ligase inhibitors in relevant cancer models, said Tyers. "By the end of 2011 we plan to have an *in vivo* data package on our lead compound, and we will be ready to license the IP to a company that can move the compound forward into clinical trials," said Wilkie.

Based on the results of the three-year program, Scottish Enterprise has filed multiple patent applications covering the use of *in vitro* assays to screen for compounds that modulate ubiquitination enzymes as well as patent applications covering inhibitors of ubiquitin ligases and their use to treat cancer, infectious disease, neurodegenerative disease and cardiovascular disease.

For each ITI program, Scottish Enterprise owns any IP generated by the research. The agency plans to license that IP to companies and organizations, with hopes of luring research dollars to Scotland and bolstering the national economy.

Fulmer, T. *SciBX* 4(9); doi:10.1038/scibx.2011.242
Published online March 3, 2011

COMPANIES AND INSTITUTIONS MENTIONED

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
Millennium Pharmaceuticals Inc. (NASDAQ:MLNM), Cambridge, Mass.
Scottish Enterprise, Glasgow, U.K.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
The University of Edinburgh, Edinburgh, U.K.
University of Glasgow, Glasgow, U.K.
University of Strathclyde, Glasgow, U.K.
University of Toronto, Toronto, Ontario, Canada