Harnessing iNKTs to Boost Cancer Immunotherapies

About iNKTs

- Invariant natural killer T-cells (iNKTs) are a distinct class of innate-like immune cells that recognize lipid and glycolipid antigens presented by (CD1d), a molecule on the surface of various immune cells (e.g., dendritic cells, B lymphocytes and macrophages) as well as some cancer cells.
- Upon binding to the lipid-CD1d complex, iNKT cells initiate the production of cytokines that activate a broad innate and adaptive immune response.
- iNKT knock out animals develop cancer while normal mice can fend off a cancer challenge.
- 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).

iNKT Agonist Mechanism of Action: IMM60

- Portage's iNKT agonist (PORT-2, or IMM60) stimulates both the adaptive and innate immune system and corrects the tumor microenvironment (TME) for an anti-cancer response:

INNATE IMMUNE SYSTEM

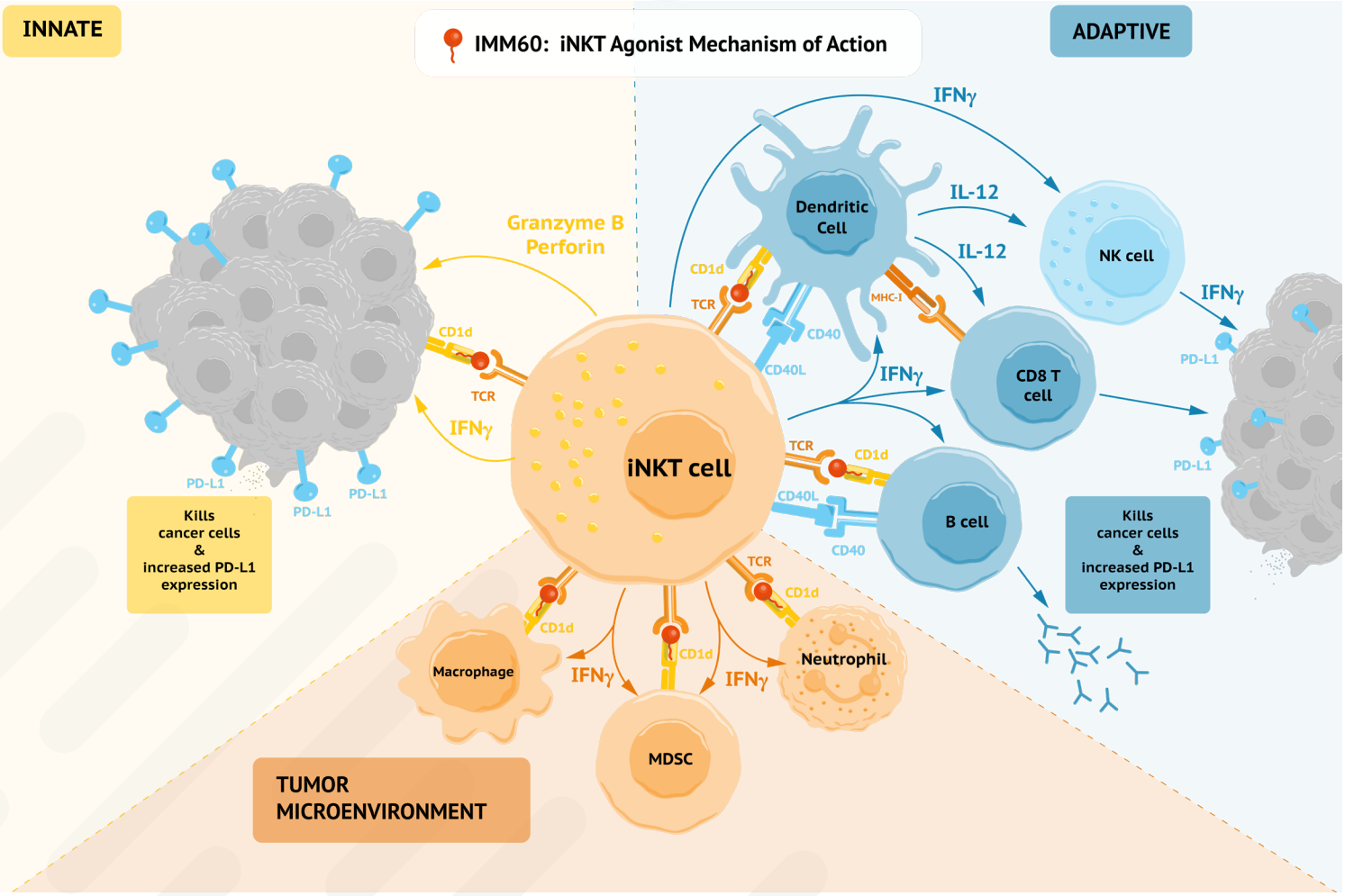
- Direct killing
- Increase in PDL-1 expression
- Synergize with PD-1 antibodies
- Reverse PD-1 antibody resistance

ADAPTIVE IMMUNE SYSTEM

- Activate dendritic cells
- Transactivate Natural Killer (NK) cells
- Increase antigen specific CD8 T cells
- B Cell activation, humoral response
- Immunologic memory

TUMOR MICROENVIRONMENT

- Repolarize macrophage
- Decrease Myeloid-derived Suppressor Cells (MDSCs)
- Decrease suppressive neutrophils



Our iNKT agonist programs

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 further advance its iNKT agonists through 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 immunotherapy targets such as PD-L1. Animal studies support monotherapy activity of PORT-2 in PD-1 antibody-resistant animals, and the ability to re-sensitize animals to checkpoint inhibitors. Preliminary Phase 1 data from the ongoing IMP-MEL trial suggests PORT-2 is well tolerated when administered as a monotherapy, with no severe adverse events or dose limiting toxicities and only low grade (1/2) toxicity.

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 coformulation 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 with one product 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 $26.5 million raise with institutional investors interested in the potential of iNKTs.
- Appia Bio 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 announced a collaboration with Kite Pharma, a Gilead company, and it was for up to $875M in upfront and milestones to develop CAR-iNKT cells for allogeneic cell therapy, further validating the versatility of iNKTs in the cancer space.
- Athenex/KUUR Therapeutics' autologous CAR-NKT cell therapy for relapsed/refractory high risk neuroblastoma demonstrated evidence of therapeutic efficacy with 25% Overall Response Rate (ORR) at the 2022 American Society of Gene & Cell Therapy annual meeting.
- Athenex/KUUR Therapeutics shared interim Phase 1 data evaluating allogeneic CAR-NKT cell therapy in relapsed or refractory lymphoma and leukemia that demonstrated encouraging response rates at low doses including a 57% ORR and 29% Complete Response Rate at the 2021 Tandem Meetings of the American Society of Transplantation and Cellular Therapy.

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