Stemming melanoma

By Joanne Kotz, Senior Editor

A **University of Cologne** team has reported that targeting CD20-positive melanoma stem cells, which make up as little as 2% of a tumor, can completely eradicate the disease in mice.¹ The results provide both strong evidence that melanoma stem cells drive the cancer and a rationale for moving anti-CD20 therapies from the blood cancer setting into melanoma.

Cancer stem cells can initiate tumor formation and are thought to play a role in cancer progression and relapse following therapy.² In 2005, a team led by **The Wistar Institute's** Meenhard Herlyn reported in *Cancer Research* the first evidence of stem cells in melanoma and suggested CD20 as a potential melanoma stem cell marker.³

Herlyn is a professor in the Molecular and Cellular Oncogenesis Program and director of the institute's Melanoma Research Center.

Since 2005, there have been additional reports identifying other small populations of cancer stem cells in melanoma,^{4,5} but there have also been reports suggesting that melanomas do not contain discrete cancer stem cells.^{6,7}

New findings from a Cologne team led by Hinrich Abken, professor of molecular medicine, tip the scales in favor of the CD20 stem cell hypothesis.

In biopsies from 4 out of 5 patients, about 2% of the total cells in their melanoma lesions coexpressed CD20 and a known melanoma cell marker. In the fifth patient, no CD20-expressing cells were detected.

Next, the researchers directly tested the therapeutic benefit of targeting CD20-expressing cells. To do so, the group engineered cytotoxic T cells expressing antibody domains directed against CD20. In mice with tumors derived from the 4 melanoma patients who had CD20 expression, the cytotoxic T cells eradicated disease in 13 of 17 animals. The 13 mice showed no evidence of relapse for up to 36 weeks.

In mice with tumors derived from the one melanoma patient with no detectable CD20 expression, the cytotoxic T cells caused little to no tumor regression.

Results were published in the *Proceedings of the National Academy of Sciences*.

"The major clinical implication is that, at least in melanoma, future therapeutic strategies do not need to eliminate all cancer cells but just a small, specific cell population in order to eradicate an established cancer lesion," said Abken. "However, there is the caveat that we only found CD20 expression in tumors from 4 out of 5 melanoma patients, which

means that there may be another, so far not identified, cell population that needs to be eliminated in about 20% of melanomas."

"This paper is very important because it is one of the first that I've seen to show that by selectively targeting cancer stem cells in a primary tumor you can cure an animal" and in particular in melanoma, which is the cancer in which the presence of stem cells has been the most controversial, said Max Wicha.

Wicha is director of the **University of Michigan Comprehensive Cancer Center** and a cofounder of cancer stem cell company **OncoMed Pharmaceuticals Inc.** He told *SciBX* that unpublished work from his lab also supports the potential for eradicating tumors by targeting cancer stem cells. "We have seen that microRNAs that induce breast

cancer stem cells to differentiate can also cure mice," he said. These observations from Wicha's lab support the cancer stem cell hypothesis that stem cell-like cancer cells, not differentiated cancer cells, are responsible for driving tumor maintenance and progression.²

Sean Morrison, director of the **University of Michigan Center for Stem Cell Biology**, was not convinced by the paper. "It is hard for us to understand the results because we have not been able to detect any CD20 expression in melanoma cells from patients," he told *SciBX*.

Detecting CD20 in melanoma has been challenging, agreed Herlyn, because CD20 levels are very low and can vary substantially between

patients. "This is the first paper since our 2005 *Cancer Research* paper saying that there is CD20 in melanoma. Even more importantly, this is the first paper showing that you can target it."

Therapy options

The Cologne team now is studying the safety of the engineered cytotoxic T cells in mice and is looking at the prevalence of melanomas containing a CD20-expressing subset of cells in a larger cohort of patients. Abken hopes to have a T cell-based therapy ready for the clinic in about two years.

Herlyn's group is taking an alternative path in melanoma—testing anti-CD20 antibodies. These include a pair of mAbs marketed for blood cancers: Rituxan rituximab from **Biogen Idec Inc.** and the **Genentech Inc.** unit of **Roche** and Arzerra ofatumumab from **Genmab A/S** and **GlaxoSmithKline plc.**

This year, Herlyn and Stephan Wagner, professor of dermatology at the **Medical University of Vienna**, plan to start a Phase II trial of ofatumumab in metastatic melanoma.

GSK confirmed it is providing the antibody for the trial but is not providing additional funding at this time. The company declined to comment on the results in the *PNAS* paper.

In 2007, Wagner ran a Phase I trial of Rituxan as an adjuvant therapy in nine metastatic melanoma patients, but the study's small size precluded any efficacy data. Herlyn told *SciBX* that preclinical results from

"The major clinical implication is that, at least in melanoma, future therapeutic strategies do not need to eliminate all cancer cells but just a small, specific cell population in order to eradicate an established cancer lesion."

—Hinrich Abken,
University of Cologne

his lab suggest that, similarly to CD20-directed T cells, CD20-targeting mAbs may provide therapeutic benefit in melanoma.

Because some melanomas lack CD20-expressing cells, the Cologne team is also working to identify stem cell markers in CD20-negative melanomas, said Abken.

Abken said the results are unpatented.

Kotz, J. *SciBX* 4(9); doi:10.1038/scibx.2011.244

Published online March 3, 2011

REFERENCES

- Schmidt, P. *et al. Proc. Natl. Acad. Sci. USA*; published online Jan. 31, 2011; doi:10.1073/pnas.1009069108
Contact: Hinrich Abken, University of Cologne, Koln, Germany
e-mail: hinrich.abken@uk-koeln.de
- Zhou, B.-B.S. *et al. Nat. Rev. Drug Discov.* 8, 806–823 (2009)
- Fang, D. *et al. Cancer Res.* 65, 9328–9337 (2005)
- Schatton, T. *et al. Nature* 451, 345–349 (2008)
- Boiko, A.D. *et al. Nature* 466, 133–137 (2010)
- Quintana, E. *et al. Nature* 456, 593–598 (2008)
- Quintana, E. *et al. Cancer Cell* 18, 510–523 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Genentech Inc., South San Francisco, Calif.
Genmab A/S (CSE:GEN), Copenhagen, Denmark
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Medical University of Vienna, Vienna, Austria
OncoMed Pharmaceuticals Inc., Redwood City, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of Cologne, Cologne, Germany
University of Michigan Center for Stem Cell Biology, Ann Arbor, Mich.
University of Michigan Comprehensive Cancer Center, Ann Arbor, Mich.
The Wistar Institute, Philadelphia, Pa.