PepTalk
The Protein Science Week

JANUARY 18-22
SAN DIEGO 2016

Cambridge Healthtech Institute's Mary Ruberry recently interviewed Dr. Dirk Spitzer, Instructor of Surgery at Washington University School of Medicine about his upcoming presentation "Targeting MUC16-Positive Malignancies with the Novel TRAIL-Based Cancer Therapeutic Meso64-TR3" in San Diego.

Q. How has your group approached the production of TRAIL in a novel way?
It is well established that recombinant soluble TRAIL requires homotrimer formation in order to become and remain biologically active. Currently, the cytokine is produced in bacteria but attempts to generate bioactive soluble TRAIL from mammalian cells fails due to particular structural features unique to this TNF superfamily member. We addressed this shortcoming by engineering a fusion protein in which the three extracellular TRAIL protomers are arranged in a head-to-tail configuration, referred to as the TR3 drug platform. This particular design offers a number of previously unmet opportunities with regard to protein stability, functionality and targeting capability.

Q. How can this new platform be used as a cancer therapeutic?
One of the most exciting features of the TR3 drug platform is the ability for further downstream modifications under stoichiometrically fully controlled conditions. These modifications can be incorporated in modular fashion to both the amino- and the carboxyl-terminus of the trimer which allows for great flexibility and further expands the applicability and versatility of this new production platform. For example, we have generated fully functional membrane-anchored TR3 variants, which follow the same stoichiometries as their fluid phase counterparts. These reagents can be used for various purposes such as cell therapies but also to interrogate fundamental aspects of native TRAIL biology.

Q. Is there something unique about the way this cancer therapeutic targets tumors?
TR3 is essentially phenotypically identical to rTRAIL. In this regard, it is important to point out that both unmodified biologics do not have the capacity per se to actively discriminate between transformed cancer cells and healthy host tissues, which are also known to express various TRAIL receptors and thus act as a "sink" for TRAIL-based therapeutics. In order to endow the cytokine with tumor selectivity and to minimize potential off-target toxicities, targeting moieties need to be incorporated into the therapeutics. We have accomplished this by inserting single chain antibodies (scFv) into the TR3 drug platform, targeted to the tumor biomarker mesothelin. More recently, we took advantage of the native, high affinity ligand/receptor interaction between mesothelin and MUC16, aka CA125, an established biomarker in ovarian cancer, by incorporating a mesothelin-derived peptide into the TR3 drug platform. Our second-generation variant, Meso64-TR3, is a fully human cancer biologic with high affinity to the biomarker MUC16. It is extremely stable, binds within minutes to the cancer cells, remains tightly tethered and induces far stronger death receptor signaling events than non-targeted TR3 alone in vitro and, most importantly, in vivo.

Q. What does the latest data show?
We have just recently completed a preclinical study, in which Meso64-TR3 outperformed TR3 in a model of MUC16-positive epithelial ovarian cancer in a single-agent, short duration trial. We are very excited about these results as it clearly shows that our drugs not only have increased affinity to the tumor cells in a petri dish but, more importantly, maintain their ability to enter tumor tissues and trigger death receptor activation on the cancer cells in their native environment, i.e. in the presence of the stromal tumor compartment.

Q. Is there something you'd like to add?
It is my firm believe that the TR3 platform has an excellent potential to become the new gold standard in the field of TRAIL-based cancer therapeutics. In support of this view, we have generated experimental evidence that biomarker-targeted TR3 variants perform synergistically with sensitizers of the extrinsic death pathway, further highlighting the great versatility of this new drug platform. Finally, the fact that TR3 can be combined with virtually any scFv targeting moiety (a continuously expanding platform technology in itself), leaves us with nearly endless possibilities to design new and more enhanced TR3 biologics for the treatment of human malignancies, alone and with pathway sensitization.

Dirk Spitzer, Ph.D., Instructor, Surgery, Washington University School of Medicine

The focus of my professional career always centered on the translational aspects of the biomedical sciences. I obtained my Ph.D. developing a packaging cell line to produce complement-resistant murine retroviruses suitable for in vivo gene therapy. Later on, I designed targeted complement therapeutics in order to protect regulator deficient RBCs from autologous complement attack. My recent endeavors revolve around the novel TRAIL-based drug platform TR3, which I recently developed and patented. Currently, TR3 variants are being developed and assessed that are selectively delivered to the surface markers mesothelin and MUC16 (CA125), established biomarkers in pancreatic and ovarian cancers. As such, I have nearly 20 years of experience in the development of protein therapeutics (biologics). More recently, I added cancer-targeted small molecules to my portfolio, which are designed to synergize with targeted TR3 drugs, further enhancing efficacy and reducing potential off-site toxicities of combination cancer therapies.and book chapters related to the BBB.

To learn more about Dr. Spitzer's presentation and the 12th Annual Recombinat Protein Therapeutics conference visit
CHI-PepTalk.com/recombinant-protein-therapeutics