Immunotherapy For Genitourinary (GU) Cancer

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Disclosure

No conflict of interest related to the content of the presentation to disclose

Major Types of GU Cancer

Prostate

Kidney

Bladder (urothelial) cancer

Testicular cancer
(No immunotherapy was attempted)

Goals

Immunotherapy for GU cancer is still at its Infancy

Will discuss today:

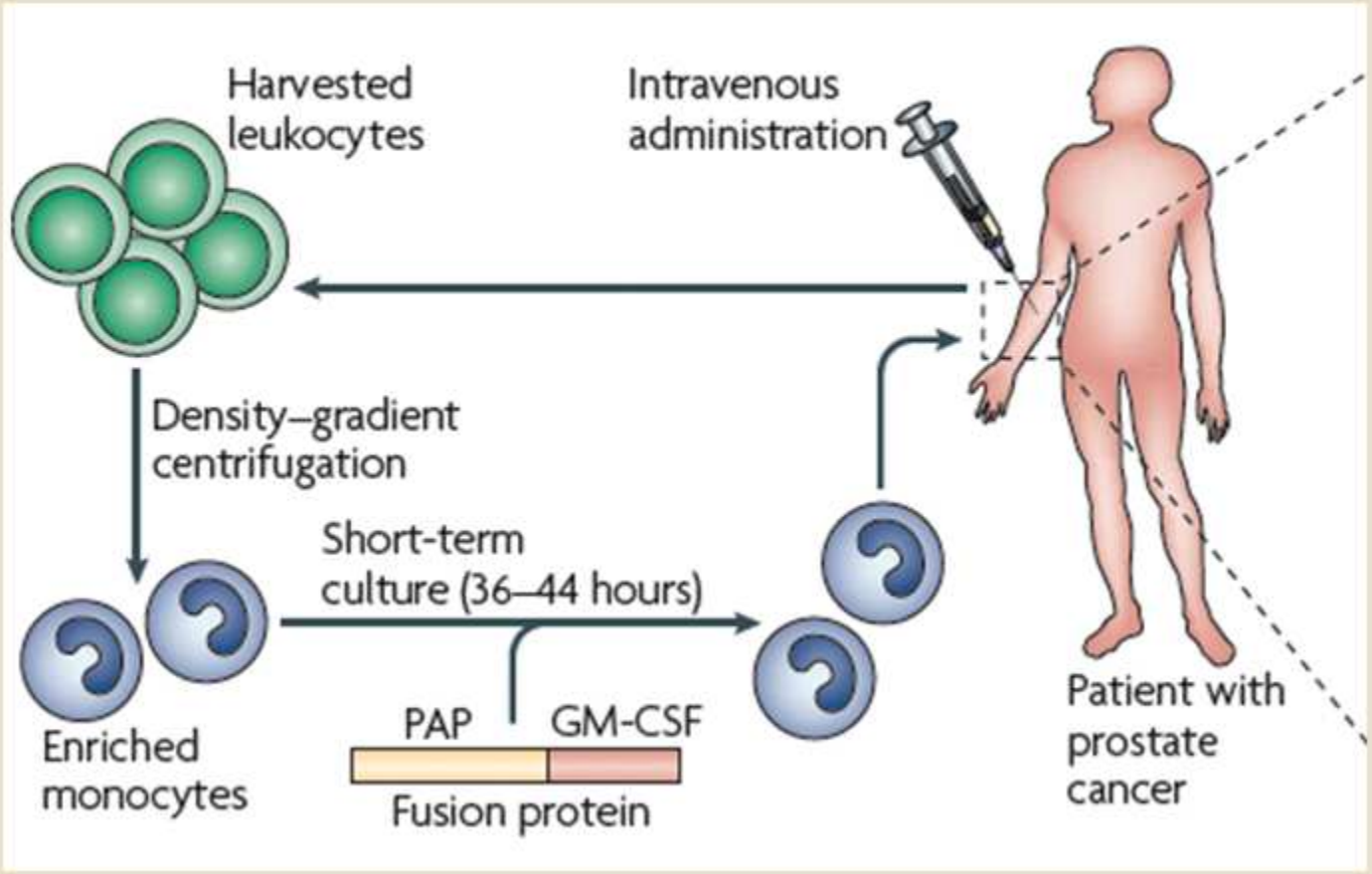
- **What has been studied clinically**
- **The worked and the NOT-worked**
- **What is currently in pre-clinical/clinical trial**
- **Perspective**

Prostate Cancer
Sipuleucel-T (Sip-T, brand name PROVENGE)

- An FDA-approved treatment option for prostate cancer before chemotherapy.
- Dendritic Cell-based Cancer Vaccine for prostate cancer. asymptomatic or minimally symptomatic metastatic HRPC
- Specifically target against prostatic acid phosphatase (PAP) antigen, which is expressed in most (>95%) prostate cancers
- The first FDA approved cancer vaccine. FDA approved in 2010.
- Phase III trial showed average survival benefit of 4 months (25.8 vs 21.7 months in median survival) (NCT00065442; N Engl J Med 2010; 363:411-422)
- A complete sipuleucel-T treatment repeats three courses, with two weeks between successive courses

Sipuleucel-T

Generate fresh (functional) Antigen-Presenting Cells (APCs) outside the body and re-infuse



(Charles Drake, Urology 2013; 83)

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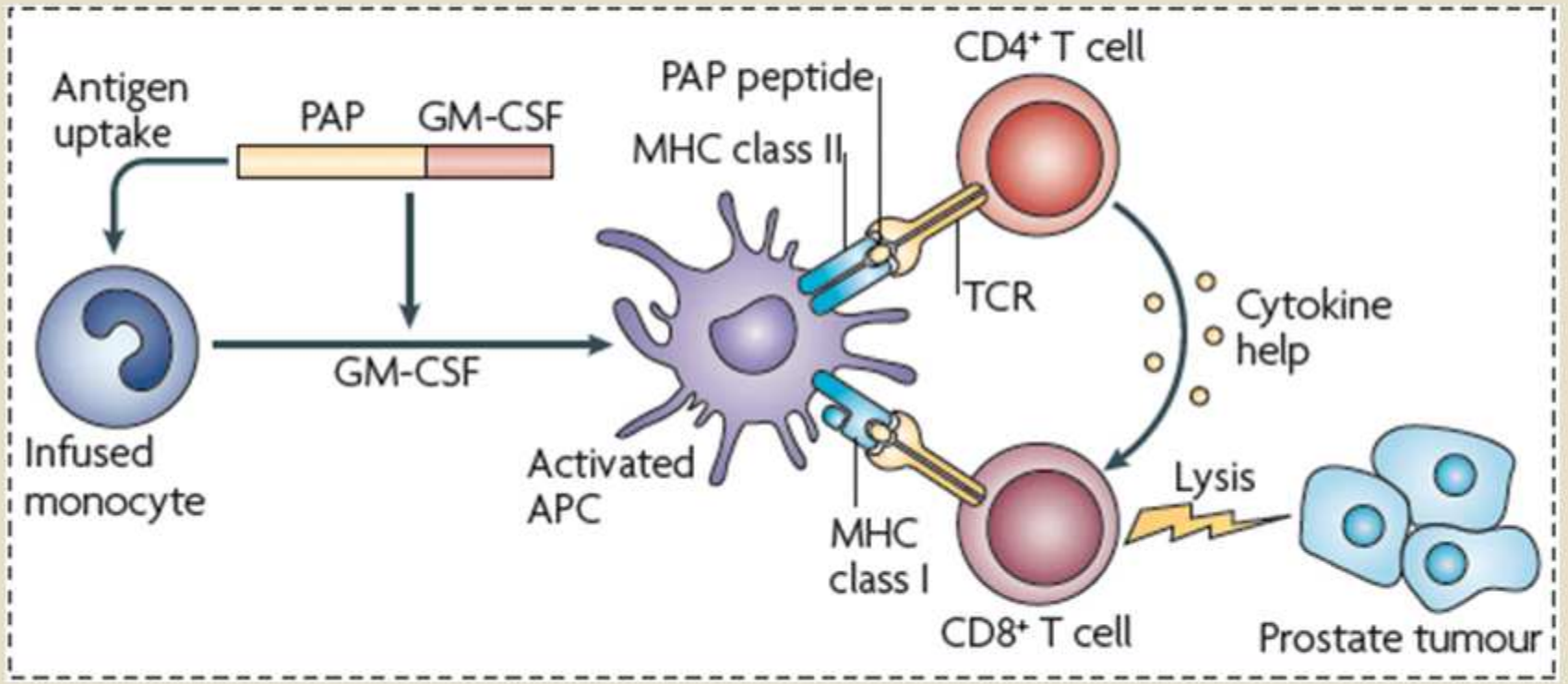
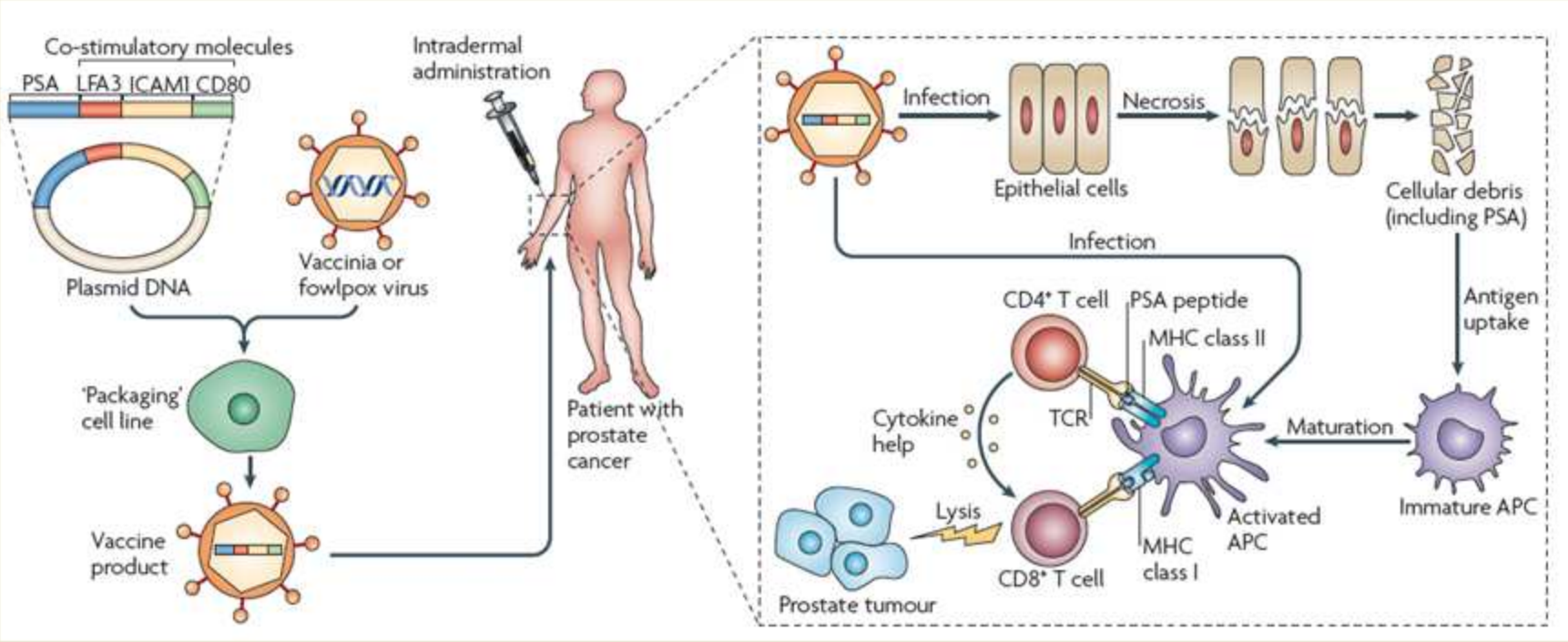


(Drake CG, Urology 2013; 83)

Prostvac VF: A Virus-based Vaccine Targeting PSA

(PSA-TRICOM)



(modified from Charles Drake, Urology 2013; 83)

PROSTVAC-VF (PSA-TRICOM)

- Initially developed at the National Cancer Institute (NCI) by the group Dr. Jeffrey Scholm and Dr. James Gulley
- Currently being developed by Bavarian Nordic.
- A randomized phase II trial with 122 patients with metastatic castrate-resistant prostate cancer: an 8.5 month improvement in median overall survival,
- A large phase III trial (PROSPECT trial; NCT01322490) was initiated in November 2011 and is currently enrolling patients. This study is being conducted at many centers in the U.S. and around the world.

GVAX

- Created in 1993 by Glenn Dranoff and Drew Pardoll
- Is composed of irradiated prostate cancer cell lines that are engineered to express GM-CSF.
- A phase III trial of GVAX was halted in 2008
- New evidence suggesting that GVAX may work best when administered along with androgen-suppressive therapy. A new phase I/II trial testing GVAX in combination with hormone therapy (NCT01696877) in men with localized prostate cancer prior to surgery is currently enrolling at The Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center.

Checkpoint Inhibitors for Prostate Cancer: Ipilimumab (anti-CTLA4)

- Ipilimumab (brand name Yervoy) was tested in two phase III trials as a treatment for advanced, castration-resistant prostate cancer after standard care of docetaxel. No overall survival benefit was achieved.

- Results of the trial in which patients received ipilimumab prior to chemotherapy are not yet available.

- On case report in 2014 from OHSU, patients received ipilimumab in combination with hormone therapy, but prior to chemotherapy showed CR (Cancer Immunol Res. 2014 May;2(5):399-403).

Prostate Cancer: Ongoing Trials with ipilimumab

- A phase II trial testing ipilimumab following sipuleucel-T (Provenge) for patients with chemotherapy-naïve metastatic castration resistant prostate cancer (CRPC) (NCT01804465).

- A phase II study of ipilimumab plus androgen suppression therapy in patients with an incomplete response to androgen suppression therapy alone for metastatic prostate cancer (NCT01498978).

- A phase II study combining ipilimumab, androgen deprivation, and surgery in men with newly diagnosed metastatic castration sensitive prostate cancer or ipilimumab and androgen deprivation in men with biochemically recurrent castration sensitive prostate cancer after radical prostatectomy (NCT02020070).

Checkpoint Inhibitors/Immune Modulators for Prostate Cancer: PD/PDL1 blockade

- Still in early stage of clinical studies
- In PD-1 blockade (nivolumab) phase I trials, 17 CRPC patients (with prior Rx) were enrolled. No objective response were reported. (N Eng J Med 2012:366:2455-65). However, recent report showed that one patient had a 28% reduction in measurable lesion.

Prostate Cancer

Other combined Clinical Trials of immune modulators

- A phase II study of sipuleucel-T, CT-011 (anti-PD-1 antibody; CureTech), and cyclophosphamide for advanced prostate cancer (NCT01420965). This study is being conducted at Georgia Regents University in Augusta, Georgia.

- A phase I/II trial of an OX40 antibody (made by AgonOx) for patients with metastatic prostate cancer who have failed prior androgen suppression therapy and docetaxel (NCT01303705). This study is being conducted at Providence Portland Medical Center in Oregon.

- A phase I study of lirilumab (anti-KIR antibody; Bristol-Myers Squibb) in combination with nivolumab (anti-PD-1 antibody; BMS) in patients with advanced solid tumors (NCT01714739). This trial is being conducted at several sites across the U.S.

Completed RCT's of prostate cancer vaccines

Agent (trial)	Outcome	Significance
Sipuleucel-T (D9901)	Prolonged overall survival (25.9 m. vs. 21.4 m) No change in time to progression	*P* = 0.01
Sipuleucel-T (D9902A)	Prolonged overall survival (19 m. vs. 15.7 m) No change in time to progression	*P* = 0.03
Sipuleucel-T (IMPACT)	Prolonged overall survival (25.8 m. vs. 21.7 m) No change in time to progression	*P* = 0.03
PSA-TRICOM (phase 2)	Prolonged overall survival (25.1 m. vs. 16.6 m) No change in time to progression	*P* = 0.01
GVAX (Vital-1)	No difference in overall Survival (20.7 m vs 21.7 m) Prematurely terminated	*P* = 0.80
GVAX (Vital-2)	Overall Survival shorter in vaccine arm (12.2 m vs 14.1 m) Prematurely terminated	*P* = 0.01
Ipilimumab	Approaching significance for overall survival (11.2 m. vs. 10 m) Prolonged overall survival in low risk pts (22.7 m. vs. 15.8 m)[a]	*P* = 0.056 *P* = 0.01[a]

Sobol et al., Current Urology Reports 2015. ***16****:34*

Kidney cancer

- Cytokines IL-2 and IFN-a are the standard immunotherapy for metastatic RCC
- Approximately 5% objective tumor regression
- Approximately 10% stable diseases with small percentage of long lasting CR in response to high dose IL-2

New Perspective immunotherapy for RCC

Modality	Therapy	Clinical Trials	
Checkpoint Blockades	Anti-PD/PDL1	Phase I, II,	NCT02014636 NCT02054806
	Anti-PD/PDL1 +anti-CTLA4	Phase III - metastatic RCC	NCT01975831, 0221749
Vaccine	DC-vaccine AGS-003	Phase III –advanced RCC	NCT01582672
	DCVax	Phase I/II – solid tumor	NCT01882946
	NY-ESO-1	Phase I - solid tumor	NCT01522820
ACT	VEGFR2 -CD8 T	Phase I/II – solid tumor	NCT01218867
	Adoptive NK cells	Phase I/II – solid tumor	NCT00720785
Monoclonal antibody to promote angiogenesis	sonepcizumab (anti-S1P)	Phase II – advanced RCC	NCT01762033
	TRC105 (anti-endoglin)	Phase I/II-advanced RCC	NCT01806064

Bladder Cancer

BCG (weakened live bacterium) immunotherapy:

- First indication of immunotherapy for cancer
- Approved by FDA in 1990
- Standard therapy for non-muscle invasive bladder cancer
- Approximately 70% remission rate
- How does it stimulate anti-tumor immune response?
  – detailed mechanisms are not well-understood

Current immunotherapy trials for bladder cancer

CG0070	Oncolytic adenovirus engineerd to express GM-CSF	Phase II/III for non-muscle invasive BCG-unresponsive
MPDL3280A	Anti-PDL1 antibody	Metastatic bladder cancer - Phase I showed 52% response in tumor shrinkage - Phase II in progress
HS-410	Vaccine made from irradiated human bladder cancer cell line that engineered to express gp96 tumor antigen presenting chaperone protein	Phase I/II for non-muscle invasive bladder cancer, post surgery therapy
ALT-801	Fusion of IL-2 with tumor antigen-specific antibody	Phase I/II for non-muscle invasive bladder cancer BCG un-responsive cancer

Open question for GU malignancy

To date evidence suggest that immunotherapy can be effective to treat GU malignancy.

The open question is:

What are

1) **the best “window”**

2) **best combination**

to achieve durable responses to control metastasis?

Pre and Post Questions:

1. Which of the following is correct pertaining current immunotherapy for GU malignancy?

a. There is evidence that all GU malignancies can be responsive to immunotherapy.

b. Prostate cancer is not responsive to PD-1 check point blockade.

c. All blade cancer patients should be given BCG therapy.

d. Renal Cancer is the most investigated GU malignancy for PD-1 checkpoint blockade therapy.

Pre and Post Questions:

2. Provenge is the first FDA approved cancer vaccine. Which of the following state is correct?

a. Provenge is intended to treat all stages of prostate cancer patients.

b. Provenge is intended to treat metastatic castration-resistant prostate cancer after failure of standard therapy

c. Provenge is intended to treat no or minimal symptomatic castration-resistant prostate cancer

d. Patients can be treated with Provenge in any Medical Center