# Cancer vaccines

***from ex vivo production to in vivo vaccination***


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# I have no financial relationships to disclose

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# Learning goals

1. **Understanding the stumbling blocks and requirements for the design of successful therapeutic vaccines: choice of antigens and adjuvants**

2. **Becoming familiar with some of the current approaches to vaccination against cancer: broader definition includes *in vivo* vaccination**

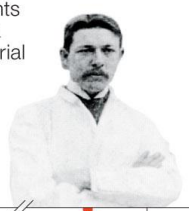
3. **Acquiring an understanding of the positioning of cancer vaccines in the developing field of cancer immunotherapy**

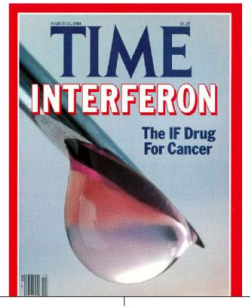
# Cancer Immunotherapy: a bit of history

## WAKING THE BODY'S DEFENDERS

***For more than a century, researchers have tried to harness the human immune system to fight cancer. But high hopes, too often, have been followed by disappointment. Here, some milestones.***

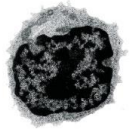
New York surgeon **William Coley** tries to rev up immune response to cancer by injecting patients with a bacterial stew.






*Time* crowns **Interferon,** a human immune substance, "The Big IF in Cancer."

NCI's Steven Rosenberg describes treatment in which a patient's re-engineered **lymphocytes** fight cancer.

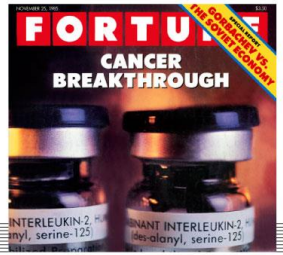


FDA approves Merck's Gardasil, first vaccine against **human papillomavirus,** which can cause cervical cancer.

Bristol's **Yervoy** gets FDA nod.


1890 1960 1970 1980 1990 2000 2010

Scientists posit **"immunosurveillance theory"** that says the immune system is always finding and destroying cancer cells; when it fails, tumors can grow.




*Fortune* runs cover story on immune-boosting molecule **interleukin-2.** Calls it a "Cancer Breakthrough."

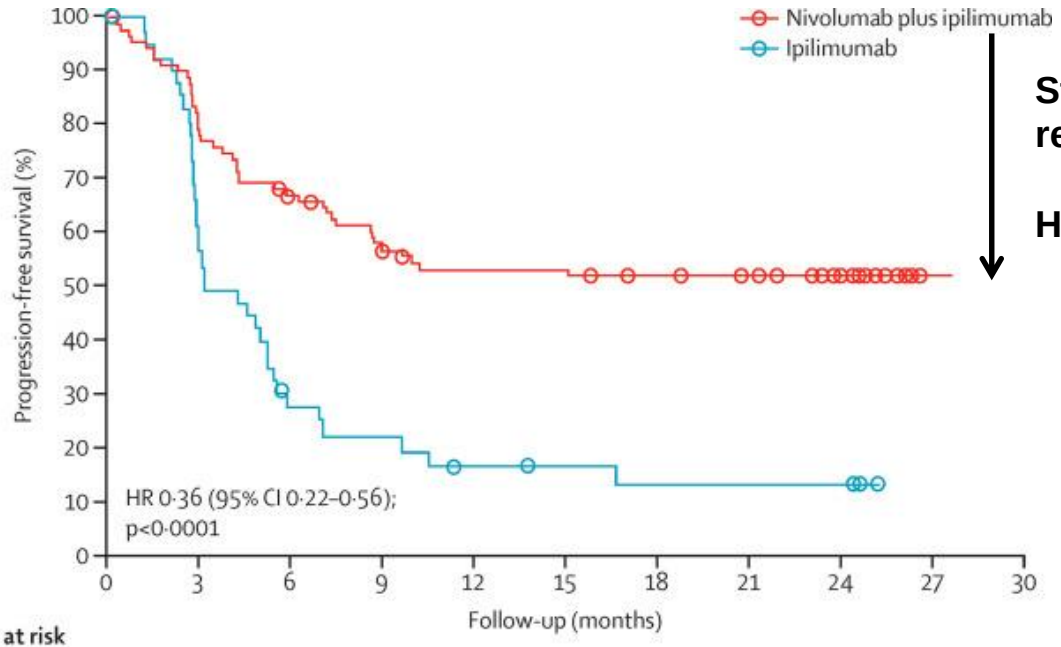
Jim Allison publishes study suggesting that blocking **CTLA-4** in mice unleashes immune cells to fight tumors.

FDA okays Dendreon's Provenge for **metastatic prostate cancer,** the first therapeutic cancer vaccine approved.

*Science* calls **cancer immunotherapy** the "breakthrough of the year."

http://fortune.com/2014/06/02/fortune-500-bristol-myers/

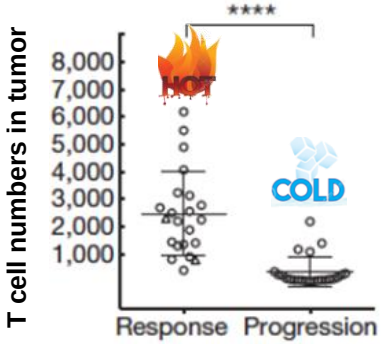
# The promise of cancer immunotherapy: durable responses




| Number at risk (censored) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab plus ipilimumab | 95 (0) | 69 (5) | 58 (7) | 47 (9) | 43 (10) | 43 (10) | 40 (12) | 38 (14) | 24 (28) | 2 (50) | 0 (52) |
| Ipilimumab | 47 (0) | 22 (6) | 10 (7) | 8 (7) | 5 (8) | 4 (9) | 3 (9) | 3 (9) | 3 (9) | 0 (12) | 0 (12) |

**Still…not everyone responds.**

**How come?**




**T cell infiltration: role for vaccination!**

*Hodi et al. Lancet Oncol 2016*
*Tumeh et al Nature 2014*

# Cancer vaccination: the basics (definitely not passive!)

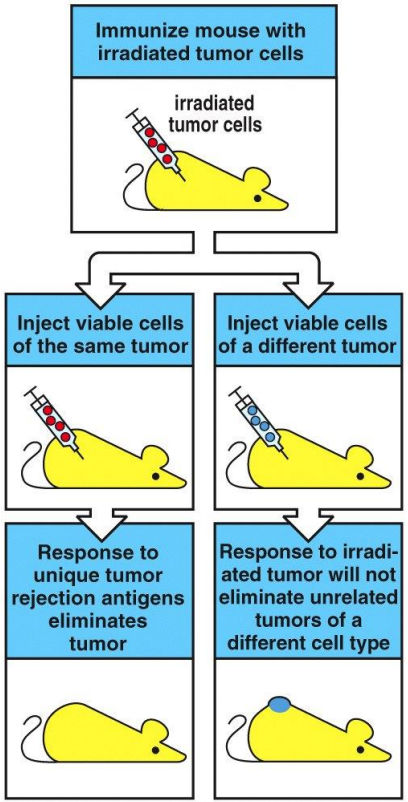



Figure 14-10 Immunobiology, 6/e. (© Garland Science 2005)

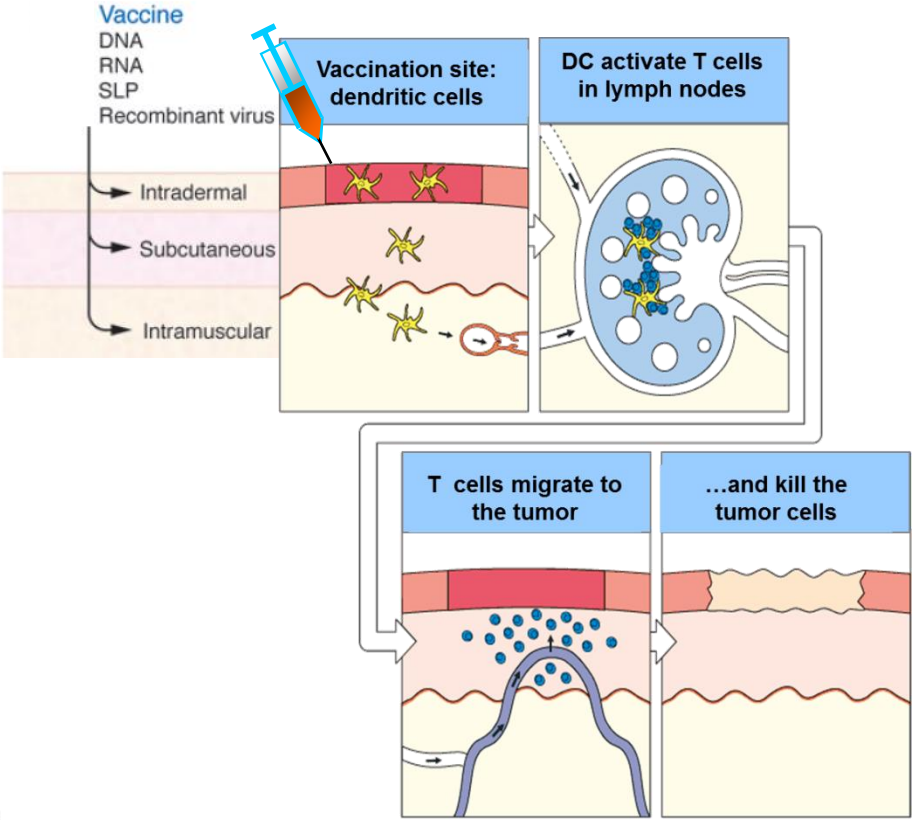
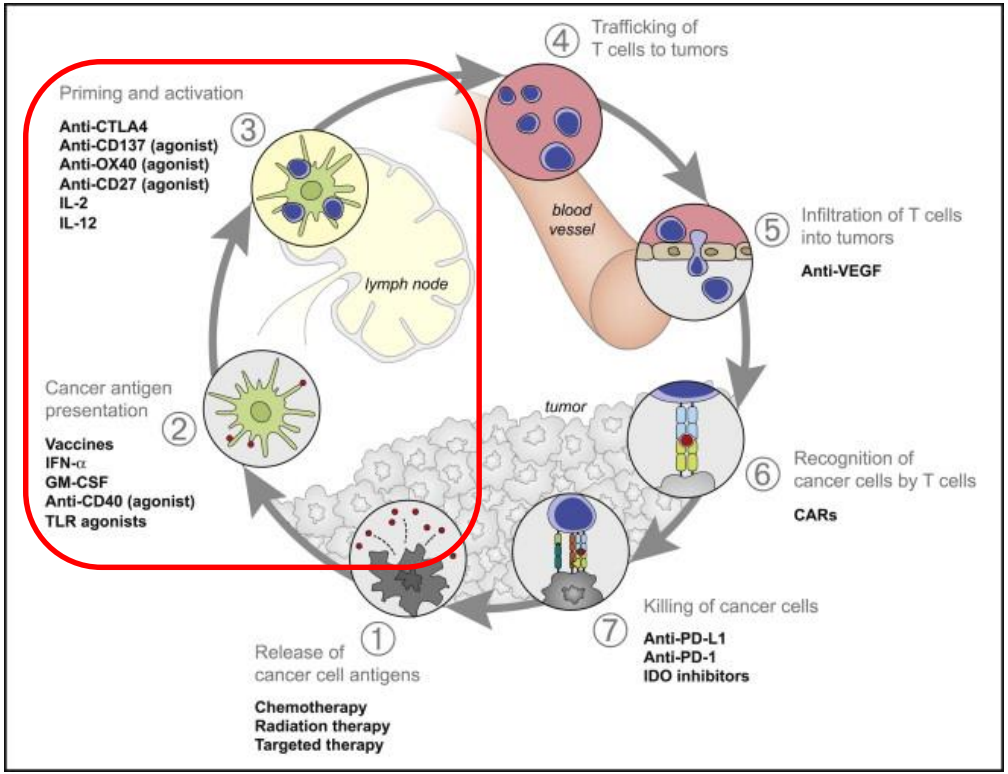



Fig 13.26 © 2001 Garland Science

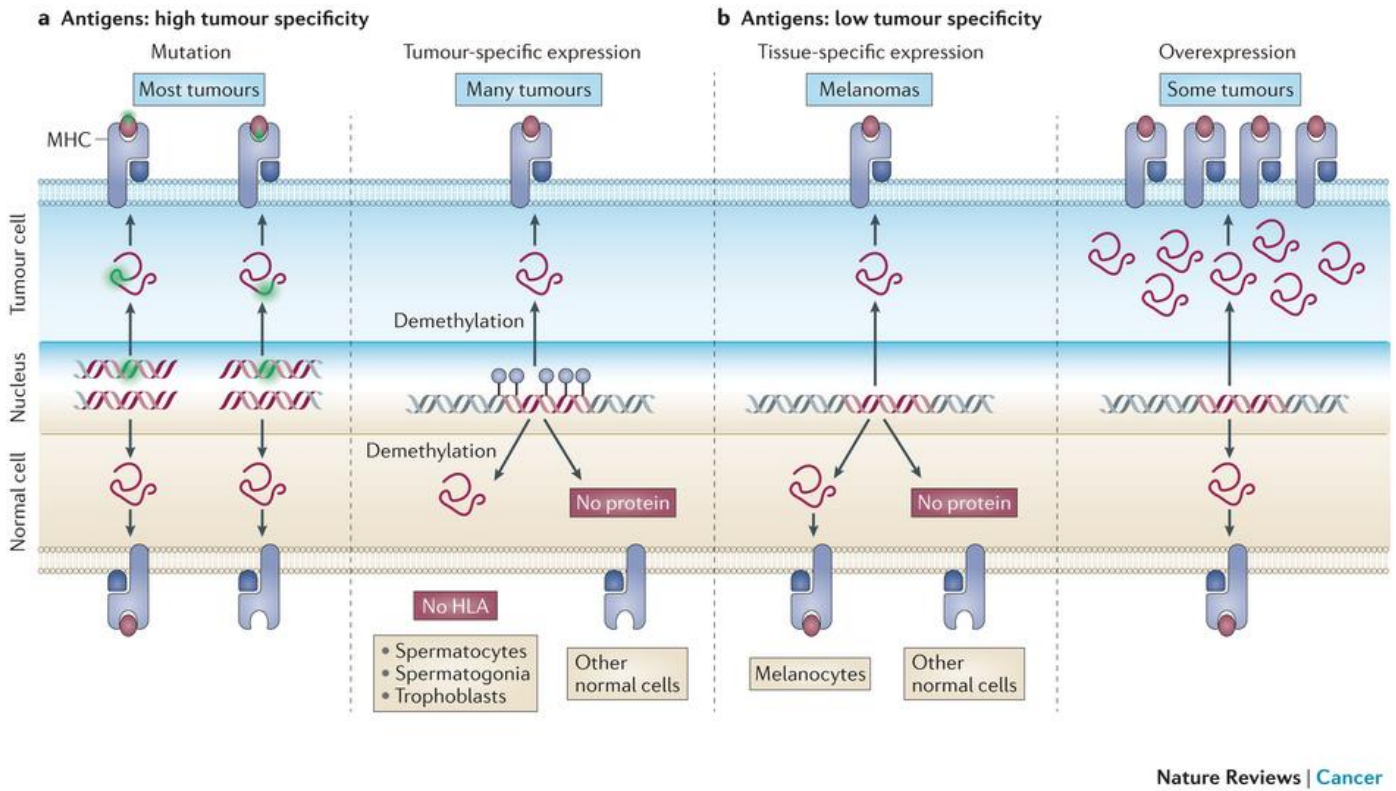
# Cancer Immunotherapy: therapeutic windows

vaccination



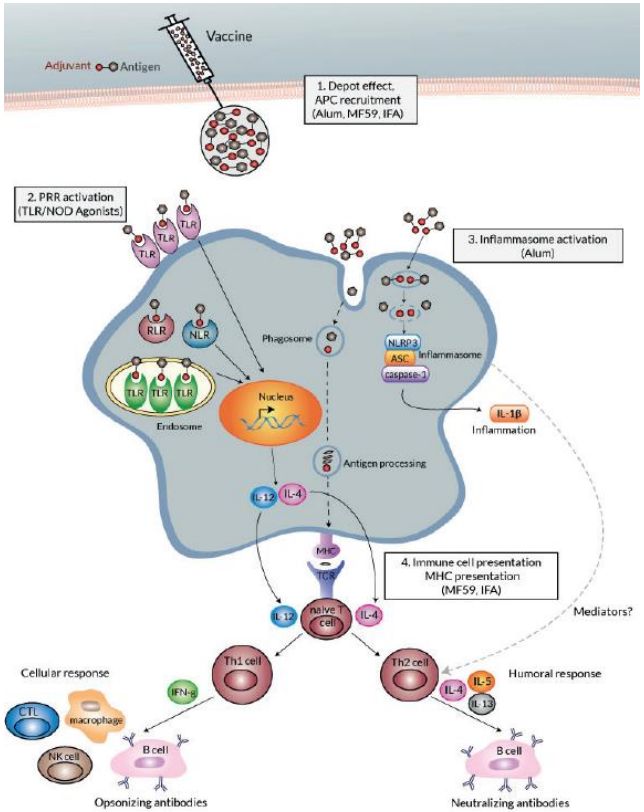

*Chen et al. Immunity. 2013 Jul 25;39(1):1-10.*

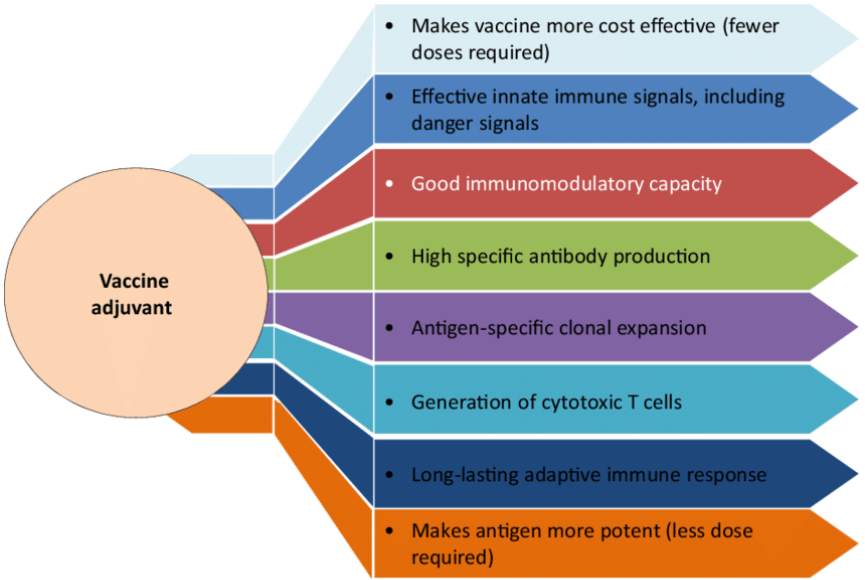
# Vaccine=Antigen+Adjuvant




Coulie *et al. Nature Reviews Cancer* 14:135-46, 2014

# Vaccine=Antigen+Adjuvant




Trends in Pharmacological Sciences

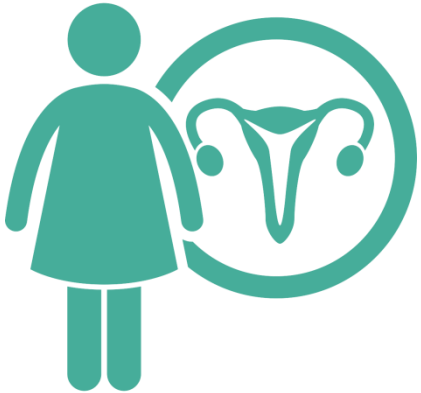
Review
InvivoGen

*Bonam et al. 2017*

# Successful (cancer) vaccines: prophylactic and antibody based

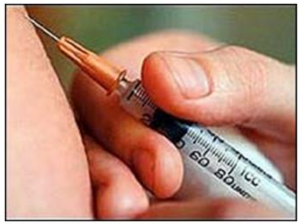
Doug Lowy & John Schiller

**Prophylactic and active:**



BBC NEWS UK EDITION

## Cervical cancer jab 'in a year'



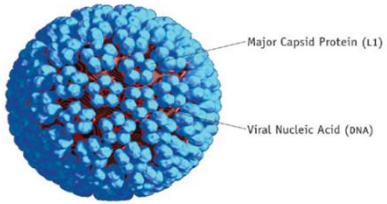
**A vaccine shown to be 100% effective against two virus strains that cause most cervical cancer could be available within a year, say manufacturers.**

Gardasil worked against the sexually transmitted human papillomavirus (HPV).
Some 12,167 women aged 16 to 23 from 13 countries, including the UK, took part in the drug company study.

Researchers believe a vaccine could work best if given before adolescence, but critics fear this could encourage under-age sex.

Merck's vaccine is in head-to-head competition with a rival from UK-based GlaxoSmithKline called Cervarix.

The two-year Future II trial found Gardasil was ***100% effective at preventing early stage cancers and pre-cancerous abnormalities*** caused by the two key strains of HPV - the 16 and 18 strains - which cause 70% of cervical cancers.

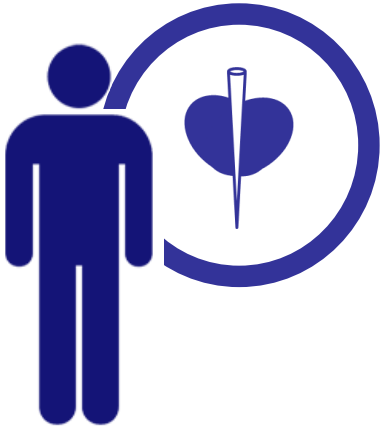


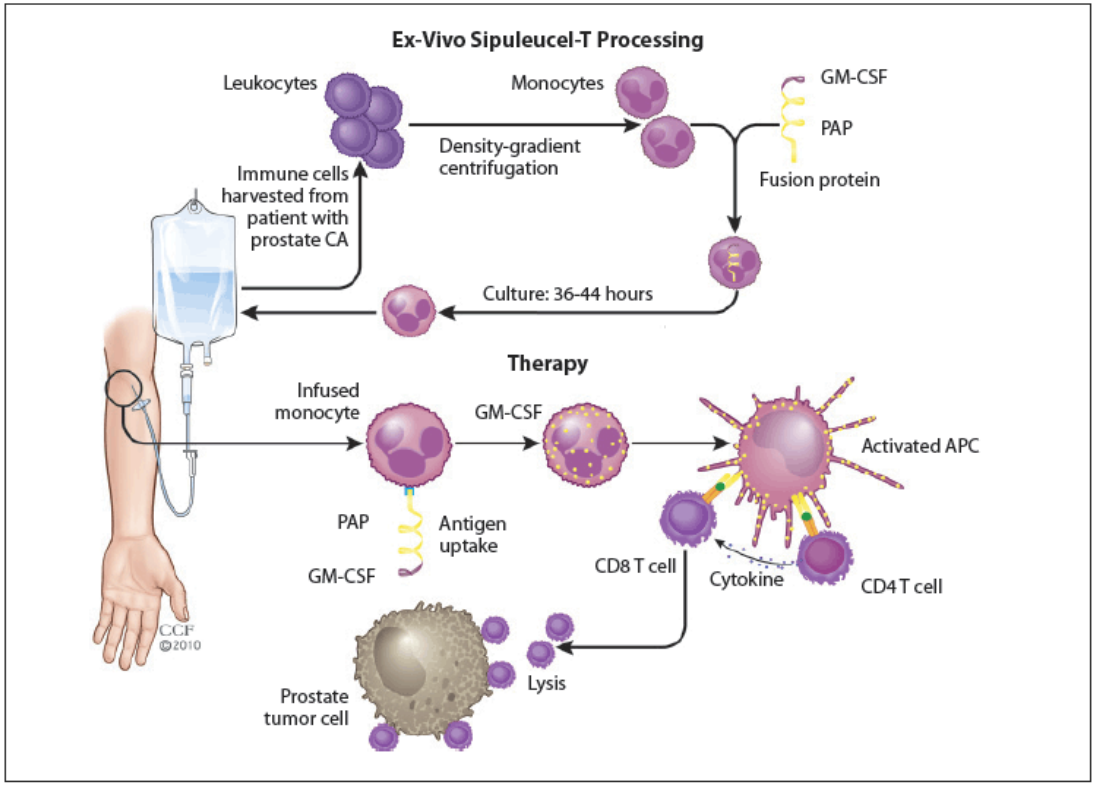

Friday, 7 October 2005, 04:31 GMT 05:31 UK

https://library.nshealth.ca/Cancer/Screening

# More challenging cancer vaccines: therapeutic and T cell based

**Therapeutic and active:**






*http://www.cancernetwork.com/prostate-cancer/immunotherapy-castration-resistant-prostate-cancer-integrating-sipuleucel-t-our-current-treatment*

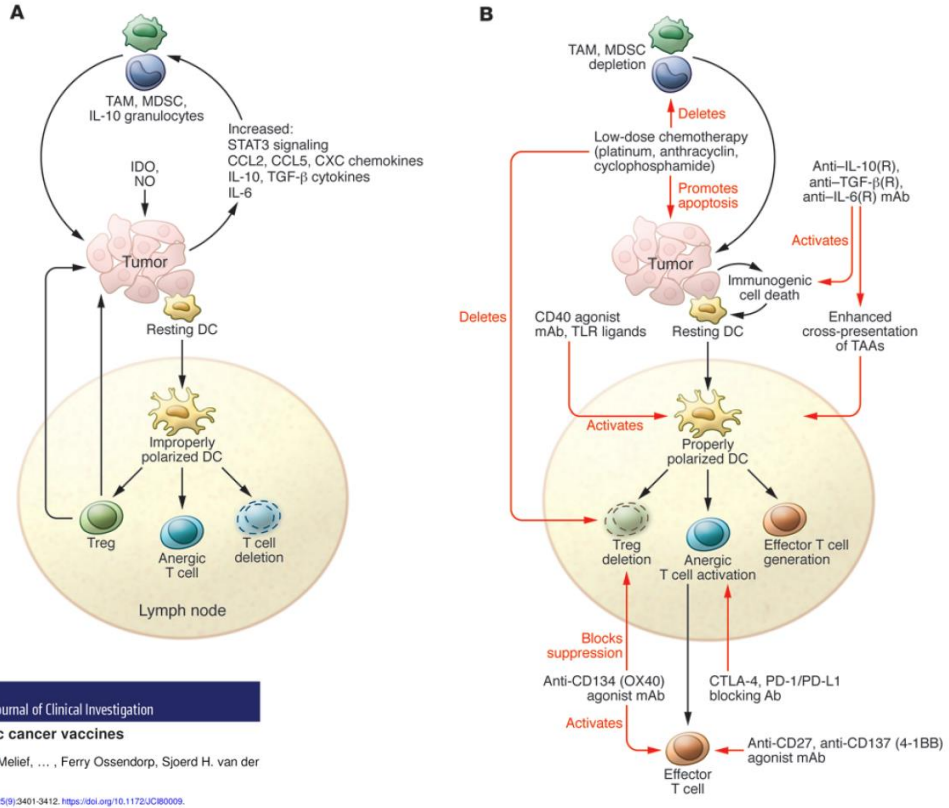
# The trouble with therapeutic cancer vaccines…

## Rosenberg *et al* Nat Med 2004

**Table 5 Results of clinical vaccine studies in patients with metastatic cancers**

| Vaccine type | Reference | Cancer type | Vaccine | Total patients | Patients responding |
|---|---|---|---|---|---|
| Peptide | 43 | Melanoma | Tyrosinase + GMCSF | 16 | 0 |
| | 44 | Melanoma | Peptides in IFA or on DC | 26 | 3 |
| | 45 | Melanoma | MART-1 + IL-12 | 28 | 2 |
| | 46 | Prostate | Peptides | 10 | 0 |
| | 47 | Melanoma | Peptides on PBMC + IL-12 | 20 | 2 |
| | 48 | Breast and prostate | Telomerase | 7 | 0 |
| | 49 | Cervix | HPV16 E7 | 17 | 0 |
| | 50 | Colorectal | Peptides in IFA | 10 | 0 |
| | 51 | Multiple | NY-ESO-1 | 12 | 0 |
| | 52 | Multiple | Ras in DETOX adjuvant | 15 | 0 |
| | 53 | Multiple | Peptides in IFA | 14 | 0 |
| Virus | 29 | Prostate | Vaccinia-PSA | 33 | 0 |
| | 54 | Prostate | Vaccinia-PSA | 42 | 0 |
| | 55 | Colorectal | Vaccinia-CEA | 20 | 0 |
| | 56 | Colorectal | Vaccinia-CEA and B7-1 | 18 | 0 |
| | 57 | Multiple | Avipox-CEA (IGMCSF) | 60 | 0 |
| | 58 | Multiple | Avipox-CEA | 15 | 0 |
| | 59 | Multiple | Vaccinia + avipox-CEA | 18 | 0 |
| Tumor cells | 60 | Melanoma | Transduced with GM-CSF | 26 | 1 |
| | 61 | Melanoma | Membranes on silicone beads | 17 | 1 |
| | 62 | Lung | Transduced with GMCSF | 26 | 1 |
| | 63 | Lung | Transduced with GMCSF | 43 | 3 |
| | 64 | Breast | Transduced with B7-1 | 30 | 0 |
| Dendritic cells | 65 | Melanoma | Pulsed with peptides | 17 | 0 |
| | 66 | Melanoma | Pulsed with peptides or lysates | 33 | 3 |
| | 67 | Melanoma | Pulsed with peptides or lysates | 16 | 5 |
| | 68 | Melanoma | Pulsed with peptides | 24 | 1 |
| | 22 | Melanoma | Pulsed with MAGE-3A1 peptide | 11 | 0 |
| | 69 | Childhood cancers | Pulsed with lysates | 15 | 1 |
| | 70 | Kidney | Transfected with RNA | 15 | 0 |
| | 71 | Colorectal | Pulsed with CEA peptides | 12 | 1 |
| | 72 | Kidney | Pulsed with tumor lysates | 35 | 3 |
| | 23 | Multiple | Pulsed with tumor lysates | 20 | 0 |
| Heat shock protein | 73 | Melanoma | Hsp-96 | 28 | 2 |
| | 74 | Multiple | Hsp-96 | 16 | 0 |
| | | | Total | 765 | 29 |

Objective response rate = 3.8%




JCI The Journal of Clinical Investigation
**Therapeutic cancer vaccines**
Cornelis J.M. Melief, … , Ferry Ossendorp, Sjoerd H. van der Burg
*J Clin Invest.* 2015;125(9):3401-3412. https://doi.org/10.1172/JCI80009.

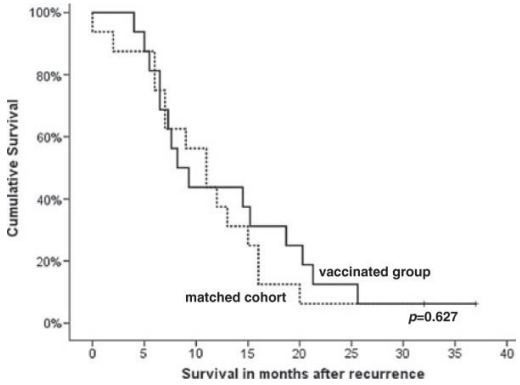
# One solution: go early

## HPV16 SLP vaccine in VIN: 16/20 PR/CR

## …but in cancer: none!

Table 3. Clinical Results at 3, 12, and 24 Months after the Last Vaccination.*

| Patient No. | No. of Vaccinations | At 3 Months | | | | At 12 Mo | | At 24 Mo |
|---|---|---|---|---|---|---|---|---|
| | | Symptoms | Lesion Response | Histologic Findings | Type of HPV Infection | Symptoms | Lesion Response | Lesion Response |
| 1 | 4 | Mild to moderate | Partial | VIN 2 | 16 | Mild to moderate | Partial | Partial† |
| 2 | 4 | Severe | None | VIN 3 | 16 | | Carcinoma | |
| 3 | 4 | Severe | None | VIN 3 | 16 | None | Partial | Partial‡ |
| 6 | 4 | None | Complete | Normal | 16 | None | Complete | Complete |
| 7 | 4 | None | Complete | Normal | None | None | Complete | Complete |
| 8 | 4 | Mild to moderate | Complete | Normal | 6b | None | Complete§ | Complete |
| 9 | 3 | None | Complete | Normal | None | None | Complete | Complete |
| 10 | 4 | None | Partial | VIN 3 | 16 | Lost to follow-up¶ | | |
| 11 | 4 | None | None | VIN 3 | 16 | None | Complete | Complete |
| 12 | 4 | Mild to moderate | None | VIN 3 | 16 | Mild to moderate | Partial | None‖ |
| 13 | 4 | Mild to moderate | Partial | VIN 3 | 16 | Mild to moderate | Partial | Partial |
| 16 | 4 | Mild to moderate | Partial | VIN 1 | 16 | Mild to moderate | Complete | Complete |
| 18 | 4 | Severe | None | VIN 3 | 16 | Severe | None | None |
| 22 | 4 | Mild to moderate | None | VIN 3 | 16 | Severe | Partial | Partial |
| 23 | 4 | Mild to moderate | Partial | VIN 2 | 16 | None | Partial | Microinvasive carcinoma** |
| 26 | 4 | None | None | VIN 3 | 16 | None | None | None |
| 27 | 3 | None | Partial | VIN 3 | 16 | None | Complete | Complete |
| 28 | 4 | None | None | VIN 3 | 16 | None | None | None |
| 29 | 4 | None | Complete | Normal | None | None | Complete | Complete |
| 30 | 4 | Mild to moderate | Partial | VIN 2 | 16 | None | Complete | Complete |




Vaccination against HPV-16 Oncoproteins for Vulvar Intraepithelial Neoplasia

Gemma G. Kenter, M.D., Ph.D., Marij J.P. Welters, Ph.D., A. Rob P.M. Valentijn, Ph.D., Margriet J.G. Lowik, Dorien M.A. Berends-van der Meer, Annelies P.G. Vloon, Farah Essahsah, Lorraine M. Fathers, Rienk Offringa, Ph.D., Jan Wouter Drijfhout, Ph.D., Amon R. Wafelman, Ph.D., Jaap Oostendorp, Ph.D., Gert Jan Fleuren, M.D., Ph.D., Sjoerd H. van der Burg, Ph.D., and Cornelis J.M. Melief, M.D., Ph.D.

N Engl J Med 2009;361:1838-47.



van Poelgeest et al. Journal of Translational Medicine 2013, 11:88
http://www.translational-medicine.com/content/11/1/88

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

HPV16 synthetic long peptide (HPV16-SLP) vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carcinoma, a phase II trial

Mariette I E van Poelgeest[1†], Marij J P Welters[2†], Edith M G van Esch[1], Linda F M Stynenbosch[2], Gijs Kerpershoek[1], Eb L van Persijn van Meerten[1], Muriel van den Hende[1], Margriet J G Löwik[1], Dorien M A Berends-van der Meer[1], Lorraine M Fathers[3], A Rob P M Valentijn[4], Jaap Oostendorp[2], Gert Jan Fleuren[5], Cornelis J M Melief[2,6], Gemma G Kenter[1,6*] and Sjoerd H van der Burg[2*†]

# Another solution: optimizing vaccines and combination therapies

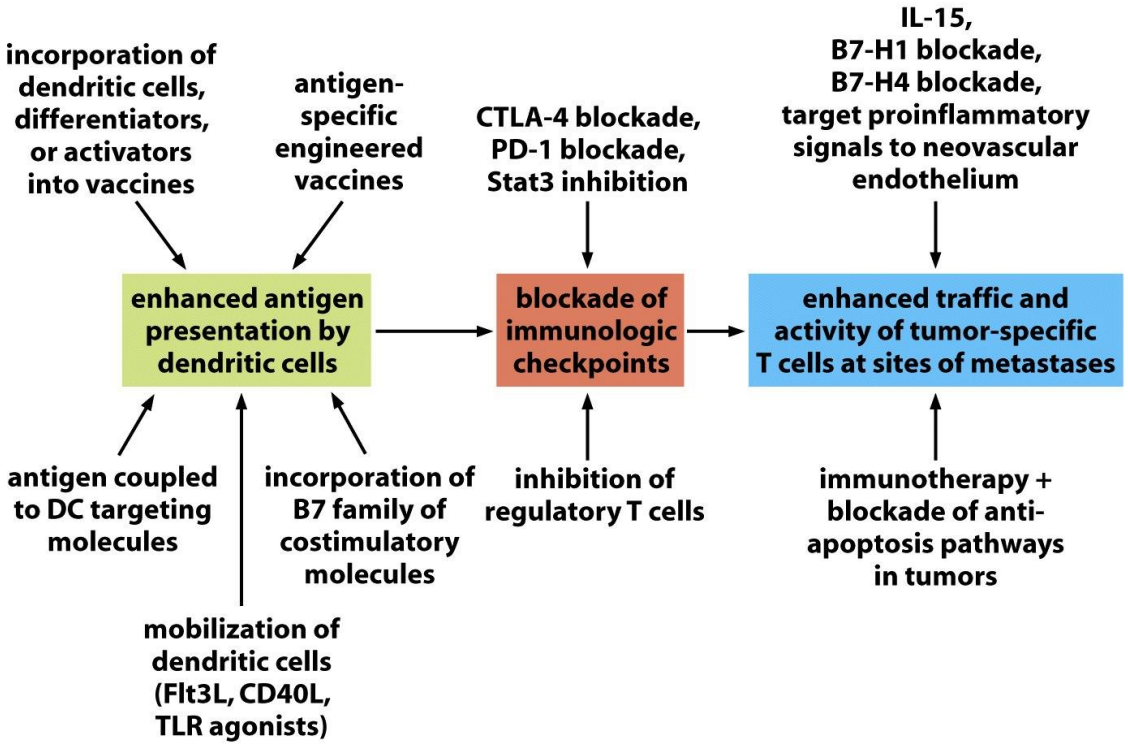
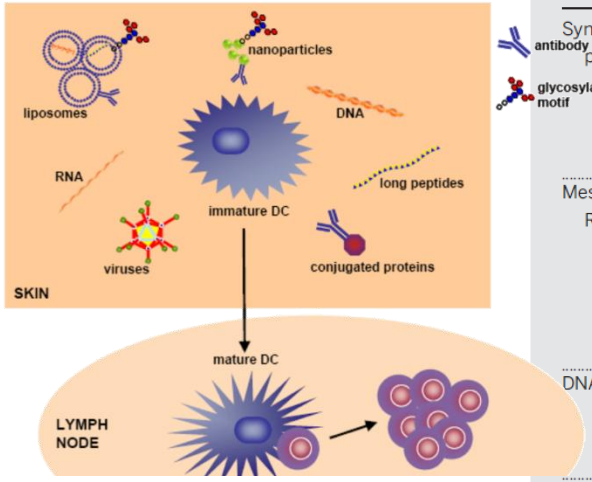



*Figure 15.45 The Biology of Cancer (© Garland Science 2007)*

# Cancer vaccine formulations and choice of adjuvant




*Oosterhoff et al. in: T.J. Curiel (ed.), Cancer Immunotherapy, 2013*

antibody

glycosylation motif

| Vaccine format | Advantages | Challenges |
|---|---|---|
| Synthetic peptides (*45*) | Cell-free manufacturing<br>Automated synthesis established<br>Proven clinical activity of long peptides<br>Compatible with a wide range of formulations to improve delivery<br>Transient activity and complete degradation | Lack of clinical-grade manufacturability of a substantial portion of sequences<br>High variability in the physicochemical properties of individual peptides, complicating manufacturing<br>Irrelevant immune responses against artificial epitopes created by peptide degradation in the extracellular space |
| Messenger RNA (*46*) | Cell-free manufacturing<br>Inherent adjuvant function via TLR7, TLR8, and TLR3 signaling<br>Proven clinical activity<br>Highly efficient systemic delivery into DCs established<br>Transient activity and complete degradation<br>All types of epitopes can be encoded | Fast extracellular degradation of mRNA if not protected by appropriate formulation<br>Interpatient variability of TLR7-driven adjuvant activity |
| DNA plasmids (*47*) | Cell-free manufacturing<br>Inherent adjuvant activity driven by TLR9<br>Cost-effective and straightforward manufacturing<br>All types of epitopes can be encoded | Potential safety risks by insertional mutagenesis<br>Successful transfection requires entry into nucleus, thereby limiting effective delivery of vaccines into DCs |
| Viral vectors (*48*) (adenoviral and vaccinia) | Strong immunostimulatory activity Extensive clinical experience with vector formats in the infectious disease field All types of epitopes can be encoded | Complex manufacturing<br>Immune responses against components of the viral vector backbone, limiting successful in vivo vaccine delivery and efficacy |
| Engineered attenuated bacterial vectors (*49*) (*Salmonella*, *Listeria*) | Strong immunostimulatory activity<br>Could be combined with plasmid DNA<br>All types of epitopes can be encoded | Complex manufacturing and "sterility" testing<br>Immune responses against bacterial components, limiting vaccine delivery and vaccine immunogenicity Potential safety risks due to delivery of live, replication-competent bacteria |
| Ex vivo antigen-loaded DCs (*50*) | Strong immunostimulatory activity<br>Proven clinical efficacy of DC vaccines<br>Can be loaded with various antigen formats | Higher costs and resources required for adoptive cell therapy approaches |

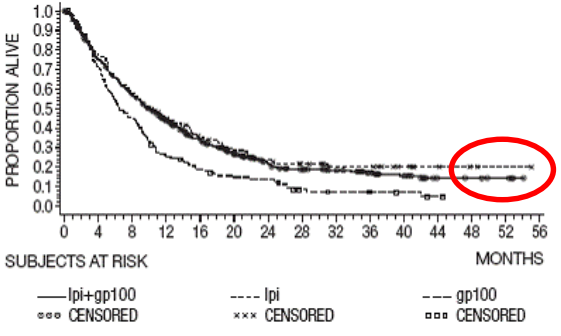
Science

**Personalized vaccines for cancer immunotherapy**

Ugur Sahin and Özlem Türeci

*Science* **359** (6382), 1355-1360.

# Cancer vaccine formulations: avoid depot formation

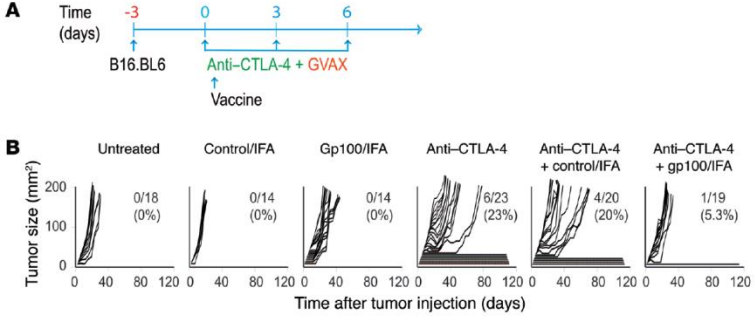



3 weeks for four treatments. In the vaccine groups, patients received two modified HLA-A*0201–restricted peptides, injected subcutaneously as an emulsion with incomplete Freund's adjuvant (Montanide ISA-51): a gp100:209-217(210M) peptide, 1 mg injected in the right anterior thigh, and a gp100:280-288(288V) peptide, 1 mg injected in the left anterior thigh.


The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 19, 2010

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

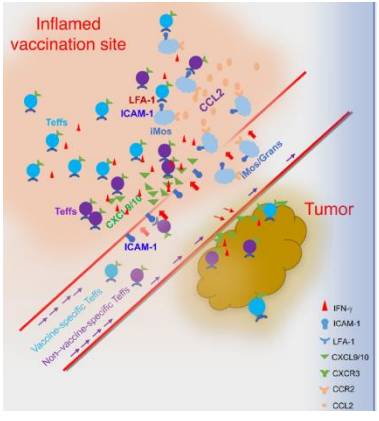


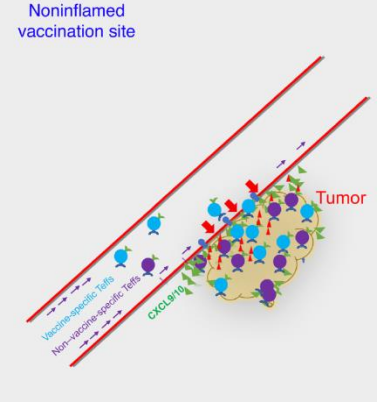

JCI The Journal of Clinical Investigation

**Cancer vaccine formulation dictates synergy with CTLA-4 and PD-L1 checkpoint blockade therapy**

Yared Hailemichael, … , Victor H. Engelhard, Willem W. Overwijk

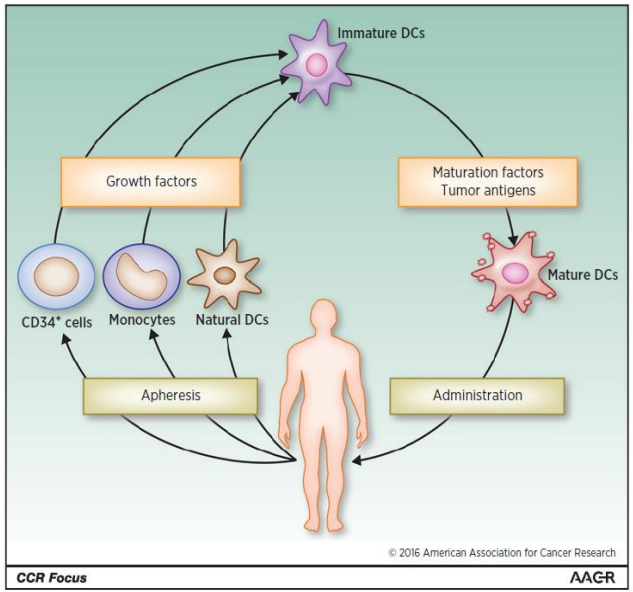
*J Clin Invest.* 2018;128(4):1338-1354. https://doi.org/10.1172/JCI93303.

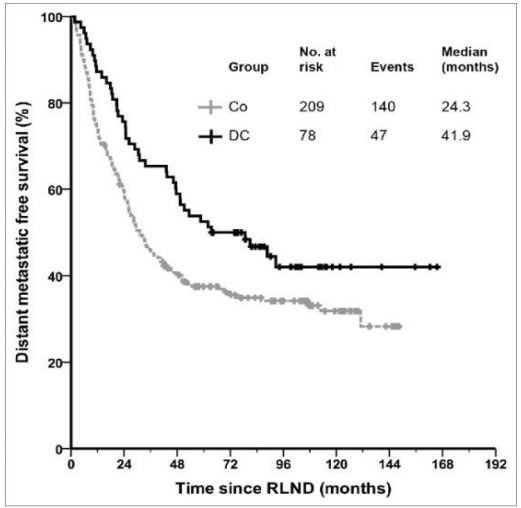


# Dendritic cell vaccines: classic approach

http://www.scharfphoto.com/fine_art_prints/archives/000605.php




CCR FOCUS

**Dendritic Cell–Based Immunotherapy: State of the Art and Beyond**

Kalijn F. Bol[1,2], Gerty Schreibelt[1], Winald R. Gerritsen[2], I. Jolanda M. de Vries[1,2], and Carl G. Figdor[1]

Clin Cancer Res; 22(8) April 15, 2016

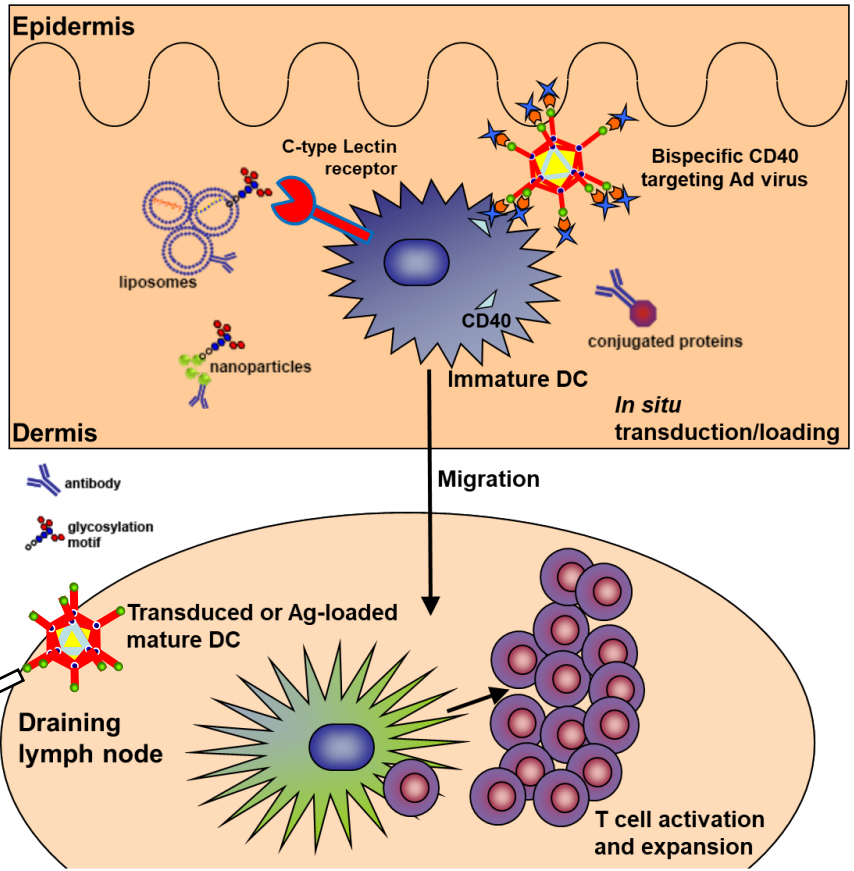
ORIGINAL RESEARCH

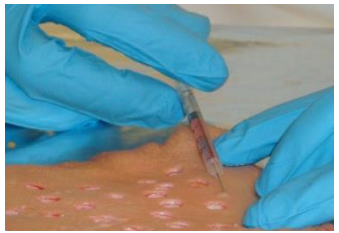
**Favorable overall survival in stage III melanoma patients after adjuvant dendritic cell vaccination**

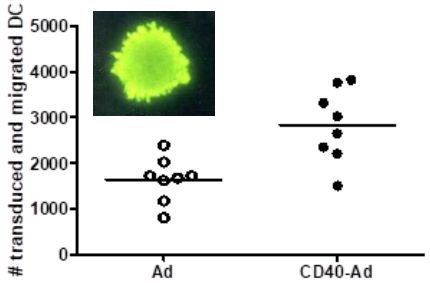
Kalijn F Bol[1,2], Erik H J G Aarntzen[1,2,3], Florentien E M in 't Hout[1,4], Gerty Schreibelt[1], Jeroen H A Creemers[1], W Joost Lesterhuis[1,5], Winald R Gerritsen[2], Dirk J Grunhagen[6], Cornelis Verhoef[6], Cornelis J A Punt[2], Johannes J Bonenkamp[6], Johannes H W de Wilt[4], Carl G Figdor[1], and I Jolanda M de Vries[1,2*]

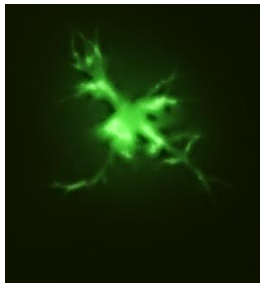
# Alternative DC vaccines: *in vivo* targeting

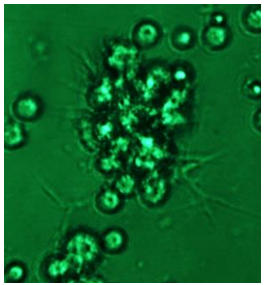
Hangalapura *et al. Cancer Res 2011, J Gene Med 2012*

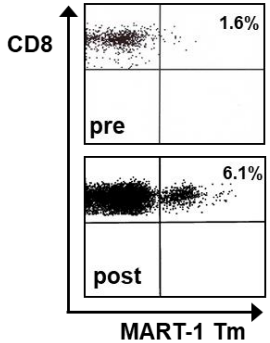


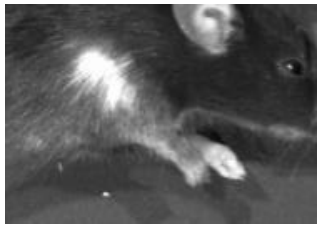









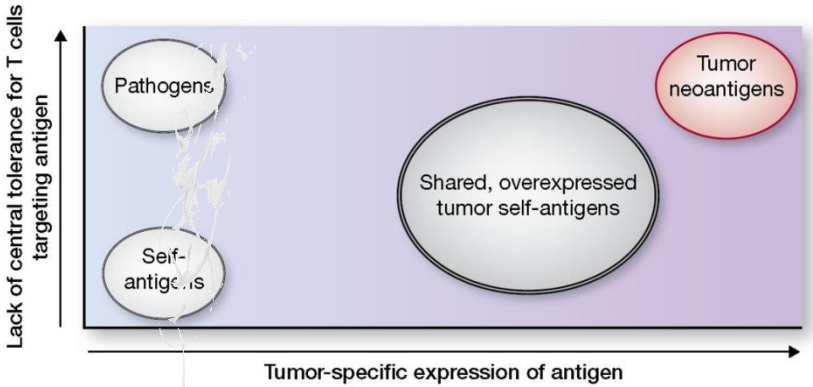
# DC vaccines: what subset to target?

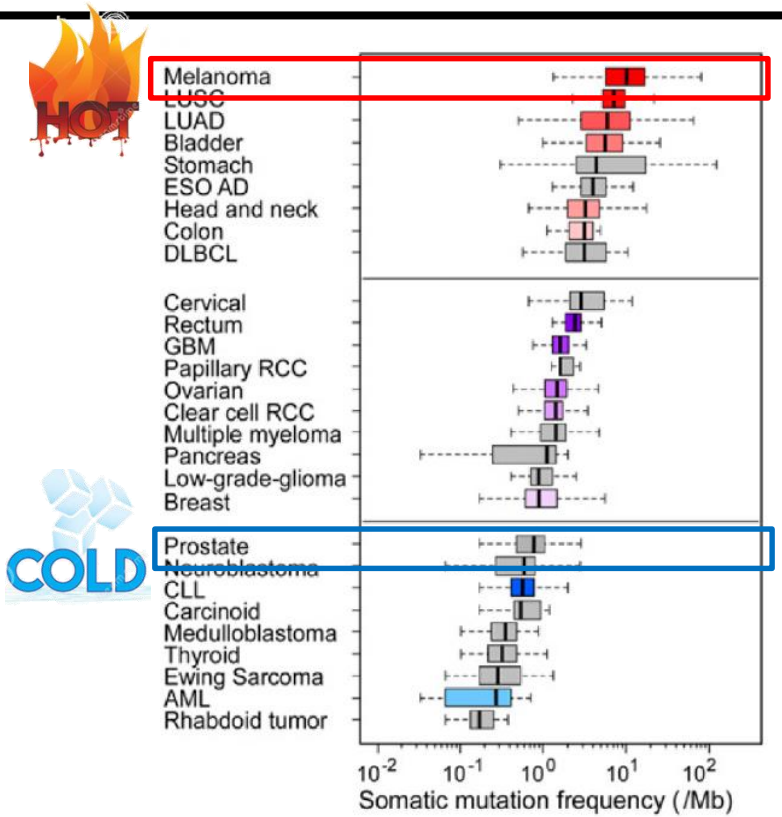
| Blood | Pre-cDC | | pDC | Classical monocyte |
|---|---|---|---|---|
| Lymphoid and non-lymphoid tissues | | | | |
| **HUMAN** | **CD141(BDCA3)$^+$ cDC** | **CD11c(BDCA1)$^+$ cDC** | **pDC** | **moDC** |
| |  |  |  |  |
| **Other markers** | XCR1$^+$<br>CLEC9A$^+$<br>FLT3$^+$ | CD172a$^+$<br>CD11b$^+$<br>FLT3$^+$ | CD303(BDCA2)$^+$<br>CD85g(ILT7)$^+$<br>FLT3$^+$ | CD14$^+$<br>CD206$^+$<br>FLT3$^{-/low}$ |
| **Proposed conserved functional specification** | TLR3-induced IFN-III production<br>High efficiency for CD8$^+$ T cell activation?<br>Cross-presentation of cell-associated antigens | Presentation of exogenous antigens to CD4$^+$ T cells<br>Th2 or Th17 induction? | TLR7/9-induced IFN-I/III production<br>Innate defenses against viruses? | Innate defenses against infections through TNF, ROI, NOI production?<br>Humoral immunity to extracellular pathogens? Th17 induction? |

*Dalod et al. 2014*

# Choice of antigens: what do T cells react to in tumors?

*Hacohen et al.*
*CIR 2013*




*Rajasagi et al Blood 2014*

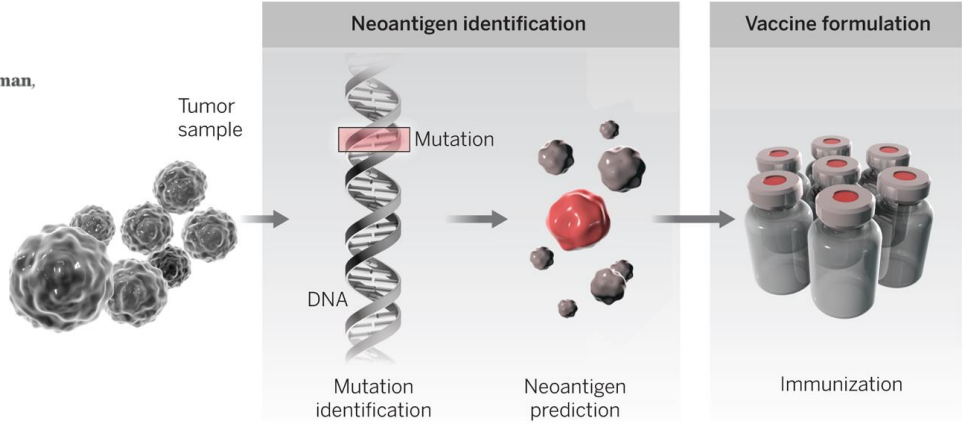
# Classic vaccines with novel antigens: personalized!

CANCER IMMUNOTHERAPY

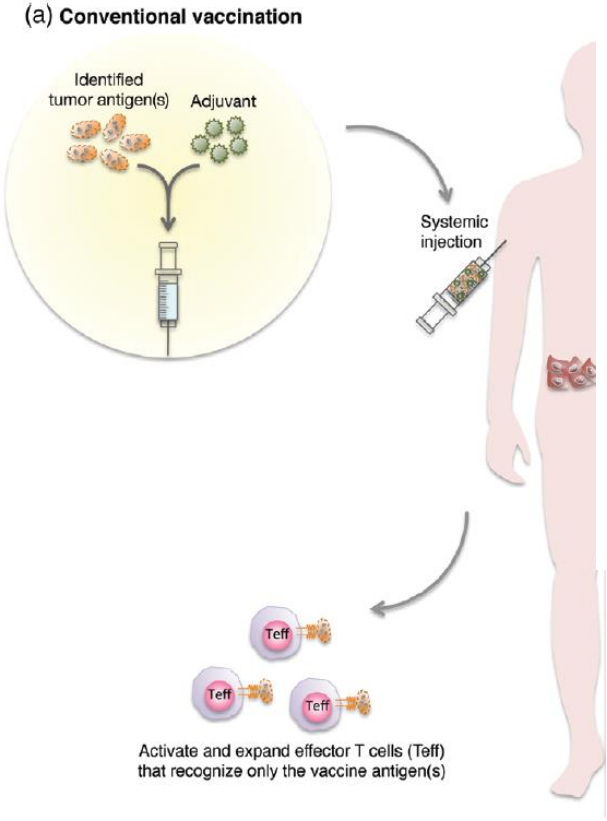
## *Neo approaches to cancer vaccines*

A neoantigen-based vaccine elicits T cell responses in cancer patients

By **Lélia Delamarre, Ira Mellman, Mahesh Yadav**

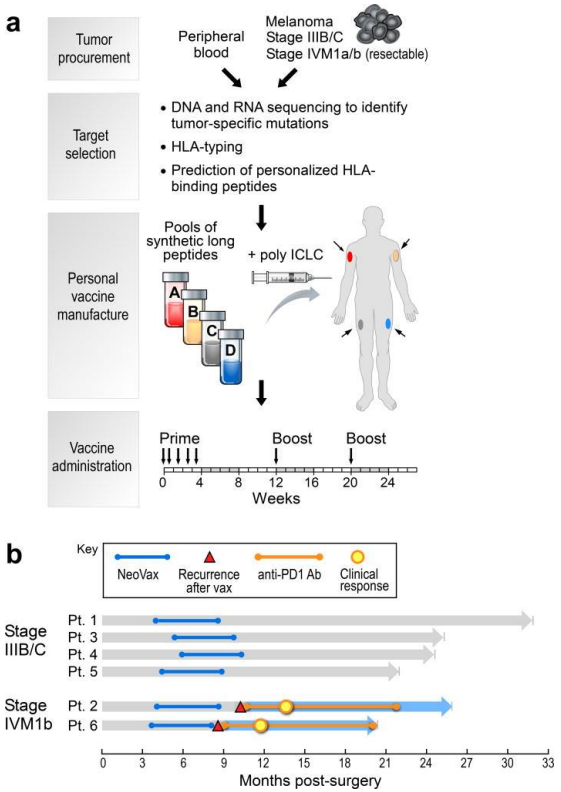



15 MAY 2015 • VOL 348 ISSUE 6236
sciencemag.org SCIENCE




SHEEN AND FIERING *WIREs Nanomed Nanobiotechnol.* 2018;e1524.

# Neoantigen vaccines



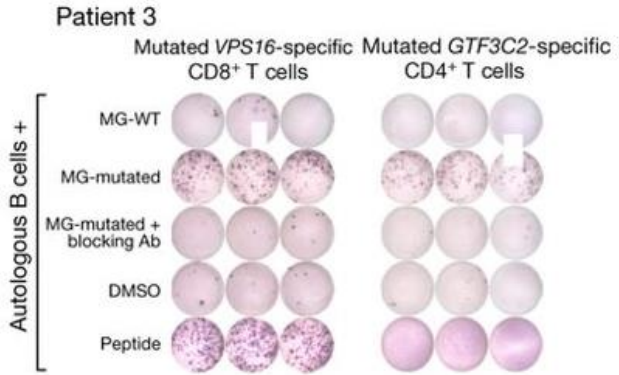

LETTER

doi:10.1038/nature22991

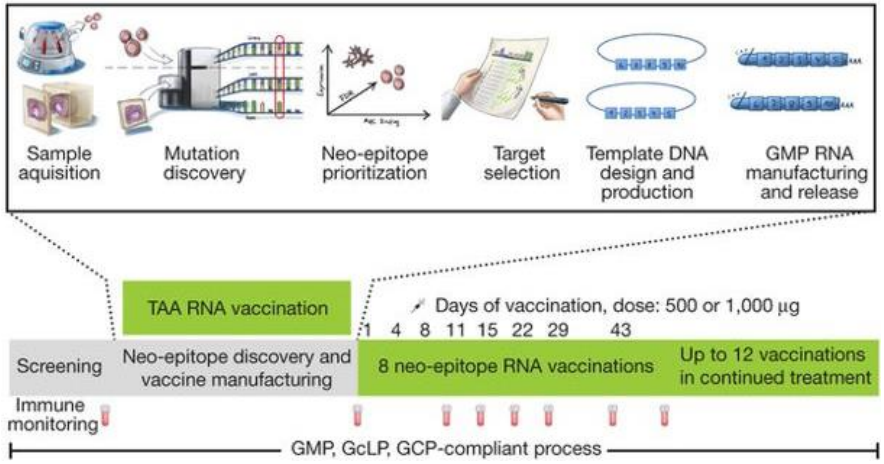
## An immunogenic personal neoantigen vaccine for patients with melanoma

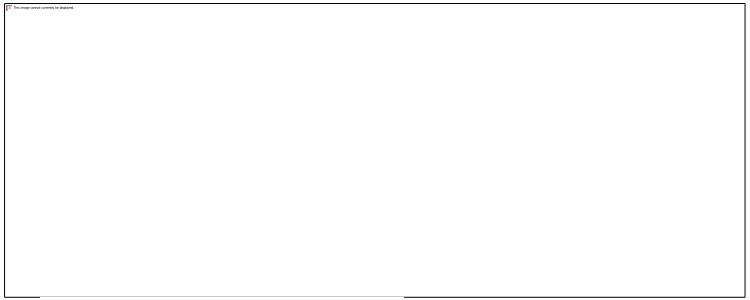
Patrick A. Ott[1,2,3]*, Zhuting Hu[1]*, Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[4], David J. Lieb[4], Thomas Eisenhaure[4], Evisa Gjini[9], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kaliappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[1], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[3,13], Maegan Harden[4], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[9,10], Dan H. Barouch[3,7,8], Jon C. Aster[3,10], Gad Getz[3,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[1,4]†, Nir Hacohen[3,4,15] & Catherine J. Wu[1,2,3,4]

13 JULY 2017 | VOL 547 | NATURE | 217



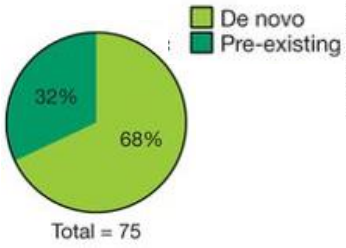
# Neoantigen vaccines

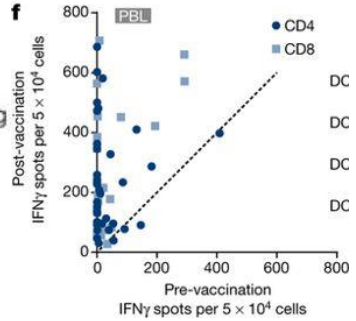


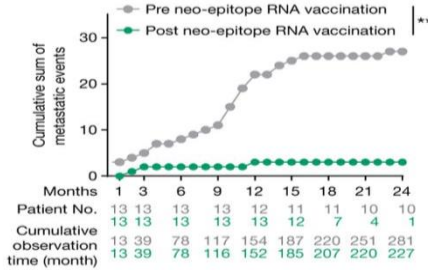
| NATURE | VOL 547 | 13 JULY 2017

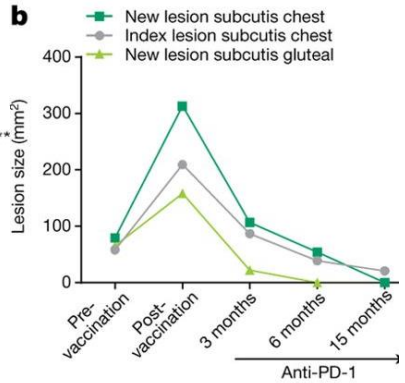
## Immune response:



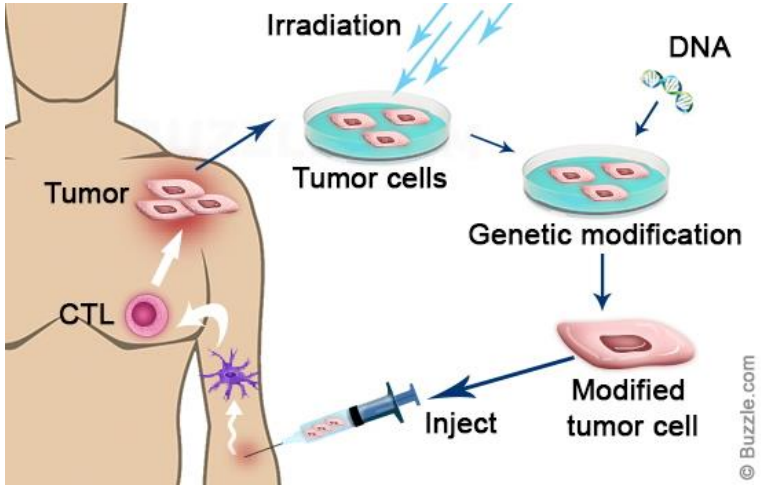

## Tumor control:



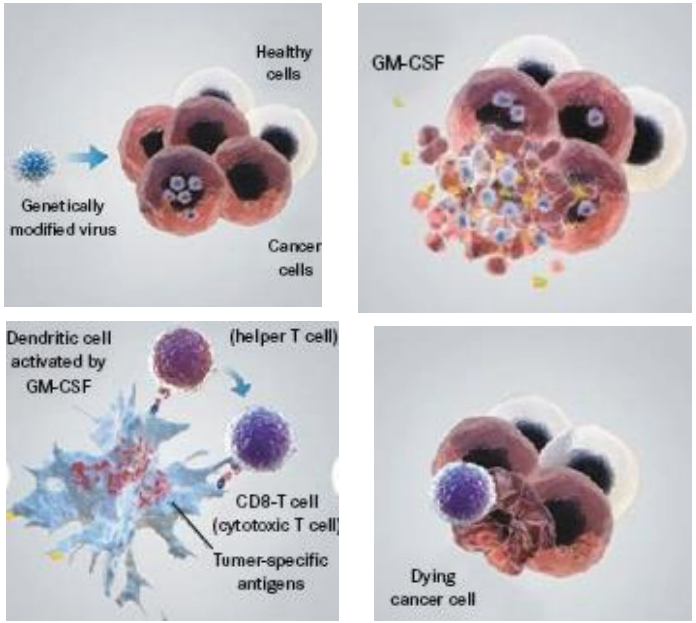
# Antigen agnostic cancer vaccination approaches

## 1) Whole cancer cell vaccines



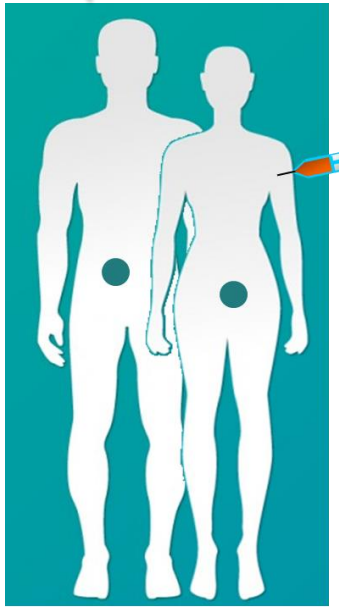

*https://healthhearty.com/strategies-for-cancer-vaccine-development*

## 2) Oncolytic virotherapy



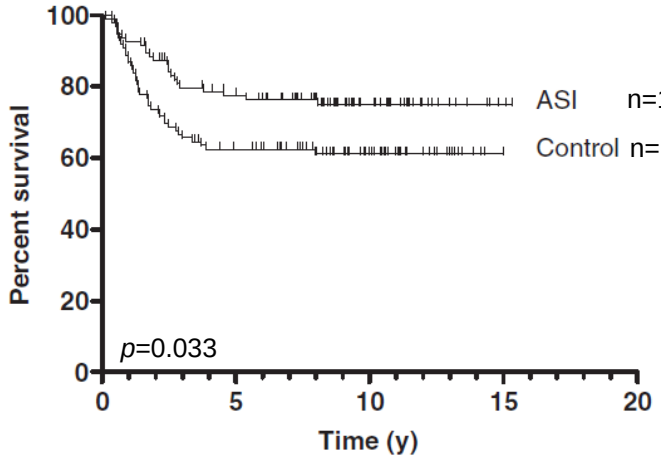

***https://www.gotoper.com/publications/ajho/2016/2016apr/an-update-on-talimogene-laherparepvec***

# Whole Cancer cell vaccines: CRC vaccination –who benefits?

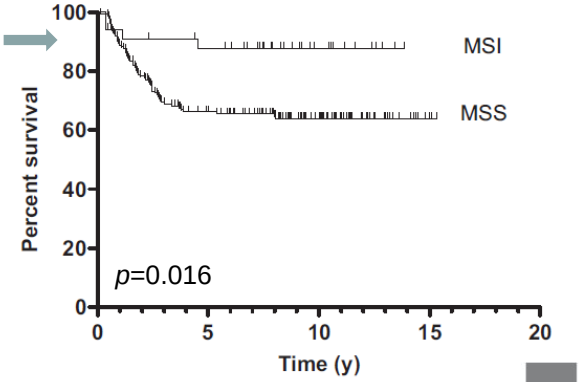


+ BCG adjuvar

Irradiated single-cell suspension from tumor




**MSI (high neoantigen load): better prognosis!**




THE LANCET • Vol 353 • January 30, 1999

**Active specific immunotherapy for stage II and stage III human colon cancer: a randomised trial**

*Jan B Vermorken, Anke M E Claessen, Harm van Tinteren, Helen E Gall, Renate Ezinga, Sybren Meijer, Rik J Scheper, Chris J L M Meijer, Elizabeth Bloemena, Janet H Ransom, Michael G Hanna Jr, Herbert M Pinedo*

*Predictive Biomarkers and Personalized Medicine*

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**Clinical Effects of Adjuvant Active Specific Immunotherapy Differ between Patients with Microsatellite-Stable and Microsatellite-Instable Colon Cancer**

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Clin Cancer Res; 18(3) February 1, 2012

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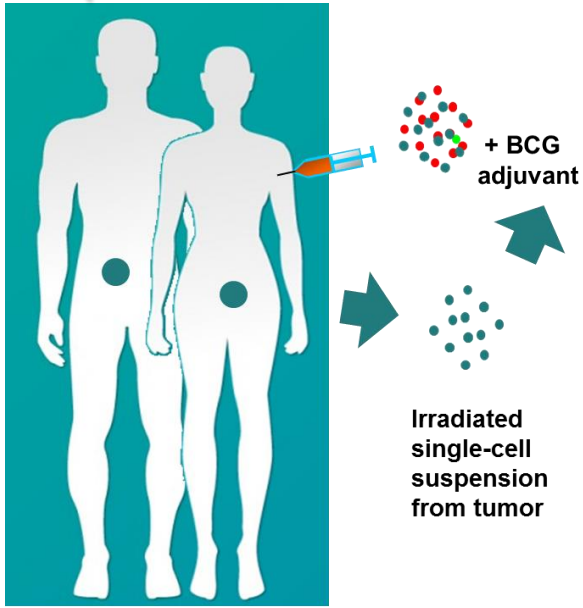


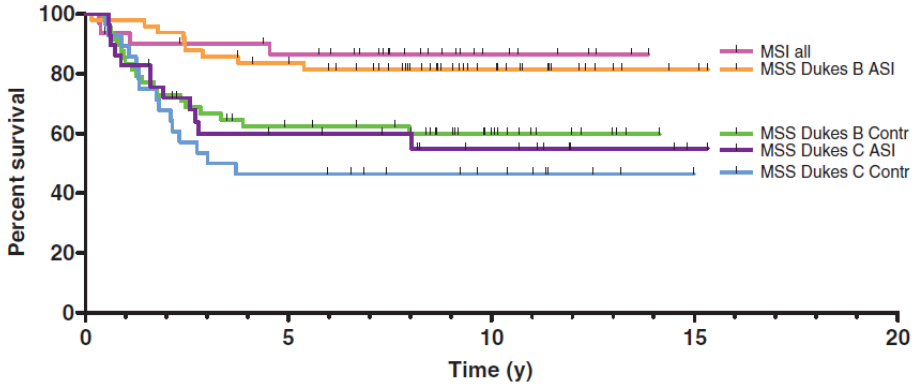


**Only patients with MSS stage II (low neoantigen load!) benefit from vaccination**

**Actionable tumor antigens!**
**Neoantigens?**

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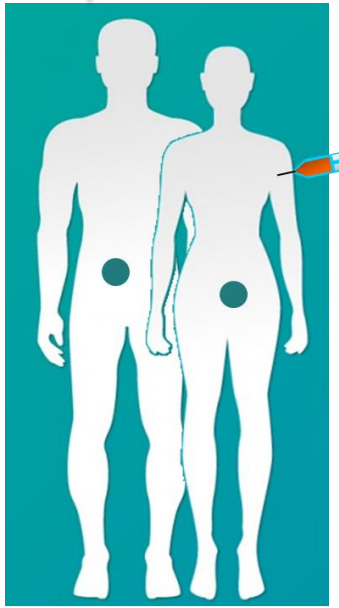
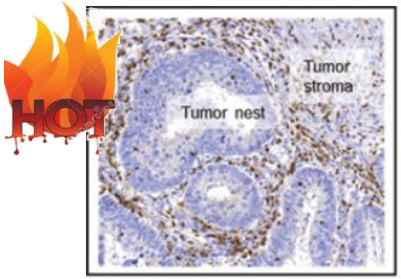
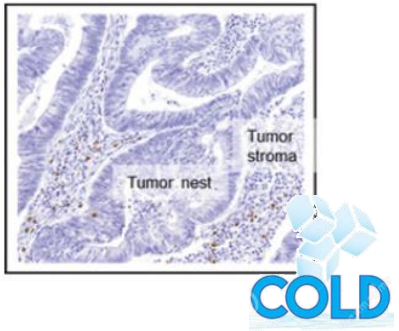


+ BCG adjuvant

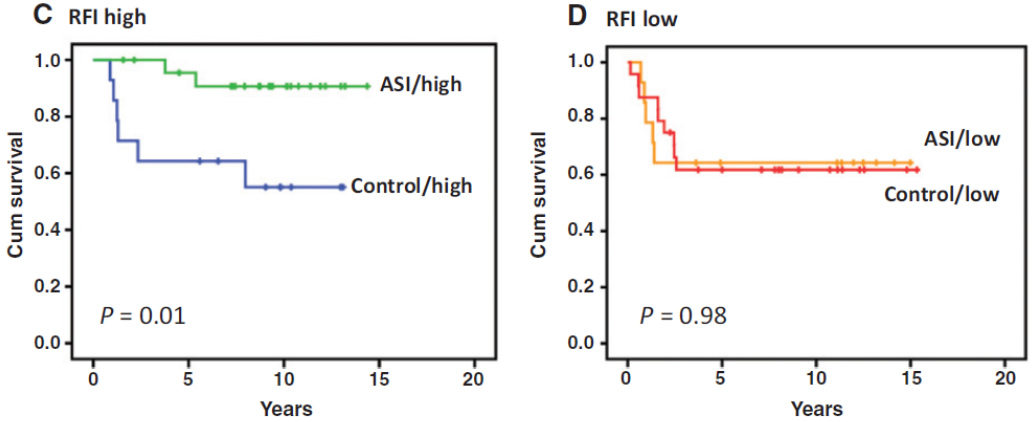
Irradiated single-cell suspension from tumor




T cell infiltration




## Only patients with MSS and T cell infiltrates benefit from vaccination

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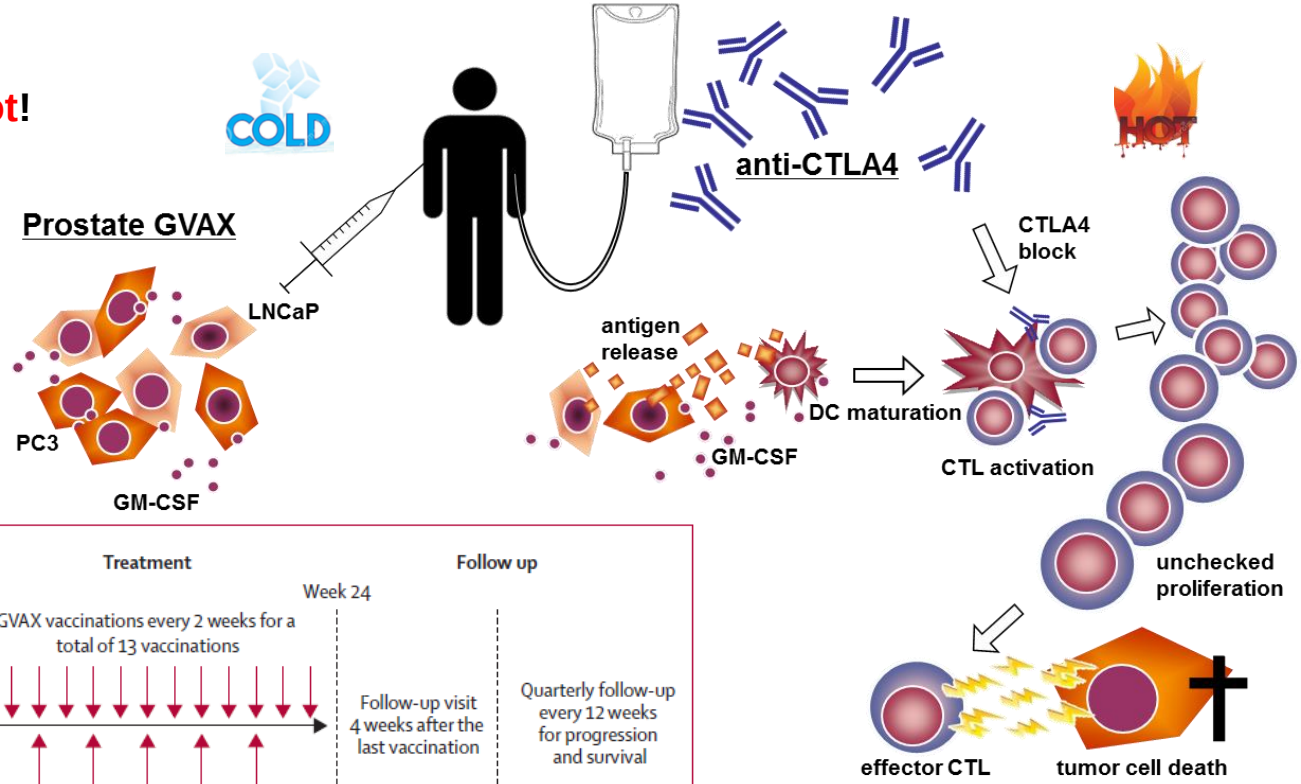
*Turksma et al Clin Cancer Res 2016*

# Whole Cancer cell vaccines: GVAX with checkpoint blockade -turning up the heat

**Turning a cold tumor hot!**

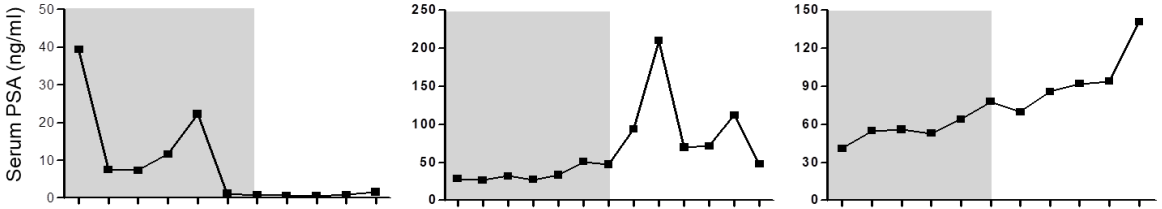


# Whole Cancer cell vaccines: GVAX with checkpoint blockade -turning up the heat

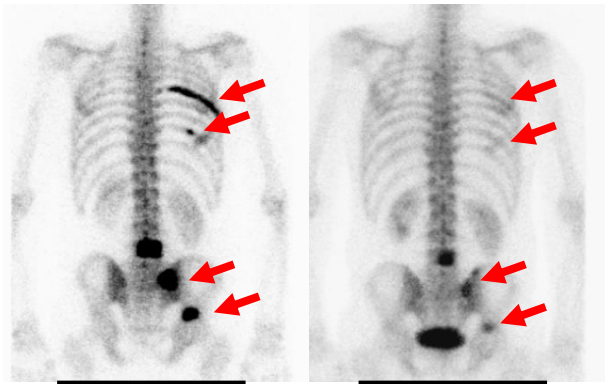
**Partial Response (PR);**
>50% PSA decline

**Stable Disease (SD);**
No PR or PD

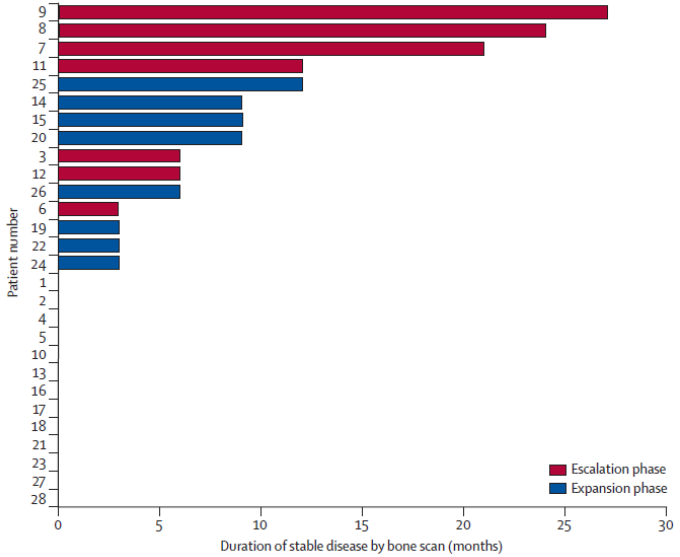
**Progressive Disease (PD);**
>25% PSA increase




| Category: | Number of patients |
|---|---|
| PSA Partial Response (PR) | 5 / 28 |
| PSA Stable Disease (SD) | 12 / 28 |
| PSA Progressive Disease (PD) | 11 / 28 |



15-9-2005 29-3-2006




*Lancet Oncol* 2012; 13: 509–17

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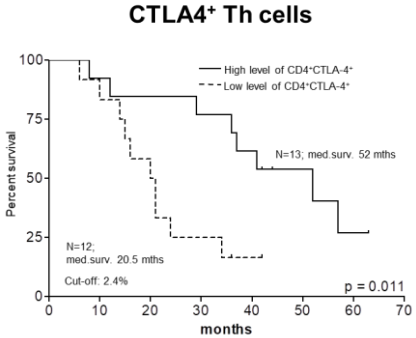
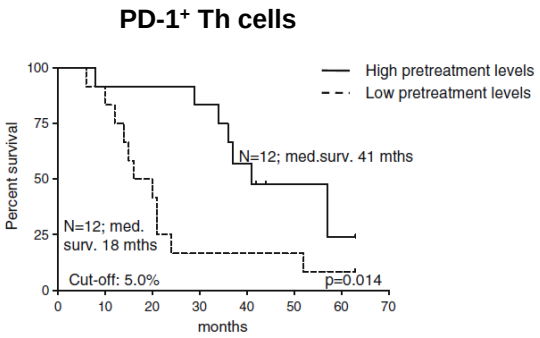
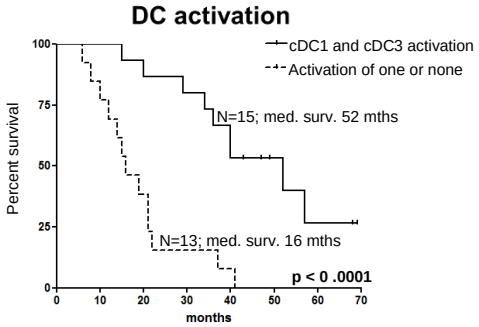
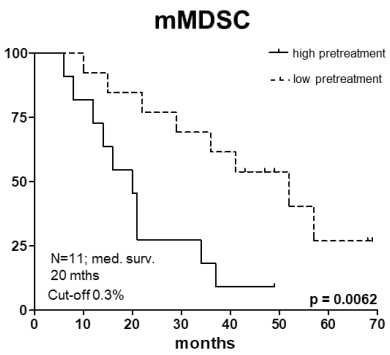
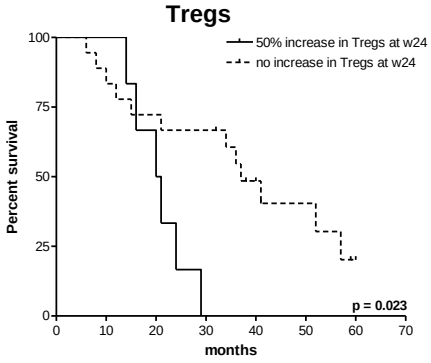
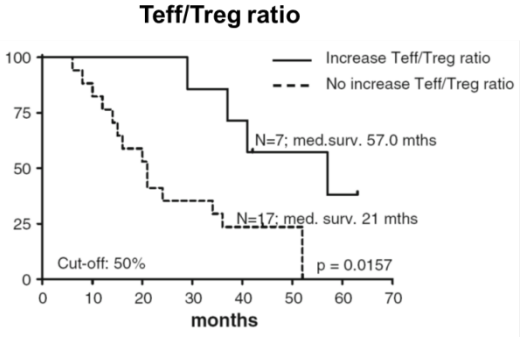


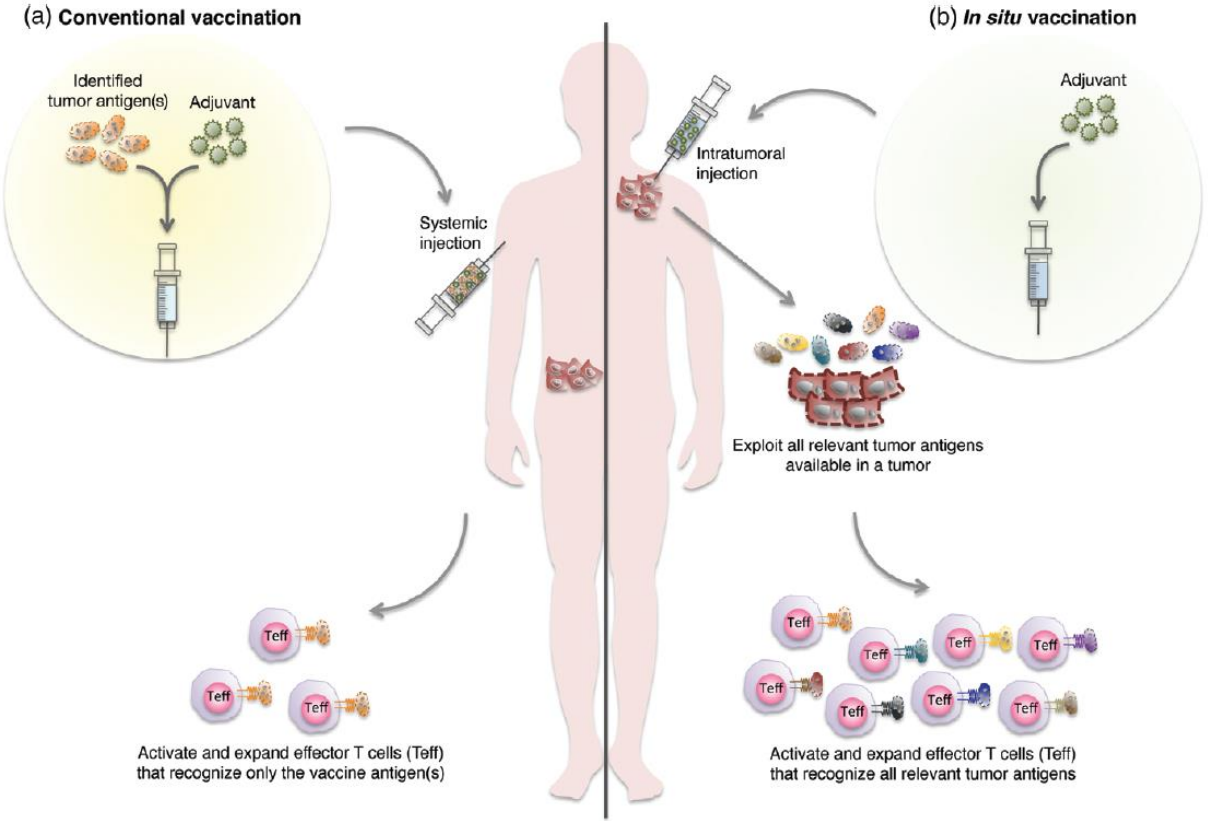



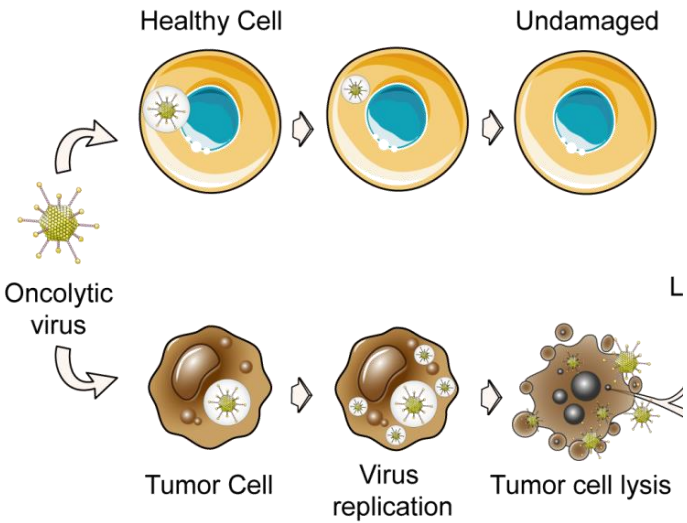

*Santegoets et al CII 2013, JITC 2014*

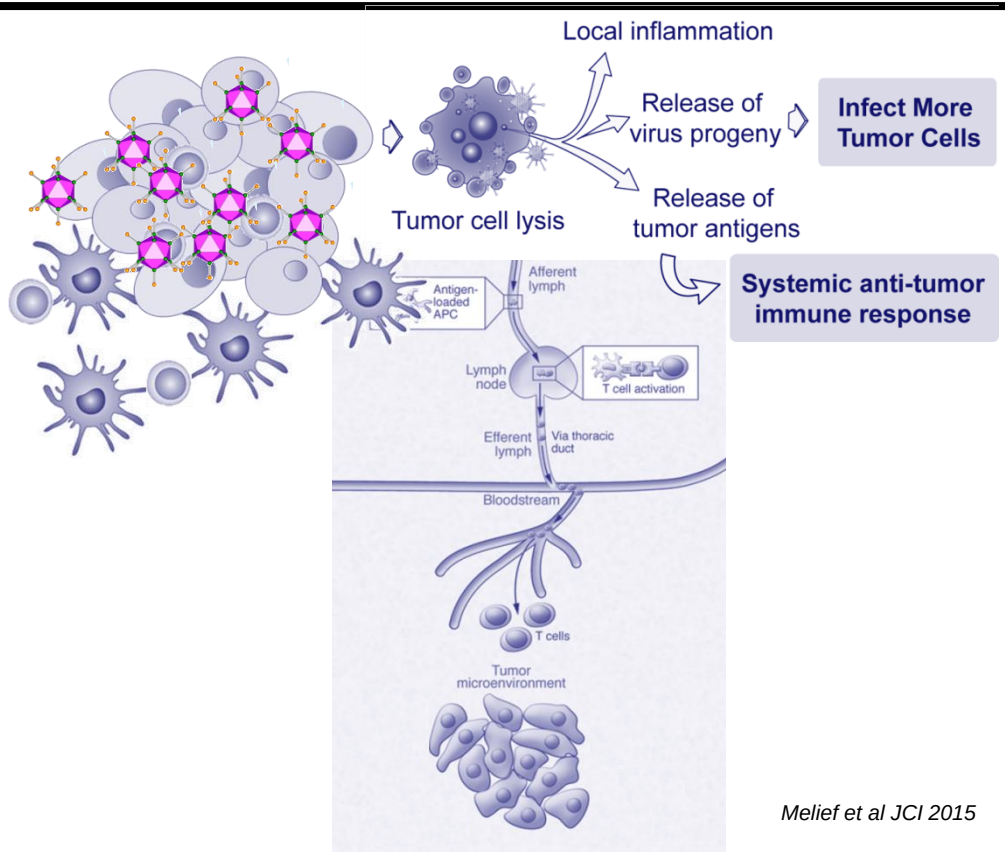
# Conventional versus *in vivo* vaccination




SHEEN AND FIERING *WIREs Nanomed Nanobiotechnol.* 2018;e1524.

# Oncolytic virotherapy: *in vivo* vaccination



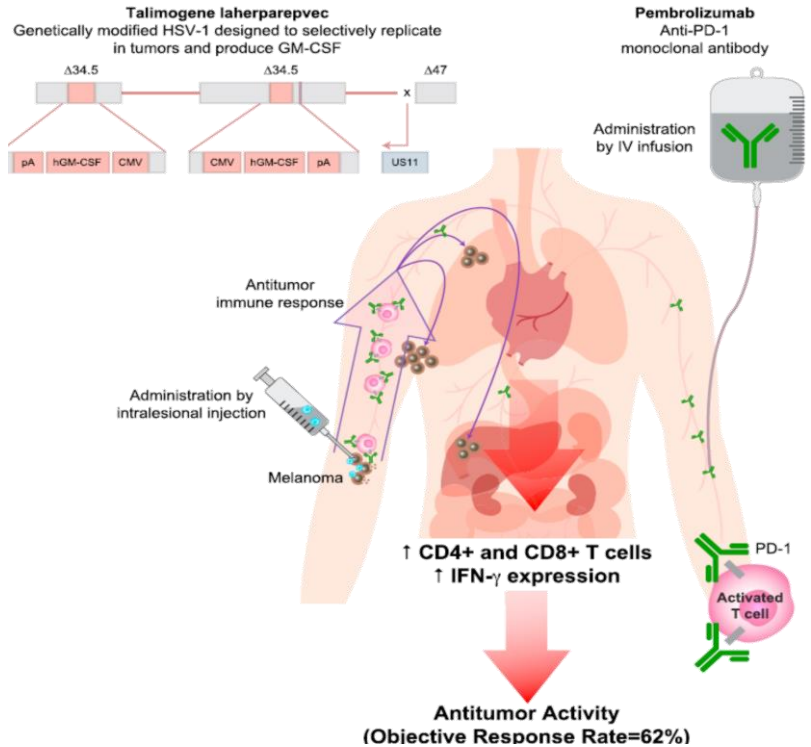



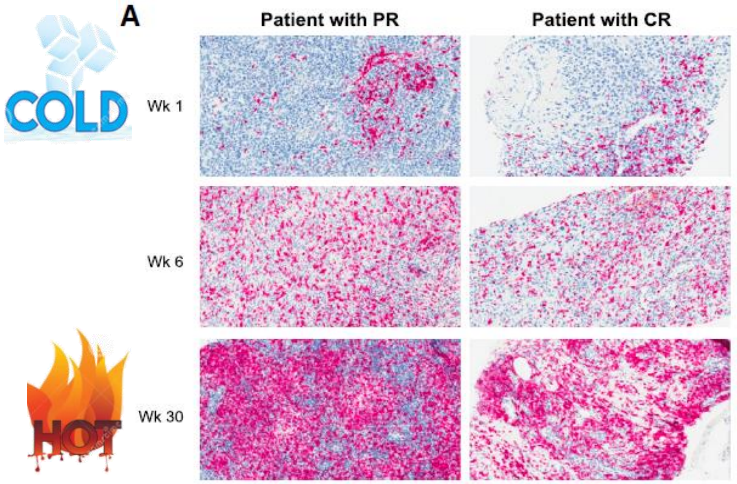

*https://www.creative-biolabs.com/car-t/oncolytic-virus-therapy-development.htm*

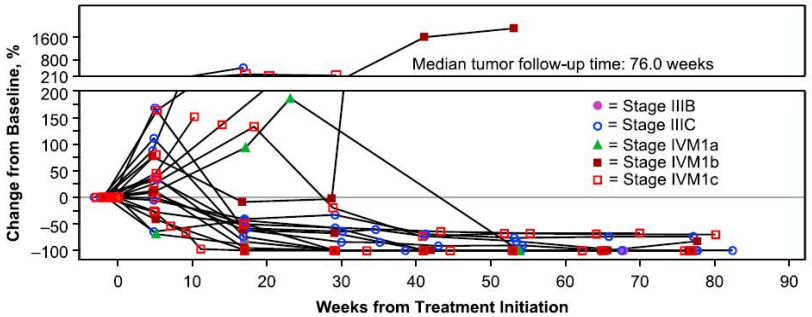
*Melief et al JCI 2015*

# Oncolytic viruses (T-vec) and immune checkpoint blockade

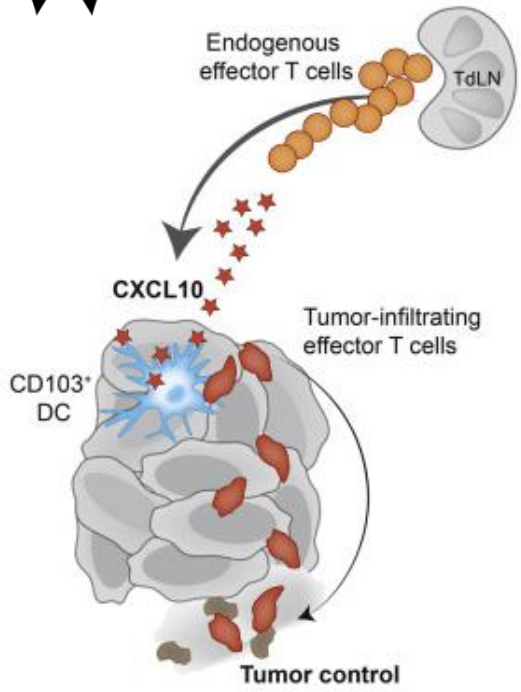
*Ribas et al. Cell 2017*

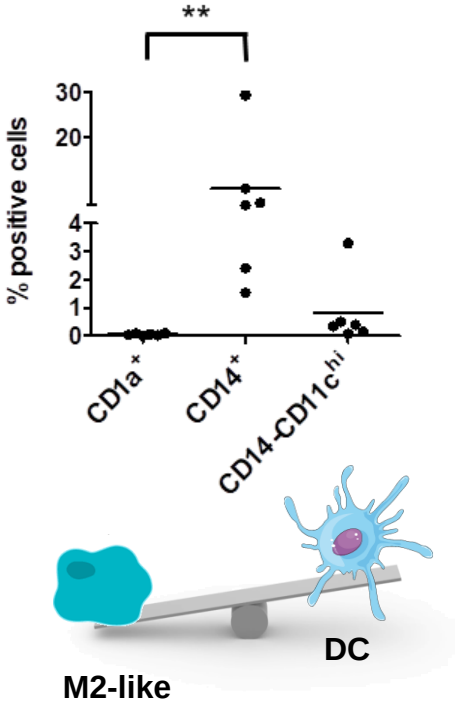


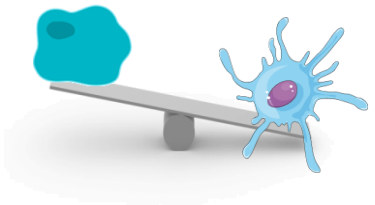



# Melanoma T cell infiltration depends on DC




M2-like
macrophage

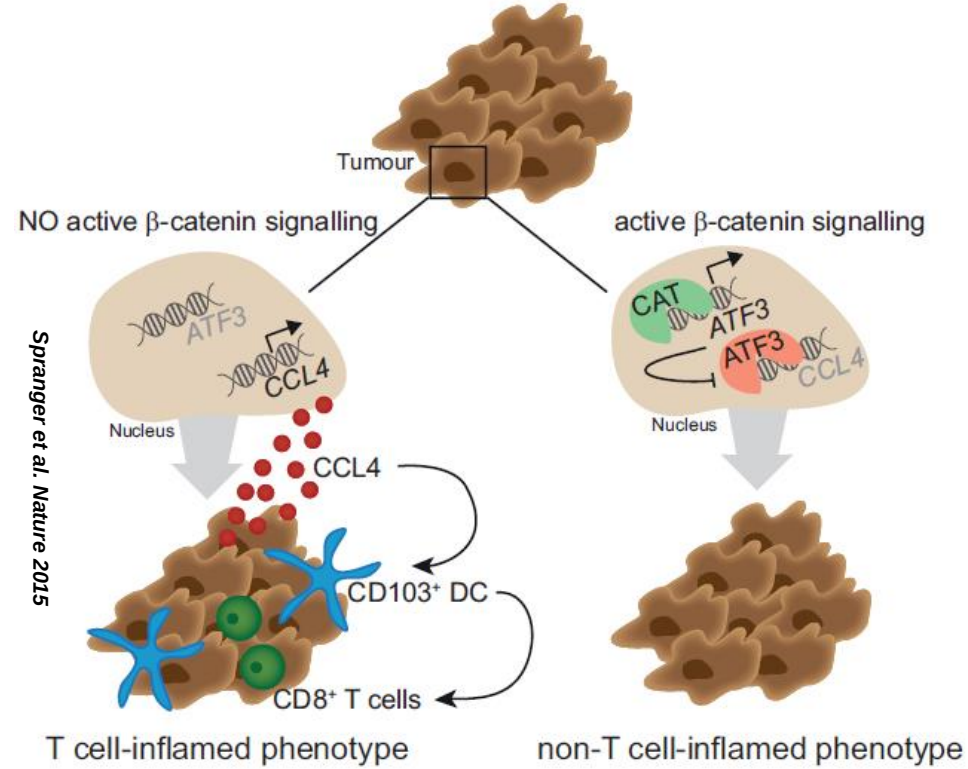


**Aim: to safeguard proper DC differentiation in melanoma and enable *in vivo* vacccination**

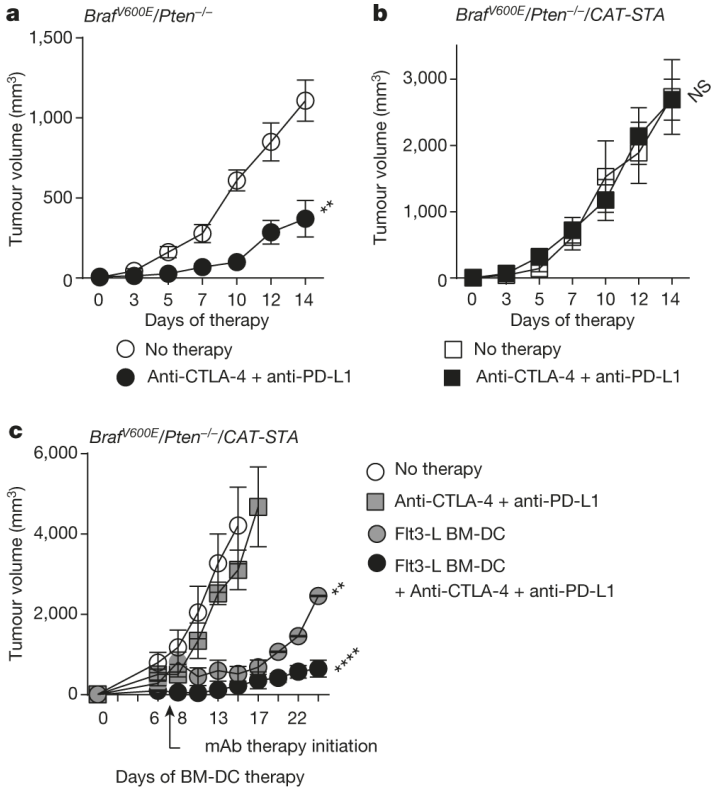
*Spranger et al. Cancer Cell 2017*

*Oosterhoff et al OncoImmunol 2012*

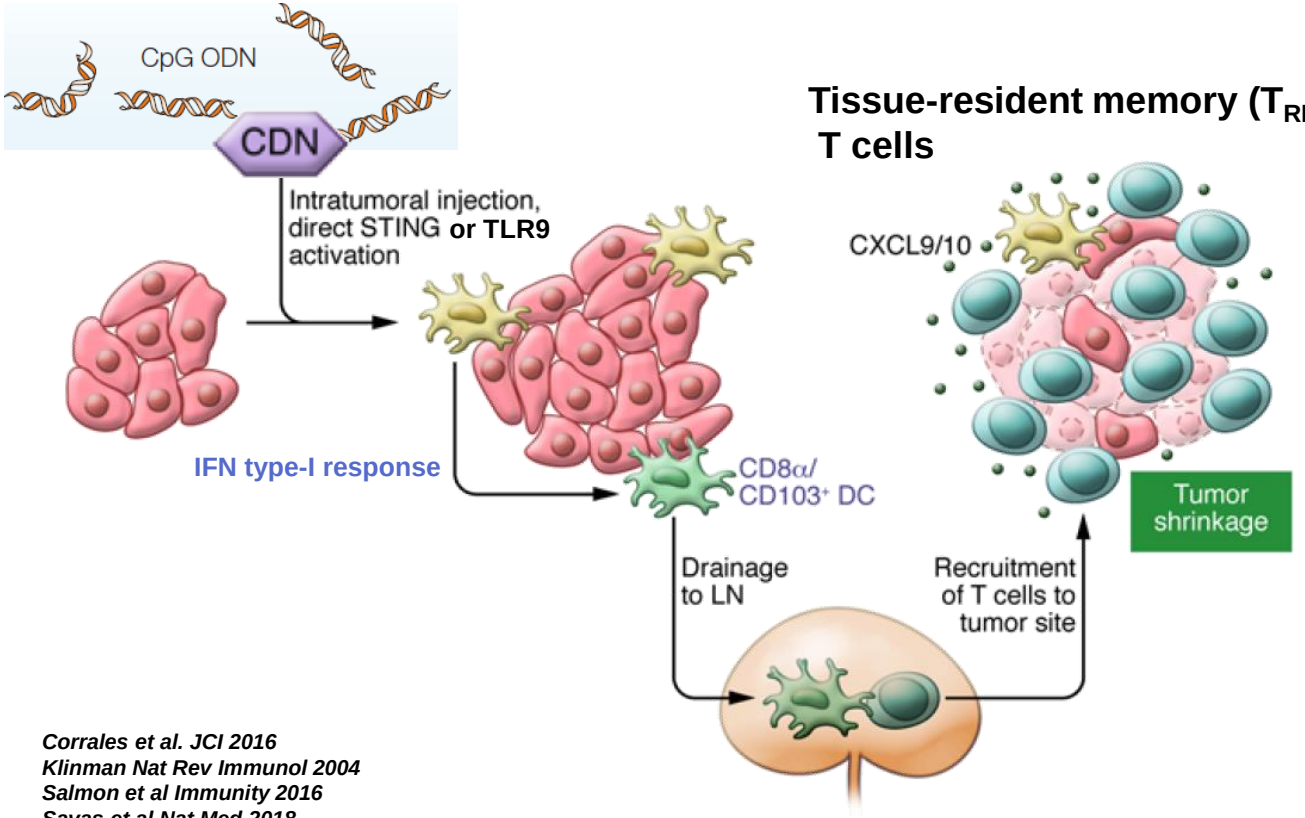
# Role for Wnt in melanoma: DC and T cell infiltration

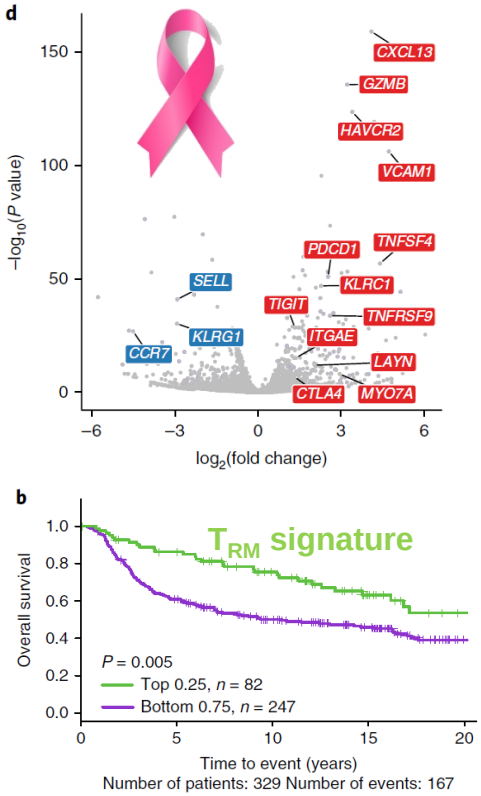



Spranger et al. Nature 2015



# Leveraging DC *in vivo*: priming and attracting effective T cells




*Corrales et al. JCI 2016*
*Klinman Nat Rev Immunol 2004*
*Salmon et al Immunity 2016*
*Savas et al Nat Med 2018*

# Options and advantages of *in vivo* vaccination

High-intensity focused ultrasound

Stereotactic body radiation therapy (SBRT)

Microwave ablation (MW)

Oncolytic viruses

Chemotherapy

Radiofrequency ablation (RFA)

Cryoablation

Irreversible electroporation (IRE)

Immunogenic cell death: Ag and DAMP release
Type-I IFN response
Ensure CD103+ DC and T cell recruitment

*In situ* vaccination (ISV) into a recognized tumor

- ISV exploits all relevant antigens in the tumor, avoiding the need to identify tumor antigens or consider the HLA type
- ISV is simple and cost effective because it utilizes standard reagents and does not require patient-specific vaccines
- ISV takes advantage of the entire antigenic repertoire of a tumor to minimize immune escape
- ISV utilizes feasible local delivery with minimal systemic side effects
- ISV has the potential for synergy when combined with other therapies
- ISV can be effectively performed prior to surgery as neoadjuvant therapy

SHEEN AND FIERING *WIREs Nanomed Nanobiotechnol.* 2018;e1524.

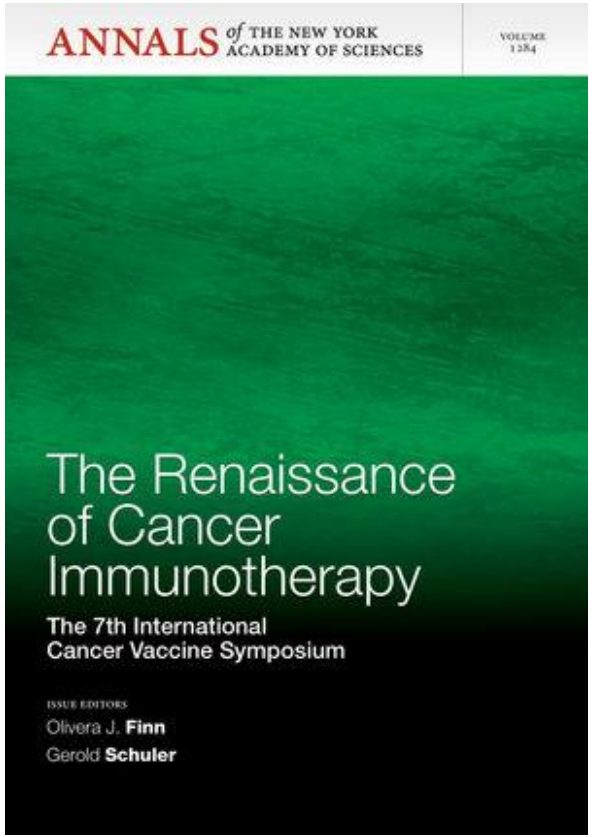
# Learning goals

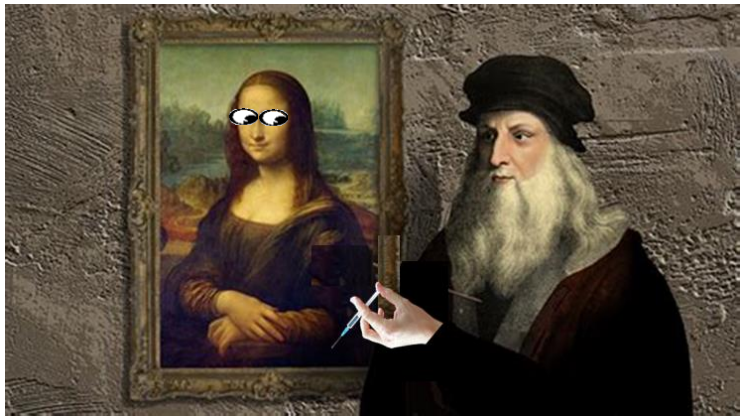
1. **Understanding the stumbling blocks and requirements for the design of successful therapeutic vaccines: choice of antigens and adjuvants**

2. **Becoming familiar with some of the current approaches to vaccination against cancer: broader definition includes *in vivo* vaccination**

3. **Acquiring an understanding of the positioning of cancer vaccines in the developing field of cancer immunotherapy**

# Cancer vaccines: a renaissance in the golden age of immunotherapy?



*https://owlcation.com/humanities/*