PEOPLE


Institute of Cancer Research, London

Johann S. de Bono, MD, PhD, of the Institute of Cancer Research (University of London) in the UK, was named Regius Professor of Cancer Research. The professorship was one of 12 bestowed by Queen Elizabeth to mark her 90th birthday. Each was awarded to a different university or college in the UK to recognize exceptionally high-quality research in a variety of scientific disciplines, with the monarch approving individual appointments. The prestigious Regius Professorships are rare; only 14 others have been granted since the reign of Queen Victoria.

de Bono is a professor of experimental cancer medicine at the Institute for Cancer Research and heads its Drug Development Unit. He specializes in developing molecularly targeted therapies for patients with prostate cancer.

Better Nanoparticle Targeting with P-Selectin

A study in mice indicates that P-selectin, an adhesion molecule involved in wound healing and metastasis, can serve as a target for the delivery of drug-filled nanoparticles to tumors (Sci Transl Med 2016;8:345ra87). The researchers used this approach—even in tumors that don't usually express P-selectin—by inducing it with ionizing radiation.

P-selectin is normally expressed on the endothelium (blood vessel walls) when triggered by inflammation: It "resembles Velcro," enabling immune cells such as leukocytes, which constantly patrol the body, to locate and stick to wounded, inflamed tissues, explains senior author Daniel Heller, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY. Inflammatory tumor types, including lung and breast cancers, often exploit P-selectin on the surrounding vasculature to recruit various cells and nutrients, designing the microenvironment to their advantage. Additionally, metastasis can occur when circulating tumor cells encounter and adhere to P-selectin on the endothelium of distant organs.

Heller's team used fucoidan, a seaweed-derived polysaccharide, for their nanoparticles—both as a scaffold to encapsulate drugs and as a targeting agent, because fucoidan has a natural affinity for P-selectin.

The researchers compared paclitaxel-loaded nanoparticles made with either fucoidan (FiPAX) or dextran (DexPAX), which does not bind to P-selectin. In a mouse model of small cell lung cancer, FiPAX accumulation in tumor tissue, measured by fluorescence, was up to four times higher than DexPAX. Mice given FiPAX also had greater, more sustained tumor regression.

Heller's group then tested FiPAX in two groups of mice with Lewis lung carcinoma, which lacks the inflammatory environment necessary for P-selectin expression. Prior to FiPAX treatment, one group of mice received ionizing radiation; the other did not. FiPAX accumulation was nearly four times higher in irradiated mice, which experienced complete and durable tumor regression. This suggests that radiation is an external trigger of P-selectin, Heller says, "making our nanotherapeutic strategy potentially applicable to almost any tumor type."

The team also loaded the experimental MEK inhibitor binimetinib (MEK162; Array BioPharma) into fucoidan nanoparticles (FiMEK), which were compared to the free drug in a mouse model of colorectal cancer. One FiMEK injection had equal efficacy to a week of oral binimetinib, Heller notes. Whereas free binimetinib temporarily suppressed MEK activity in both tumor and skin, FiMEK induced sustained inhibition, and only in the tumor. These findings are relevant to two concerns with MEK inhibitors, Heller says: the need for chronic administration and severe rash, a dose-limiting toxicity.

To date, most nanotherapeutic strategies have focused on targeting tumor cells directly, but "this hasn't worked well *in vivo*, because the nanoparticles have to first penetrate the surrounding endothelial barrier," says Chad Mirkin, PhD, director of the International Institute for Nanotechnology at Northwestern University in Evanston, IL. "P-selectin is an ingenious choice. By targeting the tumor vasculature instead, Heller's group achieved high nanoparticle accumulation within tumors."

"This study highlights the importance of understanding the tumor microenvironment when designing cancer nanotherapeutics," Mirkin says. "I believe we'll see more researchers start thinking beyond tumor cells in considering nanoparticle targets, which should produce better delivery strategies." *–Alissa Poh* ■

Regulating CAR T Cells: A Remote Control Approach

The field of chimeric antigen receptor (CAR) T-cell therapy continues to evolve rapidly, with researchers devising increasingly ingenious ways to improve the ability of these engineered T cells to seek out and eradicate tumors while minimizing side effects.

At Purdue University in West Lafayette, IN, chemist Philip Low, PhD, and doctoral student Yong-Gu Lee have synthesized small organic molecules called adaptors that direct CAR T cells to tumor cells. These molecules are outfitted with the dye FITC on one end, and a ligand with high affinity for a specific tumor antigen on the other. The individual adaptors are then administered alongside T cells engineered to bind FITC.

"Without an adaptor, our CAR T cells can't 'see' the targeted antigen," Low explains. "The adaptor serves as a bridge that forces engagement and subsequent tumor lysis." Because tumor recognition occurs through the adaptor, "we can use the same FITC-binding CAR T cells to eliminate even highly heterogeneous tumors, when they're administered with the right cocktail of different adaptors," he adds. "There's no need to engineer a new T cell to discern each unique tumor antigen. Synthesizing small molecules is much easier and less time-consuming."

These adaptors are also short-lived, Low says, surviving for no more than 60 minutes *in vivo*, which means treatment can be quickly terminated if life-threatening immune side effects—chiefly cytokine release syndrome—arise. "Once CAR T cells are infused and go to work, they're stimulated to