Antibody-Targeted Vaccines

Tibor Keler, PhD
Monoclonal Antibodies as Therapeutics

- Unconjugated mAbs: Passive vaccines
  - Target the cancer or pathogen or pathogenic molecule

- Conjugated mAbs: Toxin/radionuclide conjugates
  - Target the cancer

- Antibody-targeted vaccines: Antigen conjugates
  - Target the immune system to respond to cancer or pathogen
In vivo antigen Delivery

Targeting to endocytic receptors on DCs and other APCs

Antibody Specificity:
- Fc receptors
- C-type lectins
- Complement receptors
- MHC

- Enhance efficacy of protein vaccines
- Improved cross-presentation to CD8+ T cells
- Broad response to multiple epitopes
Antibody-Targeted Vaccines

*Recombinant fusion proteins*

- IgG-antigen
- Fab-antigen

*Chemical conjugation*
Targeting C-Type Lectin Receptors

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Specificity</th>
<th>APC Binding in human tissues</th>
<th>Affinity KD (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B11</td>
<td>Mannose receptor</td>
<td>Dermal DCs, Interstitial DCs, macrophages in most tissues</td>
<td>~7 x 10^{-10}</td>
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<tr>
<td>3G9</td>
<td>DEC-205</td>
<td>DCs in lymph nodes, tissue DCs</td>
<td>~2 x 10^{-10}</td>
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</tbody>
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Cysteine rich repeat
Fibronectin domain
CRDs-carbohydrate recognition domains
Tyrosine-based motif for targeting
Triad of acidic amino acids
APC targeting
Vaccine Uptake by human DCs in vitro

0 °C

37 °C, 60 min.

Confocal microscopy images of human DCs
Targeted delivery to APCs in vivo

- wt
- hMR-tg

B11-hCGβ
10 μg

24hrs

Draining lymph node stained for hCGβ

WT

hMR-TG
Vaccine Uptake – *in vivo*

Skin punch-biopsies taken from injection site and opposite arm-48 hrs post injection of 1mg B11-hCGβ, i.d.

IHC - rabbit anti-hCGβ
Cross-Presentation
Cross-presentation of MR-targeted antigen

Splenocytes analyzed for Proliferation (day 3) & IFN-γ (day5)

OT-I
CD8 Cytotoxic T cells

OT-II
CD4 Helper T cells

No Ag
B11-OVA 1μg
B11-OVA 10μg

Raphael Clynes, Department of Medicine and Microbiology, Columbia University, NY
Breadth of T cell response
Presentation of multiple NY-ESO-1 MHC II epitopes with $\alpha$‐DEC‐205‐NY‐ESO‐1

Stimulation of NY-ESO-1 CD4+ T cell responses from patient AS

Stimulation of NY-ESO-1 CD4+ T cell responses from patient VZ

Data from G. Ritter, Ludwig Institute for Cancer Research
Presentation of multiple NY-ESO-1 MHC I epitopes with \( \alpha \text{-DEC-205-NY-ESO-1} \)

Stimulation of NY-ESO-1 CD8+ T cell responses from patient SB

Data from G. Ritter, Ludwig Institute for Cancer Research
Translation to clinical studies
Clinical Vaccine Candidates

**CDX-1307**

- **hCGβ** - β-chain of human chorionic gonadotropin
  - expressed by various epithelial and germ cell tumors
  - expression correlates with poor outcome
  - implicated in protection of tumors from apoptosis
  - human CTLs efficiently recognize and kill cancer cell lines expressing hCGβ

**CDX-1401**

- **NY-ESO-1** – Cancer-testis antigen
  - expressed by sarcomas, melanoma and other tumors
  - immunogenicity in humans well documented
  - Adoptive transfer of NY-ESO-1 specific T cells can lead to significant clinical regressions
CDX-1307 (α-MR-hCGβ) - Clinical Trial Design

Phase 1 Study – Advanced breast, colorectal, and pancreatic cancers

2 weeks

GM-CSF (s.c.)

CDX-1307 (i.c.)
Poly ICLC (s.c.)
R848 (topical)

CDX-1307 (Single agent)

0.3 mg
1.0 mg
2.5 mg

CDX-1307 (Adjuvant combinations)

2.5 mg + GM-CSF
2.5 mg + GM-CSF + Poly ICLC
2.5 mg + GM-CSF + R848
2.5 mg + GM-CSF + Poly ICLC + R848

• 6 patients per cohort
• Safety assessment after 3 patients in each cohort
• No dose limiting toxicities
Summary of hCG-β-specific humoral responses

Humoral responses to purified hCGβ were measured by ELISA. The values reported represent the maximum titer (reciprocal dilution) for each patient that received at least 3 doses of vaccine.
Induction of hCG-β-specific T cell responses

Cellular responses were measured by IFN-γELISpot assay using T cells (CD4 and CD8) isolated from patient PBMCs after a 7-day in vitro stimulation with hCGβ-derived peptide pool. Values represent the highest hCGβ-specific T cell response (with control peptide subtracted) for patients treated in combination with TLR agonists. Significant T cell responses were not observed in cohorts without TLR agonist.
Elevated hCG-β Levels Correlate with Reduced Survival in Patients with Invasive (T2-T4) Bladder Cancer

R. Iles 1996
PHASE 2 TRIAL IN BLADDER CANCER:
The “N-ABLE” Trial Neoadjuvant and Adjuvant Bladder Cancer Trial

Randomized (1:1), controlled trial (n=60) in hCG-β expressing, muscle-invasive bladder cancer

- Neoadjuvant setting allows for pathologic assessment of tumor response to therapy (necrosis, immune infiltration, persistence of hCG-β expression).
- Outcome measures: PFS (primary), OS, safety, immune response (during neoadjuvant chemo and adjuvant vaccine), tumor response (radiographic and pathologic)
- Initial data anticipated late 2011 - 2012
Conclusions

• Delivery of protein antigens to endocytic receptors on APCs results in:
  – Robust humoral/cellular immunity
  – Requires concomitant administration of adjuvants

• Antibody-targeted vaccines provide a practical approach to vaccines:
  – Based on well established antibody technology
  – Off-the-shelf and not HLA specific
  – Can be used for multiple antigens

• Early clinical data demonstrate feasibility, safety, and immunogenicity
Acknowledgements

Collaborators

Ralph Steinman – Rockefeller U.
Michel Nussenzweig – Rockefeller U.
Sarah Schlesinger – Rockefeller U.
Raphael Clynnes – Columbia U.
Robert Seder- NIH

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Michael Morse - Duke University Medical Center
Robert Chapman- Henry Ford Hospital
Ding Wang- Henry Ford Hospital

John Powderly - Carolina BioOncology Institute