SciBX
Science-Business eXchange

Tapping into TASP1

By Kai-Jye Lou, Staff Writer

Researchers from **Washington University in St. Louis** and colleagues from other U.S. institutions have identified a potent small molecule inhibitor of taspase-1.[1] The group now plans to use the small molecule as a scaffold to design drug-like inhibitors of the cancer-associated enzyme.

Taspase-1 (TASP1) is a protease linked to proliferation and apoptosis in multiple cancer types including glioblastoma and melanoma.[2,3]

Previously, James Hsieh and collaborators at **Stanford University** used the structural data of the TASP1 active site to help rationally design peptide-based inhibitors.[4] However, the resulting compounds lacked potency and were unlikely to be useful *in vivo* because TASP1 acts on intracellular targets.

At the time, Hsieh was an assistant professor of medicine at Washington University in St. Louis. He is now a laboratory head in the human oncology and pathogenesis program at **Memorial Sloan-Kettering Cancer Center**.

Hsieh and collaborators have now switched gears and used a cell-based, dual-fluorescence functional assay to screen a library of synthetic compounds from the **National Cancer Institute** (NCI) for molecules that target TASP1. The best hit was the arsonic acid compound NSC48300, which inhibited TASP1 with an IC_{50} of about 7.5 μM.

NSC48300 did not compete with any substrates of TASP1, indicating that the compound is allosterically inhibiting the enzyme's activity. Thus, the data suggest the possibility of developing TASP1 inhibitors that do not target the enzyme's active site.

In mouse models of TASP1-overexpressing human breast cancer and glioma, NSC48300 decreased tumor growth compared with vehicle.

Results were published in *Cancer Research*.

The team included researchers from the Washington University in St. Louis, Memorial Sloan-Kettering, the **Rosalind Franklin University of Medicine and Science**, the **Dana-Farber Cancer Institute** and NCI. Hsieh carried out the study while at Washington University in St. Louis.

Gearing up for drug discovery

Although NSC48300 is a clear step in the right direction, the compound itself is unlikely to advance into the clinic.

> **"This series of preclinical studies has demonstrated the feasibility of targeting taspase-1 to treat cancer."**
> ***—James Hsieh, Memorial Sloan-Kettering Cancer Center***

"This series of preclinical studies has demonstrated the feasibility of targeting taspase-1 to treat cancer," Hsieh told *SciBX*. "Although the short-term use of NSC48300 in mice is relatively safe, the fact that NSC48300 is an arsenic acid–containing compound is expected to have undesirable toxicities upon long-term use. It provides a scaffold and serves as a tool in the discovery of actual therapeutic compounds."

Enrique Zudaire Ubani noted that NSC48300 is a promiscuous compound that can affect a broad range of molecular targets. Zudaire Ubani is a staff scientist at the Angiogenesis Core Facility at NCI and a co-inventor on a patent application describing NSC48300 as an antiangiogenic small molecule.

Thus, Hsieh said the group's future work with TASP1 will focus on four areas.

"First, we are working with the Chemical Biology Consortium through NCI to develop more potent, more specific and less toxic compounds than NSC48300. Second, we would like to identify the most appropriate types of cancers to treat. Third, we would like to develop a probe that can be easily utilized to examine the *in vivo* activity of taspase-1 and the efficacy of taspase-1 inhibitors. And fourth, we need to understand whether taspase-1 inhibitors can synergize with other anticancer drugs," he said.

In addition, Hsieh noted that the group is working with collaborators at **Columbia University** to cocrystallize NSC48300 and TASP1 to better understand the compound's mechanism of action.

Roland Stauber, professor of molecular and cellular oncology at the **Johannes Gutenberg University Mainz**, said that "characterizing the active form of taspase-1 *in vivo* will be important for the rational design of strong taspase-1 inhibitors."

Stauber and colleagues developed the first cell-based assays to dissect the function of TASP1 and also used them to identify two small molecules that partially inhibited the enzyme's activity.[5,6]

He went on to point out that the existing crystal structure for TASP1 (ref. 7) might not accurately mirror the form of the protease that should be targeted for therapeutic applications. Indeed, he thinks the rational design of potent TASP1 inhibitors has been challenging in part because the structure of the active protease *in vivo* is still unclear.

Stauber also wanted to see additional studies directly linking TASP1 to various types of cancer, including breast and brain cancer, as well as additional *in vivo* data showing that NSC48300 is indeed a specific TASP1 inhibitor.

Washington University in St. Louis has filed a patent application covering TASP1 inhibitors and their uses. The work is available for licensing.

Lou, K.-J. *SciBX* 5(5); doi:10.1038/scibx.2012.116
Published online Feb. 2, 2012

REFERENCES

1. Chen, D.Y. *et al. Cancer Res.*; published online Dec. 13, 2011; doi:10.1158/0008-5472.CAN-11-2584

Contact: James J.-D. Hsieh, Memorial Sloan-Kettering Cancer Center, New York, N.Y.
e-mail: hsiehj@mskcc.org

2. Chen, D.Y. *et al. Cancer Res.* **70**, 5358–5367 (2010)
3. Takeda, S. *et al. Genes Dev.* **20**, 2397–2409 (2006)
4. Lee, J.T. *et al. Bioorg. Med. Chem. Lett.* **19**, 5086–5090 (2009)
5. Bier, C. *et al. J. Biol. Chem.* **286**, 3007–3017 (2010)
6. Knauer, S.K. *et al. PLoS ONE* **6**, e18253; published online May 25, 2011; doi:10.1371/journal.pone.0018253
7. Khan, J.A. *et al. Structure* **13**, 1443–1452 (2005)

COMPANIES AND INSTITUTIONS MENTIONED

Columbia University, New York, N.Y.
Dana-Farber Cancer Institute, Boston, Mass.
Johannes Gutenberg University Mainz, Mainz, Germany
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
National Cancer Institute, Frederick, Md.
Rosalind Franklin University of Medicine and Science, Chicago, Ill.
Stanford University, Palo Alto, Calif.
Washington University in St. Louis, St. Louis, Mo.