Neo enough in glioma?

By Tracey Baas, Senior Editor

A mutation in isocitrate dehydrogenase 1 commonly found in gliomas alters the enzyme's conformation and triggers pathways that lead to the disease. A Heidelberg group has developed a peptide vaccine that distinguishes mutant from normal enzyme and reduces tumor size in mice.¹ The team is hoping the vaccine could join the race for a glioma immunotherapy but needs to show that it can generate enough neo-antigen-specific T cells and antibodies to spark an effective immune response in patients.

The group is preparing an IND and planning to start recruiting patients with glioma in 2Q15 for Phase I testing to assess the peptide's safety and immunogenicity.

The R132H mutation in isocitrate dehydrogenase 1 (IDH1) occurs in more than 70% of diffuse grade II and grade III gliomas and creates a gain-of-function change that leads to formation of an oncogenic metabolite.

The mutant enzyme has been targeted by **Agios Pharmaceuticals Inc.**, which has the small molecule IDH1 inhibitor AG-120 in Phase I testing for hematological malignancies and solid tumors.

The changed conformation of IDH1 creates a mutant epitope that can be distinguished from wild-type epitope by antibodies. Thus Michael Platten and colleagues thought they might exploit the epitope to stimulate an antitumor response by creating a vaccine based on the mutant peptide.

Platten is a professor of neurology and vice chair of neuro-oncology at **Heidelberg University Hospital** and head of experimental neuroimmunology at the **German Cancer Research Center**.

Discriminating peptide

To investigate the immunogenic potential of mutant IDH1, the Heidelberg team created peptide libraries that included the region containing the R132H mutation and the corresponding wild-type residue of IDH1.

The peptides interacted with major histocompatibility complex class II (MHCII) molecules and produced a CD4⁺ T cell response in MHC-humanized mice that could discriminate between the mutated and wild-type peptides. The engineered mice lack murine Mhc and express human MHC molecules, thereby providing a system to mimic vaccine peptide presentation in humans.

In the mice, a peptide containing amino acids 123–142 of IDH1 (R132) elicited mutation-specific anti-IDH1 antibodies.

To test the peptide vaccine in a mouse model of cancer, the team used MHC-humanized mice bearing subcutaneous mouse sarcomas expressing mutant IDH1. Vaccination with the 123–142-amino-acid peptide caused a mutation-specific CD4⁺ T cell and antibody response that suppressed tumor growth by about 60%.

Finally, to find clinical evidence of mutant IDH1 as a target, the team screened patients with gliomas for endogenous T cell responses against mutant IDH1. It found mutation-specific CD4⁺ T cell responses in 4 out of 25 patients with gliomas containing mutant IDH1. By contrast, no such responses were found in 29 patients with glioma who had wild-type IDH1.

Although only a low percentage of patients produced mutation-specific CD4⁺ T cells, the authors concluded that the results suggest a patient's immune system can generate a mutation-specific T cell response and can thus recognize and respond to mutant IDH1.

The team included researchers from the Heidelberg University Hospital and its National Center for Tumor Diseases and from **BioNTech AG** subsidiary Ribological GmbH, which develops RNA-based drugs for targeted cancer immunotherapy.

Results were published in *Nature*.

Immune response jump-start

Pramod Srivastava told *SciBX* that although patients had a low endogenous immune response rate to mutant IDH1, the key question is whether a mutant IDH1-based vaccine could jump-start the immune system to augment that response. According to Srivastava, the next step for the researchers should be to test the vaccine in patients—although he noted several possible pitfalls.

"It is almost impossible to predict how the vaccine will translate to the clinic," said Srivastava. "Similar or better immunological activity has been shown with other tumor-associated antigens, such as MAGE [melanoma-associated antigen] and NY-ESO-1 [cancer/testis antigen 1B (CTAG1B)]. And in the case of MAGE, the vaccine did not fare well in advanced clinical studies."

However, he added, "the fact that IDH1 is a mutated antigen is an excellent departure." For example, he said, "the heat shock protein-peptide vaccine, which is also premised on mutational antigens, has shown excellent immunological activity and strong indications of clinical activity in Phase I and Phase II trials for glioma."

Srivastava is a professor of immunology and medicine and director of the Carole

and Ray Neag Comprehensive Cancer Center at the **University of Connecticut Health Center**. He is also the cofounder of cancer and infectious disease company **Agenus Inc.**

Agenus' Oncophage vaccine—first developed by Srivastava—contains heat shock 90 kDa protein β 1 (Hsp90B1; GP96; GRP94) and associated peptides purified from autologous tumor cells. Oncophage

"The fact that IDH1 is a mutated antigen is an excellent departure. The heat shock protein-peptide vaccine, which is also premised on mutational antigens, has shown excellent immunological activity and strong indications of clinical activity in Phase I and Phase II trials for glioma."

**—Pramod Srivastava,
University of Connecticut Health Center**

is marketed for renal cancer and is in Phase II testing for brain cancer and melanoma.

By contrast, Pierre-Yves Dietrich suggested that the researchers share more preclinical details before moving to clinical studies. “I’d like to see studies where they test the mutant IDH1 peptide in an animal model that better reflects the human glioma condition rather than in a subcutaneous sarcoma overexpressing high levels of mutated IDH1,” he said. “Would the T cell responses and antibodies work as well for intracranial tumors?”

“Before embarking on large-scale clinical trials, it would be also useful to explore the expression of mutant IDH1 expression—at the peptide level—by grade II and grade III gliomas. This might be done with peptide elution or functional data,” Dietrich told *SciBX*.

Dietrich is a professor of oncology, head of the Service of Oncology, director of the Centre of Oncology and head of the Laboratory of Tumor Immunology at the **University Hospital of Geneva** and has collaborations with **immatics biotechnologies GmbH**.

The company has IMA950 in Phase I trials for brain cancer. The vaccine contains 11 different human leukocyte antigen (HLA)-restricted tumor-associated peptides.

Hideho Okada, a professor of neurological surgery at the **University of California, San Francisco**, thought the low frequency of MHCII expression on glioma cells might present a hurdle for an MHCII-dependent vaccine.

“MHC class II molecules are not commonly expressed on the surface of glioma cells, so cross-presentation of the mutant IDH1 peptide would be necessary for immunotherapy targeting of this novel epitope to be effective,” said Okada.

He added that a lack of MHCII expression on tumor cells or infiltrating immune cells might help explain the relatively low rates of spontaneous, mutation-specific CD4⁺ T cells in patients.

“The team might need to incorporate some strategy to make sure that MHC class II-expressing antigen-presenting cells migrate to

the tumor in order to ensure cross-presentation of the mutant IDH1 epitope and vaccine efficacy. They might be able to do this by using therapies that recruit macrophages expressing high levels of MHC class II molecules—ideally M1 macrophages, not M2 macrophages.”

Okada developed the synthetic peptide-based vaccine SL-701, licensed by **Stemline Therapeutics Inc.** in 2011, that is now in Phase II testing for brain cancer.

There are over 12 vaccines for brain cancer in the clinic from Phase I to Phase III trials. The most advanced is **Celldex Therapeutics Inc.**’s rindopepimut, which targets epidermal growth factor variant III (EGFRvIII), a protein not found in normal brain tissue.

The findings have been patented by the German Cancer Research Center. The licensing status was not disclosed.

Baas, T. *SciBX* 7(29); doi:10.1038/scibx.2014.851

Published online July 31, 2014

REFERENCES

- Schumacher, T. *et al. Nature*; published online June 25, 2014; doi:10.1038/nature13387
Contact: Michael Platten, German Cancer Research Center, Heidelberg, Germany
 e-mail: m.platten@dkfz.de

COMPANIES AND INSTITUTIONS MENTIONED

Agenus Inc. (NASDAQ:AGEN), Lexington, Mass.
Agios Pharmaceuticals Inc. (NASDAQ:AGIO), Cambridge, Mass.
BioNTech AG, Mainz, Germany
Celldex Therapeutics Inc. (NASDAQ:CLDX), Needham, Mass.
German Cancer Research Center, Heidelberg, Germany
Heidelberg University Hospital, Heidelberg, Germany
immatics biotechnologies GmbH, Tuebingen, Germany
Stemline Therapeutics Inc. (NASDAQ:STML), New York, N.Y.
University Hospital of Geneva, Geneva, Switzerland
University of California, San Francisco, Calif.
University of Connecticut Health Center, Farmington, Conn.