# Harnessing iNKTs to Boost Cancer Immunotherapies

## The problem

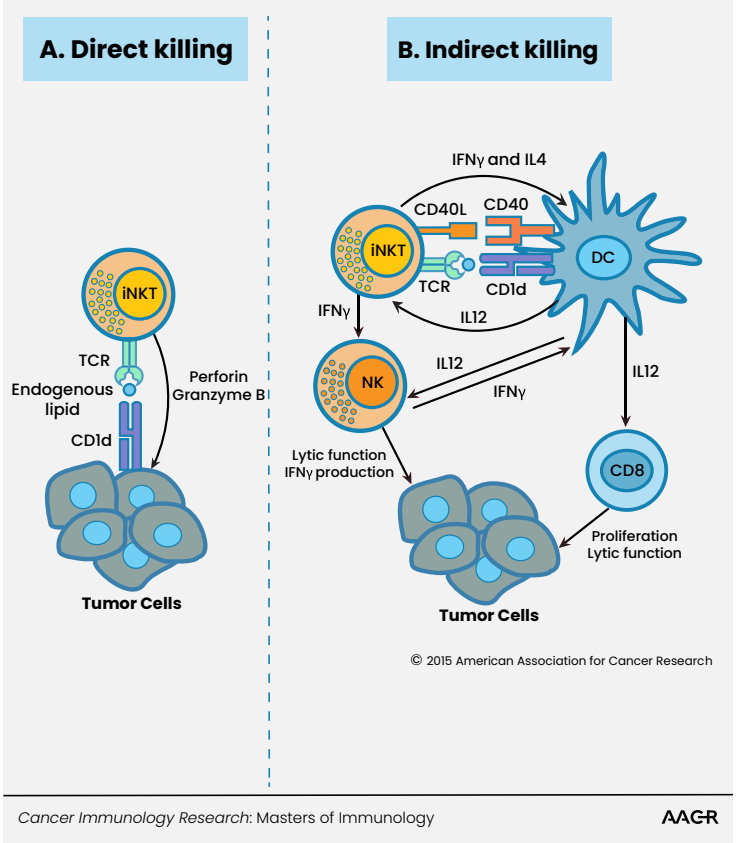
Despite advances in the immuno-oncology field, 70-80% of patients do not respond or have a limited response to existing therapies, such as checkpoint inhibitors (CPIs).

Many cancers can avoid immune detection altogether by never expressing antigens on the surface of their cells that can be recognized as being sufficiently "foreign" by the immune system.

The majority of approaches being considered for improving tumor immune responses do not address the greater need to help initiate an immune response or initiate a de novo immune response in tumors that have now become refractory to CPI therapy.

## iNKTs, part of the solution

- Invariant natural killer T cells (iNKTs) are a distinct class of innate-like immune cells that recognize lipid and glycolipid antigens (CD1d) on the surface of various immune cells (e.g., dendritic cells, B lymphocytes and macrophages) and on some cancer cells.
- Lipid antigen presentation by CD1d is analogous to the proteins required for an adaptive T cell-mediated immune response (MHC). Upon binding to the lipid-CD1d complex, iNKT cells initiate the production of cytokines that activate a broad innate and adaptive immune response.
- iNKT deficient animals are more susceptible to developing cancer.
- High numbers of iNKT cells in humans have been associated with an improved outcome in cancer patients (survival, local disease control and reduced rate of metastasis).

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# Our iNKT agonists

With over 20 years of industry experience and more than 25 years of research coming out of Oxford University and Radboud University around its PORT-2 and PORT-3 technologies, Portage Biotech is uniquely positioned to take its iNKT agonists to the clinic to help patients in need.

## PORT-2

PORT-2, or IMM60, is an iNKT agonist packaged in a liposome, with improved CD1d binding properties and in vivo pharmacology that results in a more pronounced and prolonged activation of iNKT cells. PORT-2 optimally activates iNKT cells to engage multiple components of the immune response including the innate and adaptive systems and inhibits negative signals in the tumor microenvironment. As a result of this broad immune activation, cancer cells increase the expression of lipid cell surface antigens and immunotherapy targets such as PD-L1. This increased surface expression enables the body to better recognize and fight the tumor. Animal studies support monotherapy activity of PORT-2 in PD-1 antibody-resistant animals, and the ability to re-sensitize animals to checkpoint inhibitors.

## PORT-3

PORT-3 is a nanoparticle co-formulation of the iNKT agonist IMM60 and NY-ESO-1 immunogenic peptides developed for the treatment of NY-ESO-1 positive solid tumors. Data has also shown that co-formulation of an iNKT agonist with tumor-specific antigens results in an up to five-fold improvement in efficacy compared to administering the two treatments separately. Published data with PORT-3 constructs show superior monotherapy activity compared to PD-1 in melanoma and head and neck cancer models, with added benefits when the combination of PORT-3 is combined with a checkpoint antibody. The company intends to create other constructs with different antigens if PORT-3 shows proof of concept in the ongoing PRECIOUS trial.

# iNKT agonists in combination with other therapies

**1** Engage the T cells and proliferate an inflammatory response

**2** Direct the immune cells to the cancer

**3** Address the cancer cells' ability to hide from the immune system

- Portage Biotech's invariant natural killer T-cell (iNKT) agonists, PORT-2 and PORT-3, lead to activation of the innate and adaptive immune system including NK cells, dendritic cells, T cells, and B cells. This completes step 1.
- The dendritic cell activation and cytokines drive an antigen-specific CD8 T cell response and direct the immune system on what to attack, which completes step 2.
- iNKT treatment reduces suppressive cells such as myeloid-derived suppressor cells and tumor-associated macrophages. Additionally, both PORT-2 and PORT-3 may be used alone or in combination with other therapies, like checkpoint inhibitors, to help immune cells better recognize cancer cells, even after they have developed evasion mechanisms. This completes step 3.

Having all three of these components should make treatment more efficient and more successful.

# Recent iNKT activity spotlights

The field of immuno-oncology using iNKTs is heating up. Here's a snapshot of the activity in the space:

- Portage Biotech completed a $23 million raise with institutional investors interested in the potential of iNKTs.
- Dr. Anil Bhushan, a professor at USCF, recently published a paper and started a company based on iNKTs and their role in cell aging.
- Appia Bio recently raised a $52 million Series A financing to develop their CAR-engineered invariant natural killer T (CAR-iNKT) cells and is led by Nobel Laureate David Baltimore. Additionally, Appia Bio recently announced a collaboration with Kite Pharma to develop CAR-iNKT cells for allogeneic cell therapy, further validating the versatility of iNKTs in the cancer space.
- Athenex Therapeutics acquired KUUR Therapeutics, a company developing iNKTs to boost CAR-T therapy to target hematological and solid cancers, for $185 million.

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