Exploiting T Cell Migration, Function and Residency for Cancer Immunotherapy

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HHMI
Restricted tissues

Shin & Iwasaki (2013) Immunological Reviews 255:165-81
Local infection/inflammation is required for T cell entry into restricted tissues
CD8 T cells are further restricted from access to genital tract – requires CD4 T cells
CD4 T cells secrete IFN-γ and induce chemokines, CXCL9 and CXCL10
CD8 T cells use CXCR3 to migrate to the vagina

Once recruited, CD8 T cells become tissue resident.
Can we override the requirement for CD4 T cells in CD8 T cell recruitment and retention?
Prime and Pull Vaccine Strategy

Prime

APC

CD8 T
Prime and Pull protects mice from lethal herpes infection

Prime alone
Prime and Pull

TK- HSV-2 (s.c.)
CXCL9
CXCL10 (ivag)
WT HSV-2 (ivag)

5 days
5 weeks

Can we apply “Prime and Pull” as cancer therapy?

• We need to know the antigen to “Prime”
• We need a localized accessible tumor to “Pull” effector T cells.
Natural HPV infection does not promote local T cell response

A

CD4+ cells/mm²

500
375
250
125

Normal
Regressed CIN1
Progressed CIN1
CIN3
Carcinoma

B

CD8+ cells/mm²

500
375
250
125

Normal
Regressed CIN1
Progressed CIN1
CIN3
Carcinoma
Treatment of High-Grade Pre-Neoplastic Cervical Lesions Using a Novel “Prime and Pull” Strategy

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Study Team

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Cervical cancer progression

Can we stop the progression to cancer?
Prime; Gardasil 9

9-valent HPV Vaccine

- Protects against 7 high-risk HPV strains that cause 90% of cervical cancers
- Sub-unit protein (L1) vaccine with VLPs mimicking wild type virus capsid (contain no viral DNA)
- Highly immunogenic producing a robust antibody response
- Induces L1-specific T cell response as well
Pull; Imiquimod

- Agonist for TLR7
- Has antiviral and antitumor activity
- Induces cytokines and chemokines including CXCL9 and CXCL10
- Found to be safe and tolerable when applied to cervix

Pachman et al., 2012; Grimm et al., 2012
Study Design

Women with high-grade cervical intraepithelial neoplasia (CIN 2/3)

Patients must have histologically-confirmed pre-invasive HPV lesion(s), cervical intraepithelial neoplasia grades 2 or 3 (CIN 2/3), as determined by colposcopy-guided cervical biopsies

Randomized

Control (observation)

Imiquimod (16 week course)

HPV vaccine + Imiquimod (16 week course)

Primary Outcome Assessment (Weeks 20-24)

Aim to enroll 38 patients in each arm
Study Protocol

- Imiquimod self application

Vaccine

-10 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 weeks

- Imiquimod self application

Baseline colpo
Baseline biopsy

Blood draw
High risk HPV test
HPV 16/18 genotype
Cytobrush
Urine pregnancy test

Colposcopy
Blood draw
HPV 16/18 genotype
Cytobrush
(Biopsy if necessary)
Urine pregnancy test

Colposcopy
Blood draw
HPV 16/18 genotype
Cytobrush
(Biopsy if necessary)
Urine pregnancy test

Colposcopy
Biopsy
Pap
Blood draw
High risk HPV test
HPV 16/18 genotype
Cytobrush
Urine pregnancy test

3-6 Months after final biopsy (if regression):
Pap
High risk HPV test
Interim analysis

- 57 patients enrolled
- 6 dropped out
- Age between 21-43 (average 28.8, median 28) yrs old

![Pie charts showing CIN level changes](chart.png)

- **Observation** (n=15): 30% CIN level increased or stayed the same, 70% CIN level reduced.
- **Pull only** (n=16): 20% CIN level increased or stayed the same, 80% CIN level reduced.
- **Prime and Pull** (n=15): 100% CIN level reduced during trial.

Legend:
- Red: CIN level increased or stayed the same during trial
- Blue: CIN level reduced during trial
T cell infiltration after treatment in the cervical mucosa correlates with regression below CIN1

CD4 T cell
Observation (n-15)

> CIN1
≤ CIN1

CD8 T cell

> CIN1
≤ CIN1
Conclusion

• Prime and Pull provides a safe vaccine to establish local tissue-resident memory T cells.
• Prime and Pull confers protection against primary genital herpes and controls recurrent infections.
• Prime and Pull may be used to recruit protective T cells to the cervix to destroy intraepithelial neoplasia.
• In the future, Prime and Pull can be tested against other accessible cancers.
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