Immune System Basics

Engineering the Immune System to Fight Cancer

Jonathan Schneck, M.D., Ph.D.

Professor of Pathology and Oncology
Disclosures

- NexImmune- Scientific Founder and SAB Chair
- DimerX (MHC-Ig) product line sold by BD
This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark.
Cancer-Immunity Cycle

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation
4. Trafficking of T cells to tumors
5. Infiltration of T cells into tumors
6. Recognition of cancer cells by T cells
7. Killing of cancer cells
Cancer-Immunity Cycle: Ability to Disrupt at Multiple Critical Points in the Cycle

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors
   - Blood vessel
   - Lymph node

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

aAPC Immunoswitch

E+E Adoptive Immunotherapy

Oncology Meets Immunology: The Cancer-Immunity Cycle
http://dx.doi.org/10.1016/j.immuni.2013.07.012
Cancer-Immunity Cycle: Ability to Disrupt at Multiple Critical Points in the Cycle

Immunoswitch

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Cancer-Immunity Cycle

1. Priming and activation
2. Cancer antigen presentation
3. Flow to lymph node
4. Trafficking of T cells to tumors
5. Infiltration of T cells into tumors
6. Recognition of cancer cells by T cells
7. Killing of cancer cells
Cancer-Immunity Cycle

1. Priming and activation
2. Cancer antigen presentation
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Oncology Meets Immunology: The Cancer-Immunity Cycle

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Antigen Presenting Cells Orchestrate Immune Responses

Cytokine/Chemokine Receptor

Signal 1 (MHC/Antigen)

Signal 2 (Inhibitory)

Signal 2 (Co-Stimulatory)

APC

Cytotoxic T Cells

Helper T Cell (Th1, Th2)

NKT

Suppressor T Cell

Anergic T Cell

Treg

Exhausted T Cell

Tumor Cells

Necrotic Cells

Fungi

Bacteria

Viruses

Foreign Proteins

Infected Cells

Metabolic Stresses and Hypoxia
artificial Antigen Presenting Cell (aAPC) for Treating Cancer

A Particle-Based artificial ANTIGEN PRESENTING CELL, aAPC
Trends Mol Med. 2005 Sep;11(9):412-20 Oelke M1, Krueger C, Giuntoli RL 2nd, Schneck JP.
A Particle-Based artificial ANTIGEN PRESENTING CELL, aAPC


Trends Mol Med. 2005 Sep;11(9):412-20 Oelke M1, Krueger C, Giuntoli RL 2nd, Schneck JP.
Immunoengineering:
It’s all about the bass, about the bass, about the bass no treble
Microparticles vs. Nanoparticles

Immunoengineering: It’s all about the bass, about the bass, about the bass no treble
Nano-aAPC – Overcoming Activation Threshold and Expanding Targeted T cell Populations via Naturally Occurring Mechanisms

1000’s of aAPC interactions per T cell

Multiple aAPCs simultaneously delivering specific, polarized signals to activate and expand antigen-specific T cells
Direct Administration
Simpler, less costly
Questions relate to dosing and trafficking

Nanoscale aAPC for Adoptive Immunotherapy:
1) Rapid Robust expansion
2) Targeting neo-epitopes
3) Diverse T cell response
E+E Enables Rapid Antigen-Specific in vitro T cell Expansion

ACS Nano. 2015 Jul 28;9(7):6861-71
Enrichment and Expansion with Nanoscale aAPC;
Perica K, Bieler JG, Schütz C, Varela JC, Douglass J,
Skora A, Chiu YL, Oelke M, Kinzler K1, Zhou S, Vogelstein B, Schneck JP.
E+E MART1-T cells: Stimulate Robust T Cell Expansion

Day 0
- Total number of cells: $5 \times 10^4$
- Viability: 93%
- CD8+: 99%
- Number MART1+ CD8+ Cells: 46

Day 7
- Total number of cells: $7.9 \times 10^4$
- Viability: 72%
- CD8+: 91%
- Number MART1+ CD8+ Cells: 10.5k

Day 10
- Total number of cells: $1.97 \times 10^5$
- Viability: 88%
- CD8+: 99%
- Number MART1+ CD8+ Cells: 106k

Day 14
- Total number of cells: $1.3 \times 10^6$
- Viability: 80%
- CD8+: 98%
- Number MART1+ CD8+ Cells: 750k

Fold expansion:
- Day 0 to Day 7: 120-210x
- Day 7 to Day 10: 1000-2100x
- Day 10 to Day 14: 6400-14,000x

Varela and Schneck et al., UNPUBLISHED CONFIDENTIAL DATA
Adoptive Transfer of E+E Stimulated T cells Treats Established B16 Melanoma

ACS Nano. 2015 Jul 28;9(7):6861-71
Perica K, Bieler JG, Schütz C, Varela JC, Douglass J, Skora A, Chiu YL, Oelke M, Kinzler K1, Zhou S, Vogelstein B, Schneck JP.
Targeting Neoepitopes

- Mutations in tumor provide patient-specific targets
  - Single Amino Acid Substitutions (AAS) lead to novel MHC-I epitopes
  - ‘Non-Self’ → High Avidity TCR’s
  - Personalized Targeted Cellular Therapy
E+E Validation of Predicted Neo-Epitope Responses from Naïve CD8+ Repertoire

**Predicted Affinity nM**
- KbLAY (mut17) Tnpo3: 69
- KbVDW (mut30) Kif18b: 9066
- KbVSA (mut50) Sema3b: 1487
- KbVTF (mut46) Actn4: 210

**RMAS MHC Stability %**
- KbLAY (mut17) Tnpo3: 24
- KbVDW (mut30) Kif18b: 1.9
- KbVSA (mut50) Sema3b: 3.4
- KbVTF (mut46) Actn4: 8.2

ACS Nano. 2015 Jul 28;9(7):6861-71
Enrichment and Expansion with Nanoscale aAPC; Perica K, Bieler JG, Schütz C, Varela JC, Douglass J, Skora A, Chiu YL, Oelke M, Kinzler K1, Zhou S, Vogelstein B, Schneck JP.
Advancing Neo-Antigen approach to Patient-Specific Therapy
Generation of functionally active human neo-antigen-specific CD-8+ T cells from a healthy donor

POC “Batching” 3 neo-epitopes simultaneously using AIM E+E

E+E was performed simultaneously in multiplex mode with 3 neo-epitopes identified from MCF-7 breast cancer cells. Intracellular staining analysis was performed using stimulation with single peptides (3, 9 or 15). M Oelke Neximmune confidential information
Shape in aAPC Design

APC have large surface area and planar surface area of contact for T cells

aAPC are synthesized from spherical particles, which minimize surface and contact area

Thoulouze et al. (2006).

Football-shaped aAPC are better than spherical aAPC

Ellipsoidal aAPC delay tumour growth
aAPC Platform – Differentiating Attributes

1. Engage directly with targeted T cell receptors – do not require processing and presentation by host DCs and cannot be down-regulated
   - Activate and expand both foreign and self tumor-specific T cells

2. E+E allows for batching: Target multiple tumor-specific antigens simultaneously minimizing potential for tumor escape

3. Target naïve and memory T cell repertoire
   - Results in robust, persistent anti-tumor activity and immunologic memory
   - Minimizes potential for on-target, off-tissue auto-immunity

4. Mechanistically, complements other IO approaches, CPI, that break tolerance

5. Shape: A design parameter that recapitulates biology and impacts on efficacy

6. Validates ‘predicted’ neo-antigens and deliver immunogenic neo-antigens in clinical practice setting

7. Manufacturing flexibility and precision of ‘off-the-shelf’ components provide rapid path to new product design and production
Life After aAPC?

What if we could harness a tumor’s own signal 1 antigens to allow for a polyclonal response and no required *a priori* knowledge of these peptides?

*Immunoswitch* particles target conserved molecules on tumor cells and T cells to turn an immunoinhibitory environment into an immunostimulatory one.

-Implications are:

1) *independent of HLA restriction* - 1 particle good for all people
2) *independent of known tumor antigens* - 1 particle good for all antigens
3) *Only need tumors with T cells*
Immunoswitch particles convert inhibitory checkpoint signal into CD8+ T cell co-stimulation
Immunoswitch particles delay tumor growth in multiple tumor models and in the absence of a foreign antigen.

**MC38-OVA colon cancer**

**B16-F10 melanoma**
Summary

• Immunoswitch particles link checkpoint blockade with co-stimulation more effectively than soluble antibodies in multiple tumor models
• Immunoswitch particles have an anti-tumor response in the absence of adoptively transferred cells
• Increased effector-target cell conjugation may drive immunoswitch anti-tumor response
• Immunoswitch particles alter the TCR repertoire within the tumor microenvironment
Immunoengineering: All about the bass, about the bass about about the bass, no treble

1) Immunotherapy
Oelke et al, Nat Med 9;5:619-24
Perica et al ACS Nano 2014
Perica et al ACS Nano 2015 in press (almost)

2) Diagnostic tool

3) Regulation of Polyfunctionality in CTL
Ndhlolvu et al. (2010) PNAS

NKT cell activation
Identification of an inhibitory substance in ovarian cancer ascites that suppresses immune responses
Webb et al, JIM 31;346:38-44 (2009)

Treatment of T cell mediated autoimmune diseases
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