Bromodomains on the brain

By Joanne Kotz, Senior Editor

A Dana-Farber Cancer Institute-led team has found that neuroblastomas with *MYCN* amplification, which occurs in about 25% of pediatric brain tumors, are sensitive to small molecule inhibitors of the BET family of bromodomains.¹ The findings provide a genetic marker for this emerging epigenetic target, and GlaxoSmithKline plc already is using *MYCN* amplification as one criterion to select patients for a Phase I trial of its BET bromodomain inhibitor in cancer.

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.

Two independent papers in *Nature* in 2010 first established 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.^{2,3}

One of those papers also provided the first suggestion that BET bromodomain inhibitors might have efficacy in cancer. JQ1 dramatically reduced tumors in a patient-derived xenograft

mouse model for nuclear protein in testis (C15orf55; NUT) midline carcinoma, a rare cancer in which a chromosomal translocation fuses the N-terminal bromodomains of *BRD4* to *NUT*.²

Subsequently, BET bromodomain inhibitors showed efficacy in animal models for leukemias and multiple myeloma (MM), at least in part by downregulating the expression of *c-Myc* (*MYC*).⁴⁻⁶

I-BET was identified by GSK. JQ1 was reported by a team from Dana-Farber and the Structural Genomics Consortium. James Bradner, investigator in the Department of Medical Oncology at Dana-Farber and a lead author on the study, founded Tensha Therapeutics Inc., which is developing drug-like analogs of JQ1 for cancer.

Outside of the rare *BRD4* fusion, the missing puzzle piece was genetic markers to guide patient selection. "To date, few genetic predictors of response exist for epigenomic drugs," including histone deacetylases (HDACs) and DNA methyltransferases, said Bradner.

As a result, the likelihood of identifying genetic markers that predicted response to epigenetic inhibitors, including JQ1 and I-BET, was not clear.

To look for potential markers, Bradner teamed up with Kimberly Stegmaier, assistant professor in pediatric oncology at Dana-Farber. The group screened more than 650 genetically characterized cancer cell lines and looked for ones in which JQ1 reduced viability with a submicromolar IC₅₀ value.

The cancer cell line panel was developed by researchers at the Massachusetts General Hospital and the Wellcome Trust Sanger Institute.⁷

In the screen, all four neuroblastoma cell lines with *MYCN* (*v-myc myelocytomatosis viral related oncogene neuroblastoma derived*; *NMYC*) amplification were sensitive to JQ1.

BET bromodomain inhibition also provided a therapeutic effect *in vivo*. In three distinct mouse models of *MYCN*-amplified neuroblastomas, JQ1 increased survival compared with vehicle.

Data were published in *Cancer Discovery*.

"While we expected to observe heterogeneity of response in broad cancer cell line screening, we did not expect to link discrete genetic lesions, here *MYCN* amplification, to response to an epigenomic transcriptional regulatory molecule," Bradner told SciBX.

Clinical jump

GSK already is putting the predictive capacity of *MYCN* amplification to the test.

"The results described in the paper provide convincing preclinical evidence that *MYCN* amplification is a marker of sensitivity to BET inhibitors in a broad panel of cancer cell lines," said Peter Tummino, head of biology in GSK's cancer epigenetics DPU. "The finding is strengthened by the mechanistic data demonstrating BET inhibitors induced decreased expression of *MYCN* and *MYCN* target genes. These results are consistent with GSK in-house results with GSK I-BET762 regarding both cell line sensitivity and expression changes."

GSK I-BET762 (GSK525762) is an analog of the I-BET molecule that GSK originally reported.

"There is a population of neuroblastomas with *MYCN* overexpression without gene amplification, and it will be worthwhile to determine if these tumors are highly sensitive to BET inhibition. *MYCN* amplification also occurs at a low frequency in lung cancer, both small cell and non-small cell, medulloblastoma and rhabdomyosarcoma," and these cancer subtypes may also respond to BET bromodomain inhibitors, Tummino added.

In March 2012, the pharma started a Phase I study of GSK I-BET762. The study is enrolling patients with NUT midline carcinoma, MM, small cell lung cancer (SCLC), colorectal cancer, neuroblastoma and *MYCN*-amplified solid tumors.

The Dana-Farber team also is moving toward the clinic and exploring additional markers and cancer indications that may respond to BET bromodomain inhibitors.

Stegmaier said the researchers plan to develop pharmacodynamic assays that could be used for clinical testing of BET bromodomain

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—Peter Tummino,
GlaxoSmithKline plc

inhibition in relapsed/refractory pediatric neuroblastoma. The researchers also are exploring the effects of JQ1 in *MYCN*-amplified medulloblastoma.

Although the study published in *Cancer Discovery* identified *MYCN* amplification in neuroblastoma as one potential genetic biomarker for response to BET bromodomain inhibitors, genetic markers were not identified for a number of cancers that are known to respond dramatically to BET bromodomain inhibition in mouse models, said Bradner.

As a result, it may be necessary to search for epigenetic—rather than genetic—biomarkers that predict JQ1 response. “Our sense is that new types of epigenomic biomarker measurements are needed to understand BET bromodomain inhibition,” Bradner told *SciBX*.

Tensha’s TEN-010 BET bromodomain inhibitor is in preclinical development. “TEN-010 appears to have the desired profile for a therapeutic agent in the management of neuroblastoma as well as a broad range of other indications,” said President and CEO Doug Onsi, although he declined to disclose details.

Dana-Farber has filed a patent application covering JQ1 and related analogs, and the IP is licensed to Tensha for clinical development.

Other BET bromodomain inhibitors in development include **Oncoethix S.A.**’s OTX015, which is in Phase I testing in patients with hematological malignancies. The molecule was in-licensed from **Mitsubishi Tanabe Pharma Corp.**

Constellation Pharmaceuticals Inc. has a preclinical BET bromodomain inhibitor program.

Kotz, J. *SciBX* 6(12); doi:10.1038/scibx.2013.277
Published online March 28, 2013

REFERENCES

1. Puissant, A. *et al. Cancer Discov.*; published online Feb. 21, 2013; doi:10.1158/2159-8290.CD-12-0418
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2. Filippakopoulos, P. *et al. Nature* **468**, 1067–1073 (2010)
3. Nicodeme, E. *et al. Nature* **468**, 1119–1123 (2010)
4. Zuber, J. *et al. Nature* **478**, 524–528 (2011)
5. Dawson, M.A. *et al. Nature* **478**, 529–533 (2011)
6. Delmore, J.E. *et al. Cell* **146**, 904–917 (2011)
7. Garnett, M.J. *et al. Nature* **483**, 570–575 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

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