Therapeutic Vaccines for HIV and Cancer

Angus Dalgleish
SGUL and the CVI
Sept 2012
Therapeutic vaccines

• Not the same as prophylactic vaccines which are designed to prevent infection

• Therapeutic vaccines are to prevent disease progression
Many similarities between Chronic infectious diseases and cancer

- In many cases chronic infections predispose to cancer for instance;
- EBV infection (Lymphomas and Nasopharyngeal cancers)
- Hepatitis B and C viruses which induce liver cancer
- and the Human papilloma virus (HPV) which causes cervical, peritoneal and oral cancers.
Vaccines against HBV and HPV

- HBV vaccine greatly reduces infection and liver cancer development, used for over 30 years.

- HPV vaccines, cervirax and guardasil recently approved

- No effect on disease progression after infection.
Therapeutic

• These vaccines need to target the parts of the virus that induce disease progression and/or induce oncogenesis and which are NOT involved in cell entry and early progression.

• Cancer vaccines can be prophylactic (HBV, HPV) but mainly therapeutic aimed at the tumour specific or associated antigens.
HIV

• Massive industry focused on developing HIV vaccines, Billions of dollars and over 30 years later there is no effective vaccine.

• Initial target was neutralising epitopes which are very variable and then Cell mediated epitopes which are again variable.
HIV vaccine candidates

• AUX-101 alpha virus gag based vector.
• MVA or modified Ankara virus POX, used for both HIV and cancer.
• Adenovirus vectors.
• Prime Boost:
  • Behind the large Thailand trial which combined ALVAC with AIDSVAX(gp120)
  • And protected about 30%.
HIV therapeutic

- Best data to date are from the Vacc4x study by Bionorpharma, based on gag modified peptides given to HIV infected patients on HAART which was then stopped after immunisation.
- No effect on CD4 count but a positive effect on the virus load and progression.
Long-term HIV-specific responses and delayed resumption of antiretroviral therapy after peptide immunization targeting dendritic cells

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Long-term HIV-specific immune responses and clinical outcomes were evaluated in HIV-infected patients previously immunized with p24-like peptides (Vacc-4x) targeting dendritic cells (DC). Vacc-4x-induced cellular immune responses were unchanged 1.5 years after completing immunization, and 62\% were still off combined antiretroviral treatment (CART). The magnitude of early Vacc-4x responses determined whether the resumption of CART was clinically indicated 2 years after enrolment. These observations encourage further exploration of both Vacc-4x and other HIV peptide-based immunization regimens targeting DC.
Vacc-4x: VL change Pre-ART to Post-Treatment

<table>
<thead>
<tr>
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<th>Placebo Pre</th>
<th>Vacc-4x Post</th>
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<td>Vacc-4x Pre</td>
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The role of chronic immune activation in the pathogenesis of AIDS

No immune activation no AIDS
What is the major difference between HIV infected chimps and humans?

- Both have replicating virus in blood and tissue.

- Chimps have no evidence of chronic immune activation as measured by B₂M, Neopterin, sTNFRII, Surface markers, apoptosis and lymph node changes.

- These changes precede “AIDS” in humans (Gougeon, ML et al. J Immunol 1997).

- Rare cases of progression in chimpanzees associated with hyper-immune activation (O’Neill, SP. J Inf Dis 2000)
Immune Activation in HIV+ humans

- Immune activation recognised from earliest stages prior to CD4+ T cell decline.

- Immune activation markers (eg sB₂M, sTNFRII and Surface HLA-DR and CD38) serve greater prognostic significance than viral load. (Janice Giorgi, JID 1999).

- HIV can induce TNF production, resulting in immune activation which leads to CD4 depletion (apoptosis) or dysfunction (Anergy). (Ledermann, AIDS, 2000)

- Degree of activation correlates with virus load and pathogenesis.  ¿ Is first chicken or egg!
Do non-neutralising epitopes trigger inappropriate receptors that promote immune activation?
**AIDS and GVHD**

**Similarities:** Opportunistic infections, weight loss, lymphadenopathy, lymphomas, skin lesions, pan immune activation with CD4 suppression.

**Differences:** CD4 count never falls to levels seen in AIDS but then cytopathic HIV is not present.

**NB:** Shearer reported similarities before HIV discovered (NEJM 1983)
Crystal structure and modelling

HLA DR1 + Flu peptide  GP120 + Flu peptide  GP-120 ΔC5-mutant
Predictions from model

- THAT

- HLA-B8 would be fast progressors and HLA-B27 slow progressors
  (Gore MRC)

- chimpanzees would have restricted HLA

- CTL epitopes same in HIV NP’s as chimps
## Walter Reed Cohort: Humoral responses

### Table 2. Reactivity of specific peptides with sera from Walter Reed progression cohort.

<table>
<thead>
<tr>
<th>Purpose, peptide</th>
<th>Sequence</th>
<th>Median reactivity&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td></td>
<td></td>
<td>Rapid progressors</td>
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<td>Distinguish rapid from slow progressors</td>
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<tr>
<td>101</td>
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</table>
FHI longitudinal sera: α-C5 status

C5 Concentration FHI (log ug/ml)

(Slow progressors)  (fast progressors)

p = 0.000000022
FHI Viral load: fast and slow progressors

- α-C5 weak non-sign. correlation to VL
- First VL significant diff. between slow and fast progressors
Vacc-C5 – targeted peptides

- Vacc-C5 developed on basis of modified synthetic peptides from the C5 domain of gp120, a HIV-virus surface protein and combining with the adjacent gp41 protein.
- Vacc-C5 targets B-cells for production of antibodies, blocking HIV replication (rather than T-cells for killing infected immune cells).
Molecular and preclinical profile of thalidomide, pomalidomide & lenalidomide

ImiDs are structurally similar, but functionally different both qualitatively and quantitatively.
Pomalidomide enhances the efficacy of a colorectal whole tumor cell vaccine

- Pomalidomide enhances survival of vaccinated mice
- Elicits long term protection from live tumor rechallenge
- No protection afforded in nude mice (T cells required)

Future studies

• Phase 1/2 of C5 vaccine commenced.

• Phase 1/2 of Vacc4x combined with revlimid has also commenced.

• If successful, Vacc4x will be combined with C5 and revlimid. This could also be a prophylactic vaccine if successful.
Immunotherapy and cancer;
or as well as, not instead of.
Hallmarks of cancer

- Seminal review in Cell in 2000, with over 6,000 citations.
- Drugs designed to target each feature.
- However, forgot to add “evasion of the immune system”.

Hanahan & Weinberg, Cell, 2000
Effects of targeted therapies

- RAS/MEK inhibitors (e.g. sorafenib, PD184352)
- BH3 mimetics (e.g. Abbott agents)
- PI3-K/AKT/mTOR inhibitors (e.g. GSK690693, temsirolimus)
- Telomerase inhibitors (e.g. GRN163L)

- Used with cytotoxic drugs

- Self-sufficiency in growth signals
- Evading apoptosis
- Insensitivity to anti-growth signals
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential

RAS/MEK and PI3-K/AKT/mTOR inhibitors
The hallmarks of cancer $^v_2$

- Deregulating cellular energetics
- Avoiding immune destruction
- Genome instability and mutation
- Tumor-promoting Inflammation

Hanahan et al, 2011 Cell 144: 646
Cancer and the Immune System

Swann et al., 2007 JCTI 17:1137
1890’s to 2010

• Coley’s Toxins
• BCG and other non specific agents
• Vaccines, auto and allogeneic
• Antibodies
• Genetic based therapy
• Technology, RNA,DNA,peptides
• Cell therapy, DC and T cell based
Problem with Immunology

• Analogous to 6 blind men feeling an elephant and then describing and arguing about the findings!!!!
And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right
And all were in the wrong!
Prostate Cancer Therapeutic Vaccine (Provenge™ by Dendreon)

- Recently FDA approved
- 33% alive (Rx), 23% (placebo) at 3 yrs
- At 5yrs placebo performs better than vaccine
- US$93,000 for 3 vaccinations


NASDAQ Code: DNDN
Share price US$60 - $27
Mkt Cap high = US$5.5B
2010-11

- Dendreon, Provenge, Sipuleucel T. Granted FDA approval, 2010, for hormone resistant Prostate Cancer

- Ipilimumab, an anti-CTLA-4 antibody given approval for advanced melanoma
However, the ceiling has been broken

• Tumours and the Immune system the facts that have been ignored;

• Tumours evade the immune system using many different mechanisms.

• They actively suppress immune responses.

• Other modalities including chemotherapy are not as effective in immunocompromised mice!
Immunosuppression Reversed by Tumor Debulking

Work in colorectal cancer patients by Heriot et al and Evans et al,
Both in the BJC, 2000 and 2007
IFN-γ levels in stimulated whole blood in patients with colorectal cancer, prior to, and post surgical resection, versus controls. [NS: not significant]
TNF- survival functions. (ii) IFN- survival functions.
(ii) IL-10 survival functions.
Immune Equilibrium

Innate immunity and cytokine balance
Cell Mediated

TH-1
IL-2, gIFN, IL-12

Humoural Mediated

TH-2
IL-4, IL-5, IL-6
IL-10
THE LORENZ ATTRACTOR.
Chronic infections and Cancer perturbate the dynamic balance of the cell and humoral mediated immune responses

TH-1 suppressed in chronic infections eg TB, HIV, tropical etc and many cancers
Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis.

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.

Time

Mutation inactivates suppressor gene

Cells proliferate

Mutations inactivate DNA repair genes

Proto-oncogenes mutate to oncogenes

More mutations, more genetic instability, metastatic disease

[Image: Illustration showing the progression of cancer development through multiple mutations.]
Th-1 boosters

• BCG
• Mycobacterium Vaccae

• NOTE;
• Common adjuvants like ALUM are TH-2 boosters
Mycobacterium Vaccae

• New TB vaccine which boosts the TH-1 response. Good responses in melanoma correlating with cytokine changes and trend to survival, Maraveyas et al 1999.

• Clinical responses can be enhanced with low dose IL-2, Nicholson et al 2003.
M Vaccae


- Standford et al 2008, show that re-analysis shows a significant survival for adeno cancers in patients receiving 4 or more vaccines.
Randomised clinical trial of *Mycobacterium vaccae* showed impressive survival benefit (mean = 135 days) in advanced adenocarcinoma of the lung for “compliant” patients (those receiving a minimum of 4 doses)

History

• SR pharma dropped development.

• Strong demand from patients and doctors led to an anonymous backer to resurrect it. (Check for £10m)

• Operating company called “IMMODULON”.
New vaccine

• Myco. Obuensi selected
• Phase 1/2 study in melanoma just published in Annals of Oncology, Stebbing, Dalgleish et al.
• All stage 4 patients commenced on the study in spring 2010 are still alive although most are progressing.
• Response to subsequent RT and chemo impressive.
The 3Es

A. Elimination
B. Equilibrium
C. Escape

Normal Epithelium
Mechanisms of action

• Innate Immune system stimulation ie Non adaptive processes

• Stimulation via Toll Like Receptors (TLR)

• Ideally need to stimulate TLR 2/3 and 7/8/9
IMMUNOMODULATION

ALDARA → TLR 7

TH1 stimulating cytokines, IL12

T cell Activation

TH1 cytokines, IL2, IFNγ

CD8 CELL

NK

MONO

B CELL

IL 2
Introduction

• Why are γδ T cells important in cancer?
  – Potent cytotoxicity against cell lines from a broad range of haematologic and solid malignancies.
  – Demonstrable role in protective immunity against cancer in animal models and humans.

• γδ T cells as candidate immune cells for mycobacteria-induced anti-cancer immunity.
  – Potent responses to mycobacteria.
  – Unique mode of antigen recognition. Involves stress molecules expressed by both mycobacteria and tumour cells.
  – Vast majority of peripheral γδ T cells are capable of recognising tumour.
Selection of samples  \( p<0.02 \): removal of outliers
Summary

Non-responders anolytes are all inflammatory.

Similar results from other studies; prostate and lung cancer studies.

Pre-clinical studies have reported that anti-inflammatory drugs improve responses to vaccines.
Other cancer vaccines

• Dendreon
• Prostavax
• Transgene
• Curevac
• Immatics
• Muc-1
• Biovex
Survival Full Analysis Set

\[ P = 0.0156 \text{ (stratified logrank)} \]

\[ \text{Hazard Ratio} = 0.601 \text{ (0.396 to 0.912)} \]

![Survival Analysis Graph]

- Placebo: N = 40, Deaths = 37, Median = 16.8
- Vaccine: N = 82, Deaths = 85, Median = 25.1

Months
Similarities

• Many vaccines are getting survival advantages in early studies

• One explanation is that patients who are vaccinated respond much better to radiotherapy and chemotherapy
Chemo plus vaccines

- Many chemotherapies are complimentary at non high dose regimens, eg cyclophosphamide, gemcitabine, Zometa, taxanes, etc

- The ImiDs such as revlimid and pomalidomide are immunostimulatory, suppress Treg cells and are anti-inflammatory.
Summary

• In spite of poor HIV prophylactic vaccines there is great hope for a therapeutic one involving T cell epitopes and a B cell epitope aimed at reducing chronic activation.

• Cancer vaccines are much more effective when given in the right context and with other modalities, expect many more to be approved in the future!

• The Imids are useful as adjuvants in both HIV and cancer