Novel Precision Immuno-Therapy of Cancer

(FCCC Ref. 485-JK & 544-JK)

Background

Antibody-derived therapeutics have proved to be very effective in several disease conditions where conventional therapies have failed and several therapeutic antibodies have gained clinical use for major diseases including cancers, chronic inflammatory diseases, and autoimmune diseases. However, therapeutic antibodies are typically administered in the blood circulation at high doses, and their intended targets can be present outside the disease site. For this reason, systemic antibody recognition of the target can produce undesirable adverse effects. As many therapeutic antibodies currently show dose-limiting on-target toxicity, improved spatial and temporal control of antibody activity is needed to reduce unwanted side effects.

Summary of the Invention

The use of chemical biology to modulate protein activity is a powerful strategy that can be used to engineer small molecule-dependent protein activity into specific proteins of interest. By tying protein activity to the presence of a small molecule, one can "switch on" the protein using that small molecule. By engineering a new allosteric site into therapeutic antibodies such as checkpoint inhibitors, the antibody can be produced in an "off state" by default, such that administering this inactive form of the antibody does not engage antigen. Upon introduction of the activating small molecule into the intended (tumor) site, the antibody is activated and thus elicits toxicity only in close proximity of the tumor. Thus, applying this scheme to therapeutic antibodies in cancer can reduce adverse side effects caused by antibody activity outside the tumor microenvironment.

Scientists at Fox Chase Cancer Center have successfully designed and introduced mutations that inactivate an antibody, with a partner small molecule that "rescues" the antibody activity. The inactive form of the antibody and the small molecule are envisioned administered in parallel and delivered locally to the tumor environment. By further using small molecules that are responsive to the tumor microenvironment, this strategy enables precise targeting of antibody activity to the tumor, not elsewhere in the body.

References:

(1) *Kaiser CE, et al., "Modulating antibody structure and function through directed mutations and chemical rescue." (2018) ACS Synth Biol, 7:1152-62. https://doi.org/10.1021/acssynbio.8b00124*

(2) *Khowsathit J, et al.; "Computational design of an allosteric antibody switch by deletion and rescue of a complex structural constellation." (2020) ACS Cent Sci; 6:390-403. https://doi.org/10.1021/acscentsci.9b01065*

Advantages

- Novel technology to precisely modulate activity of therapeutic antibodies using a small molecule.
- Targeted activation of antibody at tumor site solves "on-target off-tumor" toxicity.
- Approach has been validated *in vitro* using antibodies relevant to immuno-oncology applications.

IP Status

International patent application has been published WO 2020/223273 A2 . Patent applications pending in US, Canada and Europe.

For Partnering/Licensing information, please contact:

Inna Khartchenko, MS, MBA (Director, Technology Transfer and New Ventures)
Fox Chase Cancer Center; Inna.Khartchenko@fccc.edu