Expanding into new (bromo)domains

By Michael J. Haas, Senior Writer

The **Neomed Institute** has begun development of its first cancer therapeutic, a bromodomain containing 4 inhibitor from **Epigenetix Inc.** that the not-for-profit organization thinks could have a selectivity advantage over competing molecules.

Bromodomain-containing proteins are a class of epigenetic regulators. These domains bind to histones in which lysine residues are modified by an acetyl group to regulate chromatin remodeling and gene transcription.^{1,2} Two independent papers in *Nature* in 2010 first showed the potential druggability of bromodomains by identifying JQ1 and I-BET as selective inhibitors of the BET bromodomain family, which includes bromodomain containing 2 (BRD2), BRD3 and BRD4.^{3,4}

According to Mounia Azzi, Neomed's director of scientific affairs, the institute in-licensed the BRD4 inhibitor program from Epigenetix because the biotech's structure-based design approach identified new inhibitors with good selectivity, cellular permeability and activity in multiple cancer models.

Neomed will lead development through human proof of concept. **IntelliSyn**—a medicinal chemistry company located at the institute—will conduct the initial drug discovery work, and CROs will run drug metabolism, pharmacokinetics and toxicity studies, Azzi said.

Epigenetix decided to partner with Neomed because “the institute provides us access to financing and pharma expertise that we would have needed to obtain—one way or another—to develop the BRD4 program,” said Joseph Collard, the biotech's cofounder and CEO. He also is a cofounder of IntelliSyn. “Plus, we have other programs, so we

aren't out-licensing our one and only program.”

After the BRD4 inhibitors, Epigenetix's next most advanced program is in lead identification and targets oxytocin receptor (OXTR) to treat autism, Collard said.

The partners expect to identify a lead compound within six to eight months and have not yet selected a lead indication.

Financial details were not disclosed, but Azzi said that Neomed and Epigenetix will share any proceeds from out-licensing the BRD4 program. Neomed's pharma partners will have options to in-license the project at certain undisclosed milestones.

Neomed was founded in 2012 by the Quebec government, **AstraZeneca plc** and **Pfizer Inc.** to provide funding for academic labs and biotechs to develop therapeutics to human proof of concept and then out-license them.⁵

Johnson & Johnson Innovation LLC and Janssen Labs units of **Johnson & Johnson** joined Neomed last December.⁶ The institute is still seeking a fourth pharma partner, President and CEO Max Fehlmann said.

None of the three pharmas has a disclosed BRD4 inhibitor program.

At least six other companies have BET bromodomain inhibitors in the clinic (see **Table 1**, “Clinical bromodomains”).

Although the BRD4 inhibitor is Neomed's first asset that directly treats cancer, the institute was not specifically looking for an early stage cancer project, Azzi said. Instead, the partnership evolved from Neomed's and Epigenetix's link through IntelliSyn, which had been working with the biotech on the bromodomain program.

As a result of that link, “Epigenetix presented the project to Neomed, and we saw value in the program,” she said. Moreover, “IntelliSyn has the right expertise on epigenetic targets—specifically, BRD inhibitors—to develop it.”

Neomed's pipeline includes three compounds that were donated by AstraZeneca after the pharma wound down its neurology R&D in Montreal and elsewhere in 2012:⁵ NEO1940, an agonist of cannabinoid CB₁ receptor (CNR1) and CNR2, is in Phase I testing to treat cancer

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—Joseph Collard, Epigenetix Inc.

Table 1. Clinical bromodomains. At least six companies have compounds that inhibit bromodomains, including the bromodomain containing 2 (BRD2), BRD3 and BRD4 members of the BET bromodomain family, in clinical testing to treat cancer and other diseases.

Source: BCIQ: BioCentury Online Intelligence

Company	Product	Description	Status
Zenith Epigenetics Corp. subsidiary of Resverlogix Corp. (TSX:RVX)	RVX-208	Inhibitor of BRD4 and other members of the BET bromodomain family	Phase II for atherosclerosis and diabetes; Phase I for Alzheimer's disease (AD)
Constellation Pharmaceuticals Inc.	CPI-0610	Bromodomain inhibitor	Phase I for lymphoma
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	GSK525762 (525762)	Bromodomain inhibitor	Phase I for NUT midline carcinoma (NMC)
Mitsubishi Tanabe Pharma Corp. (Tokyo:4508); Oncoethix S.A.	OTX015 (Y-803)	Synthetic small molecule inhibitor of BRD2, BRD3 and BRD4	Phase I for hematological malignancies
Tensha Therapeutics Inc.	TEN-010	Small molecule inhibitor selective for the BET bromodomain family (BRD2, BRD3, BRD4 and bromodomain testis specific (BRDT))	Phase I for solid tumors

cachexia; NEO6860, a transient receptor potential vanilloid 1 (TRPV1; VR1) antagonist, is in preclinical testing to treat osteoarthritis (OA) pain; and a purinergic receptor P2X ligand-gated ion channel 3 (P2X3) antagonist is in preclinical development for painful bladder syndrome/interstitial cystitis and OA pain.

In September, Neomed in-licensed technology from the **University of Sherbrooke** to develop inhibitors of type II transmembrane serine proteases, a family of enzymes involved in the replication of influenza virus. Because the enzymes are host factors—not viral proteins—the inhibitors should target multiple subtypes of the influenza virus to treat infection and prevent the virus from developing resistance, Fehlmann said.

Haas, M.J. *SciBX* 7(15); doi:10.1038/scibx.2014.420

Published online April 17, 2014

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COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Epigenetix Inc., Miami, Fla.

IntelliSyn, Montreal, Quebec, Canada

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.

Neomed Institute, Montreal, Quebec, Canada

Pfizer Inc. (NYSE:PFE), New York, N.Y.

University of Sherbrooke, Sherbrooke, Quebec, Canada