A Biological Approach for the Treatment of Prostate Cancer

pPSA +/- pIL-18

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Rationale for treating prostate cancer with specific-active immunotherapy

- Prostate cancer patients do not have any effective treatments once they fail anti-androgen therapy (large unmet need)

- PSA (prostate specific antigen) is a tissue-specific tumor associated antigen, and is secreted by normal and transformed prostate epithelial cells

- PSA-specific immune responses are detected in some prostate cancer patients, suggesting tolerance may be broken

- An anti-PSA immune response would only destroy the prostate and the tumor; no other tissues should be affected
A DNA vaccine encoding PSA will generate a therapeutic cellular immune response against PSA-expressing tumor cells.

Skewing this response toward Th1 by co-injecting an IL-18 DNA adjuvant plasmid will enhance this immune response.
The breadth of the immune response is important.
DNA Vaccines

pPSA
- PSA cDNA
- hCMV Promoter
- polyA
- Kan'
- Col E1 ori

plL-18
- Murine IL-18 cDNA
- hCMV Promoter
- polyA
- Kan'
- Col E1 ori
Tumor model for evaluation of pPSA/pIL-18 DNA vaccine

1. Inject DNA at Days 0, 14
2. Inject tumor cells on day 21
3. Monitor for tumor growth

pPSA -/+
pIL-18

CT-26/PSA cells
pPSA DNA vaccine protects against tumor development

Long term immune memory response induced
pIL-18 enhances tumor protection in pPSA-immunized mice

100% tumor protection observed when sub-optimal doses of pPSA are co-administered with pIL-18

** p<0.0008
Both CD4 and CD8 T cells are required for PSA-specific anti-tumor immunity

![Graph showing percentage of mice protected over days after challenge](https://example.com/graph.png)
Experimental design for immune response assessments

- pPSA -/+ pIL-18
- Inject DNA at days 0, 14, 28 and 42
- Isolate splenocytes
- Proliferation assay
- Bioplex assay
- CTL assay
- Isolate sera
- Ab
- Proliferation assay
- Bioplex assay
- CTL assay
pPSA +/- pIL-18 induce antibody responses to PSA
pIL-18 enhances Th1 skewing of antibody responses to PSA

Th2/Th1 ratios after one immunization:

- pPSA
- pIL-18

Th2/Th1 ratios after four immunizations:

- pPSA
- pIL-18

Th2 = IgG1
Th1 = IgG2a
pIL-18 immunization enhances early cellular proliferative responses

1 inoculation

2 inoculations

3 inoculations
pIL-18 enhances the kinetics of the CD4⁺ and CD8⁺ T cell response
pPSA + pIL-18 elicits a stronger Th1 response than pPSA alone

**IL-2**
- EV
- pPSA
- pPSA/pIL-18

**Th1**
- IFN-γ

**IL-4**
- EV
- pPSA
- pPSA/pIL-18

**Th2**
- IL-2 pg/ml
- IL-4 pg/ml
- IL-5 pg/ml

**IL-5**
- EV
- pPSA
- pPSA/pIL-18

**IFN-γ**
- EV
- pPSA
- pPSA/pIL-18
pIL-18 enhances the frequency of IFN$\gamma^+$ CD4$^+$ and CD8$^+$ T cells
pPSA +/- pIL-18 enhances PSA-specific CTL responses

Effector:Target Ratio

% Lysis

Green – P815/PSA
Red – P815/EV
pIL-18 Immunization enhances early CTL responses

1 – Empty Vector
2 - pPSA
3 - pPSA + pIL-18

1 inoculation
2 inoculations
3 inoculations
Conclusions

♦ pPSA DNA vaccine induces protection against PSA-expressing tumors in a Balb/c syngeneic model

♦ Suboptimal doses of pPSA are protective when pIL-18 is coadministered

♦ Both CD4⁺ and CD8⁺ T cells played an important role in in vivo tumor protection

♦ pPSA DNA vaccine elicited strong Th1 immune responses in Balb/c mice with increased CD4⁺ and CD8⁺ effector T cell frequencies.

♦ pIL-18 enhanced the kinetics and intensity of the antigen-specific Th1 immune response elicited by pPSA

♦ IL-18 is a powerful adjuvant that enhances immune response induction and vaccine efficacy
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