Phosplatin Therapeutics Inc.
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PHOSPLATIN THERAPEUTICS

Harnessing immunogenic cell death for cancer

By focusing on immunogenic cell death (ICD) as a complementary mechanism to existing cancer immunotherapy strategies, Phosplatin Therapeutics is building a global network of partnerships to help advance the application of its lead ICD inducer, PT-112, against a variety of cancers.

Harnessing immunogenic cell death (ICD)—an immunostimulatory form of cancer cell death in the tumor microenvironment—to help activate a patient's immunity and trigger a tumor-specific immune response, represents a novel therapeutic modality with great potential for expanding the scope of cancer immunotherapies. Phosplatin Therapeutics Inc., a privately held, New York–based clinical stage pharmaceutical company, is developing *phosphaplatins*, a family of first-in-class pyrophosphate conjugates that stand out as superior small molecule inducers of ICD.

The company's lead compound, PT-112, has completed three phase 1 clinical studies. The first, which was as a monotherapy trial enrolling patients with various tumor types, demonstrated responses to PT-112 in non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), metastatic castration-resistant prostate cancer (mCRPC), and thymoma. Another monotherapy phase 1 was completed in relapsed/refractory multiple myeloma (RRMM). The third was a phase 1b combination study of PT-112 with avelumab, a PD-L1 immune checkpoint inhibitor, in solid tumors, with an ongoing phase 2a expansion cohort in NSCLC. Phosplatin is currently enrolling a phase 2 clinical trial of PT-112 as a monotherapy in mCRPC patients, planning the next stage of development of PT-112 as a monotherapy in RRMM, and has entered a cooperative research and development agreement for a phase 2 study in thymoma/thymic carcinoma sponsored by the National Cancer Institute. PT-112 holds US Food and Drug Administration (FDA) Orphan Drug Designation for thymoma/thymic carcinoma and RRMM.

Backed by a strong intellectual property position that includes an exclusive global license to the family of compounds, Phosplatin is advancing its R&D portfolio through collaborations with leading research institutions and biopharma companies. These include Weill Cornell Medicine, the Fred Hutchinson Cancer Research Center, the Rutgers Cancer Institute of New Jersey, the Institute for the Research of Cancer, Montpellier, France (IRCM), the University of Lausanne, Switzerland and the University of Zaragoza in Spain. On the clinical side, Phosplatin works with leading research centers, such as Memorial Sloan Kettering Cancer Center, the Mayo Clinic, the Dana Farber Cancer Institute, the University of Colorado Cancer Center, and the University of Texas MD Anderson Cancer Center. The company has an ongoing clinical trial collaboration with Pfizer and Merck KgaA, Darmstadt, Germany (EMD Serono) and a sub-licensing agreement for Greater China with Shanghai-based SciClone Pharmaceuticals.

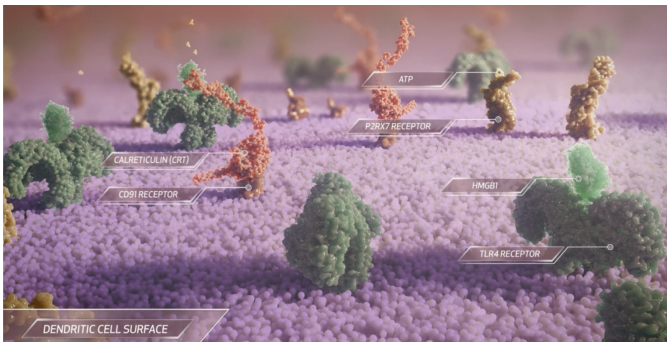

Fig. 1 | DAMP release by PT-112. ICD causes the release of damaged-associated molecular patterns (DAMPs), from dying cancer cells. These DAMPs include ATP secretion, calreticulin translocation, and release of HMGB1, each of which have binding sites on dendritic cells, which trigger the adaptive immune response. PT-112 has been shown to cause DAMP release in vitro, and to cause favorable increases in immune cell populations in tumor tissue in vivo[1]. ATP, adenosine triphosphate. Image copyright: Phosplatin Therapeutics Inc.

With an increased need for alternative treatments for rare and refractory types of cancer, and the advent of novel immune checkpoint targets and antibody-based treatments, many of which may not feature single-agent clinical activity, Phosplatin seeks to build upon its ICD-based therapeutic platform and its early success with PT-112 through additional research and development collaborations in oncology.

Harnessing ICD for immuno-oncology

To date most immunotherapies have focused on enhancing the T cell response by either targeting inhibitory pathways with immune checkpoint inhibitors, or by targeting activating pathways with chimeric antigen receptor T cells or bispecific antibodies. As the adaptive immune response is essential in fighting cancer, identifying further cancer immunomodulatory mechanisms that could be used for therapeutic purposes is a priority.

ICD is a particular type of cancer cell death that triggers an adaptive immune response and trains naïve T cells to infiltrate and kill tumors. When cancer cells succumb to ICD, the dying cells release immunostimulatory molecules called damage-associated molecular patterns (DAMPs). These DAMPs bind to specific receptors and stimulate antigen-presenting cells such as dendritic cells, leading to T cell priming in lymph nodes, tumor infiltration by primed T cells and tumor suppression as a consequence of adaptive immunity.

PT-112—the first pyrophosphate-conjugate in oncology therapeutics

PT-112 is the lead member of a family of stable pyrophosphate/platinum conjugates that promote ICD, exhibiting selective cytotoxicity towards cancer cells, and have different drug resistance profiles from traditional chemotherapies. Upon being absorbed by the tumor cell, PT-112 triggers cell death, causing the build-up of reactive oxygen species in the mitochondria, the release of DAMPs, and the downstream promotion of a tumor-specific immune response with the potential for ongoing tumor suppression (Fig. 1).

In addition, owing to its pyrophosphate moiety, PT-112 exhibits osteotropism, an affinity to bone, leading to enhanced accumulation in mineralized bone. This characteristic of PT-112 offers potential to treat cancers that originate in or metastasize to the bone, including metastases common in prostate, lung and breast cancers, as well as some hematological malignancies such as multiple myeloma.

"PT-112, either as an immunogenic monotherapy or in combination, is designed to offer a safe and effective therapy to cancer patients with limited treatment options," said Robert Fallon, Phosplatin's President and CEO. "We are excited to continue exploring the potential of PT-112 across a wide spectrum of cancers through clinical collaborations with partners worldwide."

1. Yamazaki, T. et al. *OncoImmunology* **9**, 1721810 (2020). https://doi.org/10.1080/2162402X.2020.1721810

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