Treating Cancer by Targeted Activation of the Immune System

Philip Gotwals

Executive Director, Exploratory Immuno-Oncology
Novartis Institutes for Biomedical Research

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Therapeutic Approaches to Cancer Treatment

Ancient Times
- Surgery

Early 20\textsuperscript{th} Century
- Radiation

Mid 20\textsuperscript{th} Century
- Chemotherapy

Early 21\textsuperscript{st} Century
- Targeted Therapeutics;
- Immune-based therapeutics
Cancer is a genetic disease
*Provides rationale for targeted therapies*

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<td>BCR-ABL translocation</td>
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<td>Melanoma</td>
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Cancer

- Provides rationale for targeted therapies

Melanoma

- BRAF mutation

BCR-ABL translocation

- Imatinib
Another approach is to engage the immune system

Cancer is an immunological disease

- William B. Coley – Late 19th century surgeon credited with recognizing the possibility that bacterial infection helped patients fight cancer.
  - Attenuated BCG (Bacillus Calmette-Guerin) bacteria is used in treating local bladder cancer.

- Melanoma “super-responders”
  - 3-5% of early stage melanoma patients have intra-tumoral lymphocyte infiltrates that are associated with negligible risk of disease recurrence following surgery

- Therapeutic Antibodies
  - The use of rituximab for lymphoma and trastuzumab for breast cancer are selected examples.

- Graft versus Tumor response
  - Donor T cells from an allogeneic hematopoietic stem cell transplant can eliminate the host’s tumor.
Therapeutic Approaches to cancer immunotherapy

Novartis Immuno-Oncology Portfolio

Immune Priming

- IL-15
- STING
- TIM-3

T-cell Modulation

- PD-1
- PD-L1
- TGF-β
- LAG-3
- TIM-3
- GITR
- CAR-T

Tumor Environment

- PD-1
- LAG-3
- IL-15
- PD-L1
- TGF-β
- CSF-1
- A2A Adenosine Receptor
- TIM-3
- GITR

Talimogene laherparepvec (T-VEC)

Approved by the FDA in October 2015

- Talimogene laherparepvec is an oncolytic, engineered herpesvirus with modifications that increase its therapeutic value
  - Removal of neurovirulence factor prevents neurotoxicity
  - Addition of GM-CSF promotes dendritic function
  - Deletion of ICP47 promotes oncolysis and viral replication

Andtbacka et al., JCO 2015
Local delivery may lead to systemic therapy

The abscopal effect

- Inflammation (innate immunity)
- Abscopal response (adaptive immunity)

Johnson et al, 2015, Drug Evaluation
STING (STimulator of INterferon Genes) agonists activate dendritic cells

- STING is a central sensor of cytosolic double-stranded nucleic acids from infectious pathogens, and is essential for efficient induction of a type I interferon immune response\(^1,2\)
- STING senses and binds to bacterial signaling molecules known as cyclic dinucleotides (CDNs),\(^3\) which leads to the expression of T-cell recruitment factors, including pro-inflammatory cytokines and interferon\(^1\)
- CDNs may be useful as vaccine adjuvants, given the strong immune response triggered by foreign double-stranded DNA\(^1,4\)
- In mouse tumor models, intratumoral injections of synthetic CDNs resulted in a substantial regression of injected and distant tumors, and provided immunologic memory\(^5\)

DC, dendritic cell; TME, tumor microenvironment.

ADU-S100: a potent cyclic dinucleotide STING agonist

Abscopal Effect in Dual Flank Model

ADU-S100, licensed from Aduro Biotech, Inc, compliments Novartis internal efforts.

Treated and contralateral CT26 tumor growth

ADU-S100, Innate response

Adaptive response

Graph showing Tumor Volume (mm³) over Days Post Tumor Challenge:
- **HBSS**
- **HBSS contralateral**
- **NVP-MIW815 – (25 ug)**
- **MIW815 contralateral**
Adenosine receptors (AR) are a class of G-protein coupled receptors found in all tissues, and upregulated in various tumor cells\(^1,2\)

- Subtypes include A\(_1\), A\(_{2A}\), A\(_{2B}\) and A\(_3\)

The A\(_{2A}\) AR negatively regulates immune responses, including those against tumors, upon binding to extracellular adenosine\(^1,2\)

- The tumor microenvironment is rich in adenosine, which leads to the suppression of T- and NK-cell function by the A\(_{2A}\) AR

Blockade of A\(_{2A}\) receptors may counteract the immunosuppressive effects of tumor-derived adenosine and enhance immune responses\(^2\)

Additive and/or synergistic effects may be possible by combining A\(_{2A}\) AR blockade with other cancer therapy\(^2\)

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Overview of CTL019 Therapy in the Clinic

1. **Leukapheresis:** patient’s T cells are collected\(^1-3\)
2. **T cells are genetically transduced** *ex vivo* with a lentiviral vector encoding the anti-CD19 chimeric antigen receptor\(^1,3\)
3. **CTL019 cells undergo** *ex vivo* **expansion** on magnetic antibody-coated beads\(^1-3\)
4. **Chemotherapy:** the patient may receive a preparative lymphodepleting regimen before T cell infusion\(^1-3\)
5. **CTL019 cells are re-infused** into the patient\(^1-3\)

- The University of Pennsylvania (Penn) and Novartis have entered into an exclusive global collaboration to research, develop, and commercialize CTL019 cells for the treatment of cancer
- To date, Penn has generated data with CTL019 in patients with relapsed/refractory (r/r) B-cell malignancies

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A wealth of important targets for T cell modulation

In addition to antigen specific recognition signals, T cells receive positive and negative second signals from APCs.

Costimulatory signals regulate the responsiveness of many immune cells including naïve, effector, memory & regulatory T cells and B cells.

Co-inhibitory signals in natural settings promote tolerance but can cause T cell exhaustion in pathologies having a chronic presence of an antigen (viral exhaustion) and in cancer.
Intensified anti-tumor activity with combined CTLA-4 and PD-1 blockade

Hodi et al, NEJM 2015
PD1/PDL1 blockade is active in many tumor types

Select examples in addition to melanoma

**PD-1 in Advanced Renal Carcinoma**
McDermott et al, 2015

**PD-1 in non small cell lung carcinoma**
Brahmer et al, 2015

**PD-1 in Refractory Hodgkins**
Armond et al, 2014

**PD-L1 in bladder carcinoma**
Powles et al, 2014
Response Rates range from 10-40%

Room for improvement

- Patient selection
  - PDL1 expression
  - Mutational burden
  - Signature of immune infiltration

- Combinations
  - Chemotherapy and small molecule targeted agents
  - Novel checkpoints and additional biologics

- Dose and Schedule

- Additional indications
  - For example, NPC and squamous cell carcinoma of the esophagus

- PD1/PDL1 differentiation over time
  - Will anti-PD1 and anti-PDL1 segment into overlapping but distinguishable patient populations?
Combination of targeted agents in metastatic melanoma

The combination of dabrafenib and trametinib improves overall survival of patients with BRAF Val600 mutation – positive melanoma.

Long et al., The Lancet, 2015
Targeted and immuno-modulatory therapeutics are being combined in melanoma

- Phase 1 study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib and/or MEK (trametinib) inhibitors in advanced melanoma. Ribas et al 2015 ASCO Annual Meeting (3003)
LAG-3
*Lymphocyte activation gene*-*3*

- LAG-3 is expressed across a number of activated T-cells and dendritic cells, and is frequently co-expressed with PD-1 on anergic or exhausted T-cells\(^1\)-\(^3\)
- Known ligands include MHC Class II, L-SECtin, and galectin-3\(^2,3\)
- LAG-3 negatively regulates T-cell signaling and function in effector T-cells by binding MHC class II molecules, and supports the suppressive phenotype of regulatory T-cells\(^1\)-\(^3\)
- Blockade restores activity of Teffs, diminishes suppressor activity of natural Tregs and Type 1 regulatory T-cells, and enhances anti-PD-1 antitumor activity\(^3\)
- Combined inhibition of LAG-3 and PD-1 may be more efficacious in inducing tumor regression\(^3\)


MHC, major histocompatibility complex.

PD-1/LAG3 expression is highly correlated across indications
PD-1 and LAG-3 are not functionally redundant

Woo et al Cancer Res 2012 72:917

- PD-1⁻/⁻LAG-3⁻/⁻ double deficient mice develop rapid (within 10 weeks), lethal systemic autoimmunity

- Combining anti-LAG3 and anti-PD1 increase efficacy in an MC38 colon carcinoma model
**A LAG-3 Receptor-targeting Monoclonal Antibody**

- Humanized IgG4 monoclonal antibody that binds LAG-3 with low nanomolar affinity, inhibiting LAG-3 interaction with MHC class II molecules\(^1\)

- The clinical program for LAG525 will explore whether LAG-3 blockade restores activity of antitumor effector cells and enhances anti-PD-1 antitumor activity, as a monotherapy, and in combination with anti-PD-1 therapy\(^1,2\)

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**Trial ID**

1. Novartis, Data on File, 2015;

**Treatment/Setting**

- Advanced/metastatic solid tumors, including NSCLC, melanoma, renal cancer, gastric cancer, esophageal adenocarcinoma, nasopharyngeal cancer, and CRC

**Phase**

1/2

**N**

\(\approx240\)

**Primary Endpoint**

- Part 1: DLTs
- Part 2: ORR
TIM-3
T-cell immunoglobulin mucin

Blockade of TIM-3
- Restores activity of exhausted T cells
- Suppresses tumor growth
- Enhances antitumor activity of PD-1 inhibition

- TIM-3 is expressed on effector and regulatory T cells, NK cells, and multiple subsets of myeloid and dendritic cells
- Tumor overexpression of TIM-3 is associated with poor patient outcomes
- TIM-3 blockade restores or enhances effector activity of T cells and NK cells, diminishes suppressor activity of regulatory T cells, and enhances stimulatory activity of myeloid cells and dendritic cells
- Anti-TIM-3 monoclonal antibodies promoted rejection of solid tumors in murine models
- Additionally, targeting both TIM-3 and PD-1 pathways was more effective in suppressing tumor growth than targeting each pathway alone

Role of TIM-3 in Cancer

**Potential consequences of global TIM-3 blockade on immune activity**

**TIM-3 blockade may impact multiple TIM-3–expressing cell populations, leading to enhanced immune response**

Constitutive TIM-3 expression associated with less immunogenic antigen-presenting cells

TIM-3+ regulatory T cells (Tregs) have a more immunosuppressive phenotype and are associated with disease severity in non-small cell lung cancer

PD-1+TIM-3+ T cells display an exhausted phenotype; proliferation/cytokines increased by co-blockade in virally-exhausted and cancer patient peripheral blood mononuclear cells

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DC, dendritic cell; MΦ, macrophage; CTL, cytotoxic T cell; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell.


Towards complete, durable remission for cancer patients

- Surgery, radiation and chemotherapy remain the foundation of cancer treatment.

- Targeted therapies often demonstrate profound, but not durable, clinical responses in genetically selected patients.

- Immune-modulators such as “checkpoint” inhibitors have demonstrated durable responses, but not in all patients.

- Cell therapy has shown profound, durable responses in select patient populations, but the current technology may not be generalizable to all tumor types.

- Combining therapeutic approaches along with our expanding immuno-modulatory therapeutic approaches aimed at establishing a memory response to tumors focus our research efforts toward “curing” cancer.