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Cancer

AACR-NCI-EORTC 2023: From glycobiology to novel immunotherapeutic approaches

By Coia Dulsat, Staff Writer

Increasing knowledge of the cancer glycome and the need for new options to overcome resistance to immune checkpoint inhibitors are leading to an expansion of glycoimmunology.

Stanford University professor Carolyn Bertozzi, who won the 2022 Nobel Prize in Chemistry together with Morten Meldal and Barry Sharpless, demonstrated that cell-surface glycans may be tagged to become targetable glyco-immune checkpoints.

Antibody-lectin chimeras

In a session focused on new glycoimmunology options in cancer treatment, Jessica Stark, a postdoctoral scholar in Bertozzi's lab, presented work on antibody-lectin chimeras (AbLecs) for glycol-immune checkpoint blockade.

Siglecs are sialic-acid binding proteins found at the surface of immune system cells. Ligand strategies tested so far to engage with siglecs have had limitations such as limited binding to glycans in the case of antibodies, or low affinity in the case of decoy receptors. Thus these approaches fall short to date.

Stark, Bertozzi and their colleagues have been working to address these issues by creating a chimera.

"The idea here was to create a bispecific "half antibody" and "half decoy receptor," Stark told the audience.

This was done to overcome the problems and at the same time profit from the advantages of both types of molecules.

AbLecs are antibody-like molecules comprising a tumor-targeting arm together with a lectin decoy receptor domain that blocks the ability to engage lectin by binding tumor glycans.

"We used an established technology called knobs-into-holes to facilitate self-assembly," she explained.

The proposed T7 and T9 AbLecs combined a Fab domain from a trastuzumab antibody with the extracellular domains of siglec-7 or -9 fused to an Fc domain.

When tested for their binding ability to HER2+ cell lines, the decoy receptors siglec-7 and siglec-9 bind only at low levels. However, AbLecs displayed a similar binding to trastuzumab.

"With our molecules, we were able to successfully block siglec receptor engagement," Stark said.

AbLecs were able to elicit strong tumor reduction over trastuzumab through intense macrophage phagocytosis and NK cell cytotoxicity.

"Excitingly, we have preliminary data showing that our in vitro data translates into in vivo efficacy," she said.

In this sense, after testing both T9 AbLec and trastuzumab in a humanized model of metastatic HER2+ cancer expressing high levels of ligand siglec-7/9, animals receiving the AbLec displayed a higher reduction in tumor burden compared to the ones receiving the monoclonal antibody.

"We saw that this enhancement of antitumor response was siglec-dependent," she added.

The team benchmarked the efficacy of AbLecs compared to combination immunotherapy and found that, unexpectedly, AbLecs outperformed combination.

"It raises the possibility that perhaps proximity matters."

Stark attributed this enhanced activity to the ability to block siglec engagement at the same immune synapse formed by the tumor-targeting antibody suggesting that "this allows to block the right siglecs at the right time."

Other features were the capacity to synergize with CD47 blockade, and importantly, the potential of AbLecs to be redesigned to target additional tumor antigens.

In summary, glycans profoundly influence immunology and it is important to have tools for systematically interrogating their functions and for targeting them therapeutically.

"These are the gaps that our work with AbLecs addresses, to create tools to understand the role of glycans in the immune

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system and to develop new engineered immunotherapy modalities," Stark concluded.

Human sialidase engineering

In a second talk, Li Peng, chief scientific officer at Palleon Pharmacetucials Inc., reported on Palleon's work in the field of glyco-immunotherapy.

Based on Bertozzi and her colleagues' work showing the desialylation of cancer cells enhanced NK cell-killing antitumor activity, Palleon generated the Enzyme-Antibody Glyco-Ligand Editing (EAGLE) therapeutic platform to engineer human sialidase.

"The wild-type human sialidases are not developable," Peng said.

However, through engineering work, they were able to achieve a good developability profile.

The applicability of EAGLE-related desialylation was based on their enhancement of NK, macrophages, and T-cell antitumor immune responses.

With engineered bi-sialidase, E-602, they confirmed that desialylation of T cells enhanced T-cell priming and activation.

"That was very encouraging to show the direct impact of sialoglycans in T cells," she told the audience.

In vivo, E-602 showed 40% tumor growth inhibition in the B16F10 tumor model whereas anti-PD-1 MAb monotherapy achieved only a 20% reduction at the same dose.

After extensive testing in several animal models, they found that "EAGLE responders had higher degrees of desialylation of circulating immune cells than non-responders."

E-602 has moved to clinical testing with clinical safety and proof-of-mechanism established in phase I and currently under phase II trials.

"We are very encouraged by the safety data and proof-of-mechanism data of bi-sialidase. We are developing multiple targeted bi-sialidase in the pipeline where we can target B cells, T cells or stromal cells," Peng concluded (Stark, J.C. 35th AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 11-15, Boston) 2023, Abst; Peng, L. 35th AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 11-15, Boston) 2023, Abst).