Immuno-Prevention of cancers not associated with infectious agents

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Overview

• What is “Cancer Immunoprevention”?  

• Why is it an *attractive strategy* for cancer prevention?  

• Attributes of *targets/antigens (Ags) & strategies* used in cancer immunoprevention.  

• What Ags can we target for prevention of tumors NOT associated with infectious agents?  

• Vaccines currently being investigated in studies conducted at DCP:  
  * WOKVAC  
  * VADIS  
  * MUC-1  
  * PROSTVAC  

  *breast cancer prevention  
  *colon cancer & lung cancer prevention  
  *prostate cancer prevention
Cancer Immunoprevention

Modulation of the host immune system to prevent the initiation of carcinogenesis and progression to cancer
Immune Modulation as an Attractive Strategy for Cancer Prevention

- Specificity & adaptability of immune responses
- Memory immunity (potentially life-long)
- Safety profile (vaccines)
- Ease of administration and potentially improved compliance
Immunity During Carcinogenesis
Attributes of targets/antigens & strategies used in cancer immunoprevention

**Targets:**

1. Relevant for cancer development

2. Expressed on tumor tissue *(or predominantly)* and NOT *(or to much lesser degree)* on normal tissue –
   - Tumor Specific Antigens – TSA
   - Tumor Associated Antigens - TAA

3. Capable to induce “specific” immune response, especially T cell responses
   (break immune tolerance to “self”) – be *immunogenic* – but NOT inducing autoimmunity

4. Overall safety of targeting given antigen

**Strategies:**

1. **SAFETY** --- > Vaccines

   * Autoimmunity? --> continued question
### What Targets/Antigens Can We Use for Cancer Immunoprevention?

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<th>Cancers associated with infectious agents</th>
<th>Cancers not associated with infections agents</th>
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<tr>
<td><strong>Foreign Antigens</strong></td>
<td><strong>Self Antigens</strong></td>
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<td>HBV, HBsAg</td>
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<tr>
<td>HPV, E6, E7</td>
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**Most promising Tumor Associated Antigens (TAA)**

→ “self” antigens or normal cellular proteins that become immunogenic during the malignant process

**Mechanisms by which normal cell protein becomes aberrant in cancer “abnormal self”**

- *acquisition of stable mutations i.e. MAGE1*
- *overexpression of ca. associated proteins i.e. Her2/neu*
- *post-translational modification such as abnormal glycosylation i.e. MUC-1*
**HER-2**

*Her2* receptors send signals telling cells to grow & divide

**NORMAL CELL**

- HER2 receptor
- HER2 gene (ERBB2)
- nucleus

**HER2+ CELL**

- HER2 receptor
- HER2 gene (ERBB2)
- nucleus

**Too many Her2 receptors send more signals, causing cells to grow too quickly**

Breast Cancer Development

- Normal duct
- Ductal hyperplasia
- Atypical hyperplasia
- DCIS
- Invasive ductal carcinoma

(Images and diagrams depict the stages and development of breast cancer, highlighting the role of HER2 receptors.)
MUC-1 - Mucin 1

Colon Cancer Development

& Overexpressed on abnormal tissues
**PSA - Prostate Specific Antigen**

- A protein
- Almost exclusively produced by the epithelial cells of the prostate in normal and in pathologic conditions such as:
  - infection
  - urinary retention
  - enlargement of the prostate (BPH)
  - **prostate cancer** (PSA overexpressed on tumor)
Types of Cancer Vaccines

- Inexpensive production
- Easier & faster manufacturing
- “Off the shelf” products
- Long-shelf life

Important!
aside from generating target-specific immune responses...

“Epitope Spreading”
Broadening of generated immune responses against epitopes not included in the vaccine.
(intra-Ag; inter-Ag spreading)
Approaches to reducing cancer morbidity and mortality
Vaccines - "active immunity"
Adaptive Immune System

KEY COMPONENTS OF VACCINES

the specific component:

the Antigen

Peptide-long vs short

Epitope (antigenic determinant) = the part of an antigen that is recognized by the immune system (antibodies, B cells, T cells)

Viral-like Protein/VLP
Pentamer of a protein

• Viral vector

Cell-based vaccines

the nonspecific component:

the Adjuvant

Adjuvants = agent/strategy added to vaccine formulations that enhance the immunogenicity of antigens in vivo
Breast Cancer Prevention

VADIS trial

• Target: Her2/neu

• Agent/Vaccine construct: **short (9aa; 369-377) peptide + GM-CSF** (adjuvant) (E75; NeuVax; Nelipepimut-S)
Adaptive Immunity: Cellular Immunity

- **CD4/helper** versus **CD8/cytotoxic T cells**

- Infection
- Cancer

**APC**/

- antigen presenting cell

**MHC** = Major Histocompatibility Antigen

**TCR** = T cell receptor

**HLA** = Human Leukocyte Antigen

**Processed Bad Antigen**

**T cell**

**CD8** T cell

- CD8 / cytotoxic T cell / CTLs (cytotoxic T lymphocytes)
- MHC class I - restricted

**CD4** T cell

- CD4 / Helper T cell
- MHC class II - restricted

Typically 8-10aa

*(short peptide)*
Breast Cancer Prevention

**VADIS trial**

- **Target:** Her2/neu
- **Vaccine construct:** short (9aa)peptide + GM-CSF (E75; NeuVax; Nelipepimut-S)
- **Adjuvant:** GM-CSF
- **Special requirement:** HLA restriction to HLA-A2 participants only
- **Route of administration:** Intradermal injection
- **Study:** Ph II randomized (w/GM-CSF alone), pre-surgical (tissue in place) study in pts with DCIS evaluating safety; systemic/local immune responses; epitope spreading; histologic changes at resection

- **Anticipated toxicity:** well studied in BrCa pts; safe; (+) epitope spreading; in Ph II ↓ relapse in early dz.; though Ph III (-)
  - *from target:* cardiac (potential), ...
  - *from the vaccine construct:* predominantly GM-CSF related
    - local: injection site reactions: induration, erythema, warmth, pain, swelling, pruritus
    - systemic reactions: flu-like symptoms, bone pains, fatigue

*** No e/o autoimmunity
Breast Cancer Prevention

**WOKVAC trial**

- **Targets:** Her2, IGF-1R, IGFBP-2  (vaccine construct targeting *several* antigens ---> *polyvalent* vaccine)
IGF-1R & IGFBP-2

Membrane-bound protein (e.g., Integrin)

Various effects depending on IGFBP

IGF-1R & IGFBP-2

Unphosphorylated IGF-1R

Phosphorylated IGF-1R

Various effects depending on IGFBP

Nucleus

Proliferation

Glucose Metabolism

Protein Synthesis

Her-2

Normal Cell

HER2+ Cell

HER2 gene (ERBB2)

Overexpression - multiple HER2 genes

Breast Cancer Development

Normal duct

Ductal hyperplasia

Atypical hyperplasia

DCIS

Invasive ductal carcinoma

Basement membrane

Myoepithelium

Ductal epithelium
Breast Cancer Prevention

**WOKVAC trial**

- **Targets:** Her2, IGFBP-2, IGF-1R
- **Agent/Vaccine construct:** DNA plasmid
- **Route of administration:** *Intradermal inj.*
- **“Adjuvant”:** bacterial plasmid; selected epitopes; intradermal inj.
- **Study w/Her2+IGFBP-2:** good tox; mainly inj site rx & flu-like sx.
- **Study:** Ph I dose finding study, assessing safety & immunogenicity of WOKVAC in non-met. LN (+), Her2 (-) BrCa pts in remission after curative standard Rx.

- **Anticipated toxicity:**
  * from the **target:** cardiac, glucose control?, ...
  * from the **vaccine construct:** local (plasmid Ø get into circulation; Ag persistent @ site/depot, systemic: flu-like symptoms, ...
  **surveillance:** labs for autoimmunity, off target effect(s), ...

**WOKVAC designed to:**
*include sequences of immunizing Ags to induce predominantly TH1/Type I immune response (immune-stimulatory) Th1 cells & cytokines esp. IFN-gamma.*

**Electroporation**

**What is a plasmid?**
- A circular piece of autonomously replicating DNA
- Originally evolved by bacteria

**WOKVAC plasmid produces 1 single polypeptide of 70kDa expressing 3 extended epitope segments.**
**T\(_H\)CD4** cell subtypes

T helper/T\(_H\) cells are functionally of 2 types:

- **TH1/Type 1 versus TH2/Type 2**

**Immune Response**

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**Clinical Immunology Spectrum 1994**

We want Type 1/TH1 response to fight cancer
Breast Cancer Prevention

WOKVAC trial

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WOKVAC designed to:
* include sequences of immunizing Ags to induce predominantly TH1/type I immune response (immune-stimulatory) Th1 cells & cytokines esp. IFN-gamma.

WOKVAC plasmid produces 1 single polypeptide of 70kDa expressing 3 extended epitope segments.
Colon Cancer Prevention

- **Target:** MUC-1
- **Agent/Vaccine:** long (100aa) peptide + PolyICLC (Hiltonol) as adjuvant
- **Adjuvant:** PolyICLC (Hiltonol) => agonist of TLR 3
- **Route of administration:** *Subcutaneous* injection
- **Study:** Ph II randomized, placebo(*normal saline*) controlled study in pts with recently(≤1y) dgn advanced (≥1cm) colonic adenoma(s). Efficacy study. Accrued. F/u for 3y w/recording of polyp/adenoma recurrence.

**Anticipated toxicity:**

* from the *target:* ...

* from the *vaccine construct:* predominantly due to *adjuvant*
  - local: injection site reactions (erythema, soreness, warmth, swelling)
  - systemic: flu-like symptoms, muscle aches;

  1 pt with NASH developed transient elevation of LFT hence, NASH excluded

*No evidence of autoimmunity

*Pre-vaccination MDSC* – associated with inability to respond to vaccine/generate anti-MUC1 immunity
TLRs
*Immediate
*Non-specific immune responses

-Toll-like receptors (TLRs) = proteins of the innate immune system (on macrophages, dendritic cells)
-TLRs respond to danger signals (microbes/pathogen-associated molecular patterns (PAMPs))

-Innate Immune Response (Immune cells, Cytokines)
Colon Cancer Prevention

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**Anticipated toxicity:**
- * from the target: ...
- * from the vaccine construct: predominantly due to adjuvant
  - local: injection site reactions (erythema, soreness, warmth, swelling)
  - systemic: flu-like symptoms, muscle aches;
    1 pt with NASH developed transient elevation of LFT hence, NASH excluded

*No evidence of autoimmunity

*Pre-vaccination MDSC – associated with inability to respond to vaccine/generate anti-MUC1 immunity
Lung Cancer Prevention

- **Target:** MUC-1
- **Agent/Vaccine:** long (100aa) peptide + PolyICLC (Hiltonol) as adjuvant
- **Adjuvant:** PolyICLC (Hiltonol) => agonist of TLR 3
- **Route of administration:** *Subcutaneous injection*
- **Study:** Ph I trial in current & former smokers at high risk for lung cancer (55-80yo; ≥30py)
  Evaluating safety & immunogenicity in these pts w/local & systemic inflammation from smoking (? impact on respiratory status; ability to immunize successfully,...).

- **Anticipated toxicity:**
  * from the target: ...
  * from the vaccine construct: mainly due to adjuvant,...
    - local: injection site reactions: (erythema, soreness, warmth, swelling)
    - systemic: flu-like symptoms, muscle aches,... ? ↓/↑ local/lung inflammation,
      ? impact on systemic inflammation (hsCRP, IL-6), ...
Prostate Cancer (*progression*) Prevention

- **Target:** PSA
- **Agent/Vaccine:** PROSTVAC®
  - rV-PSA-TRICOM (prime) -> rF-PSA-TRICOM (boosts)

  * Virus – vehicle/vector for delivery of PSA & B7+ ICAM-1 + LFA-3 = TRICOM
  * Priming -> vaccinia virus based construct; *Boosting-* fowlpox virus based construct

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**Adaptive Immunity:**
- **Cellular Immunity (T cells):**
  - **Antigen Presentation & T Cell Activation**
  - Generalized part of T cell activation

  - Infection (virus) Cancer
  - Bad Antigen
  - Processed Bad Antigen (epitope)
  - APC/antigen presenting cell
  - T cell
  - IFN-γ
  - IL-17

  - MHC = Major Histocompatibility Antigen
  - TCR = T cell receptor
  - HLA = Human Leukocyte Antigen

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**Prostate:**
- Absorption into the bloodstream
- Prostate Specific Antigen
- Prostatic ducts
- Free PSA
- ACT bound PSA
- γMG bound PSA
Prostate Cancer (progression) Prevention

• **Target:** PSA

• **Agent/Vaccine:** PROSTVAC®
  - rV-PSA-TRICOM (prime) -> rF-PSA-TRICOM (boosts)
  * Virus – vehicle/vector for delivery of PSA & B7+ ICAM-1 + LFA-3 = TRICOM
  * **Priming** -> vaccinia virus based construct; **Boosting** -> fowlpox virus based construct

• **“Adjuvant”:** viral vector

• **Route of administration:** *Subcutaneous injection*

• **Study:** Ph II randomized, placebo (*empty viral vector*) controlled trial in pt with localized PrCa on active surveillance
  
  Evaluating vaccine impact on change in CD8(+) & CD4(+) cells in the tumor and adjacent stroma.

• **Anticipated toxicity:**
  * from the **target:** ...
  * from the **vaccine construct** – mainly due to viral vector

  - **local:** injection site reactions: Vaccinia->potential for vaccinia dissemination->specific care w/contacts & wound care (needs to crust off); individuals w/eczema/skin breaks excluded
    - induration, erythema, warmth, soreness, swelling
  - **systemic:** flu-like symptoms, muscle aches, fatigue
Summary:

• Multiple vaccination strategies
  * targeting single or multiple antigens
  * with variable side effect profiles
  * at different level of development
  * aiming at stimulating different arms of immunity

• No understanding of immune regulation of premalignancy

• No good understanding of long-term safety as most vaccine constructs tested in cancer patients

• Difficult to develop standardized toxicity criteria (CTCAE for cancer vaccines) at this stage of field (cancer immunoprevention) development.
Thank you