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REPRINT FROM AUGUST 1, 2019

EMERGING COMPANY PROFILE

NeoPhore: Driving neoantigen production via DNA mismatch repair

BY MARY ROMEO, ASSISTANT EDITOR

NeoPhore is turning cold tumors hot by inhibiting DNA mismatch repair to produce more of the neoantigens that trigger immune attack.

Immuno-oncology companies are developing therapies based on neoantigens -- tumor-specific peptides that the immune system regards as non-self -- including T cell therapies and cancer vaccines that either target or deliver the newly formed antigens.

NeoPhore Ltd. wants to take a different tack by creating the neoantigens in the patient to make the tumors more visible to the immune system. The company is developing small molecules to inhibit DNA mismatch repair (MMR) and create a pool of neoantigens to turn "dark" tumors "light" that can be treated with immunotherapies.

"Evidence suggests MMR inhibition will re-program a wholly new, diverse collection of neoantigens and related immune signaling inside patient cancers," CEO Jeff Roix told BioCentury.

NeoPhore spun out of U.K. cancer company PhoreMost Ltd. in 2017, in collaboration with co-founders Alberto Bardelli and Giovanni Germano at University of Turin, to focus on inhibiting mismatch repair with small molecule inhibitors.

Inhibiting genes in the DNA mismatch repair pathway creates a microsatellite instability state. Studies have shown microsatellite instability creates indels and frameshift mutations; additional research has suggested these produce immunogenic neoantigens, and at least two studies have connected frameshift mutations with checkpoint inhibitor responses in patients (see "Alt-neoantigens").

Bardelli and Germano published a *Nature* study in 2017 that reported inactivation of DNA mismatch repair by knocking out MLH1 in cancer cells increases the tumor mutational load and triggers neoantigen production in cancer cells, which accumulated over time. The researchers found expanded T cell receptor (TCR) repertoires and increased levels of cytotoxic T cells in mouse cancer models.

NEOPHORE LTD.
Cambridge, U.K.

Technology: Small molecules targeting DNA mismatch repair to stimulate neoantigen production and immune signaling for combination immunotherapy approaches

Disease focus: Cancer

Clinical status: Discovery

Founded: 2017 by Alberto Bardelli and Giovanni Germano

University collaborators: University of Turin

Corporate partners: Undisclosed

Number of employees: 5

Funds raised: £3 million ($4 million)

Investors: Sixth Element Capital LLC

CEO: Jeff Roix

Patents: None issued

Bardelli's team demonstrated in preclinical models that mismatch repair inhibition creates neoantigen stimulation, Roix said. "Our founders showed that inhibiting these factors brightens tumors so they can be seen by the immune system."

Another study from NeoPhore advisers Bert Vogelstein and Luis Diaz at Johns Hopkins University, published in *Science* in 2017, linked high rates of checkpoint inhibitor responses in patients with mismatch repair deficient (dMMR) cancers to rapid expansion of T cells specific for neoantigens.

The approval of PD-1 inhibitors Keytruda pembrolizumab from Merck & Co. Inc. and later Opdivo nivolumab from Bristol-Myers Squibb Co. validated the company's strategy, Roix said, that tumors with microsatellite instability are prime targets for immunotherapies. Keytruda is approved for advanced microsatellite instability-high (MSI-H) or dMMR solid tumors regardless of the cancer's tissue of origin; Opdivo is approved for advanced MSI-H or dMMR metastatic colorectal cancer.

Roix declined to disclose the company's targets but said its "inhibitors are directed against validated classically understood genes in the mismatch repair pathway."

The lead and backup programs are in discovery, and NeoPhore expects to select a candidate in 2020.

NeoPhore is aiming to target cancers that are neoantigen poor, and are therefore not good candidates for immunotherapies. While Roix declined to disclose specific indications, he did say pancreatic and prostate cancer and gliomas are "generally thought to be neoantigen poor."

The strategy could also treat MSI medium or high cancers to enhance immunotherapies, he added. "There may be some cancers that we can push even further."

NeoPhore wants to pair its small molecules with PD-1 checkpoint inhibitors, in particular, and has been seeking partnering opportunities.

"There could be other immune cell effector pathways that could complement" NeoPhore's strategy, he added.

Multiple companies are pursuing neoantigen-based strategies to treat cancer, but most are developing biologics like vaccines or proteins. One company, Nouscom AG, has identified hundreds of neoantigens that frequently occur in patients with MSI-H cancer and plans to deliver them in a single vaccine.

Roix is not aware of any other companies specifically targeting DNA mismatch repair pathways to create neoantigens. "We think we're the first and only mismatch repair company" in the neoantigen space, he said.

Grey Wolf Therapeutics is also developing small molecules to increase tumor visibility to the immune system, but is targeting ERAP1 and ERAP2 -- proteins in the antigen presentation pathway.

Roix estimated the company's £3 million ($4 million) initial funding from Sixth Element Capital will take it into 2020, during which time NeoPhore will consider pursuing a financing or partnering.

COMPANIES AND INSTITUTIONS MENTIONED

Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Grey Wolf Therapeutics, Oxford, U.K.
Johns Hopkins University, Baltimore, Md.
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Nouscom AG, Basel, Switzerland
PhoreMost Ltd., Cambridge, U.K.
University of Turin, Turin, Italy

TARGETS

ERAP1 (ARTS1; ERAAP) - Endoplasmic reticulum aminopeptidase 1
ERAP2 - Endoplasmic reticulum aminopeptidase 2
MLH1 - DNA mismatch repair protein Mlh1
PD-1 (PDCD1; CD279) - Programmed cell death 1

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