DANSKE KRÆFTFORSKNINGSDAGE 2023

Hvor langt er vi med kræftvacciner målrettet patienterne og hvad er de mest lovende principper?

Mads Hald Andersen
Professor, Centerleder
Nationalt Center for Cancer Immunterapi, Herlev og Gentofte Hospital

#DKD2023
#SamarbejdeOmKræft

Sli.do
#131525

DANSKE KRÆFTFORSKNINGSDAGE 2023

Hvad er og hvordan virker kræftvacciner?
Hvorfor ser de ud til at få succes nu?

Mads Hald Andersen
Professor, Centerleder
Nationalt Center for Cancer Immunterapi, Herlev og Gentofte Hospital

#DKD2023
#SamarbejdeOmKræft

Sli.do
#131525

Cancer Vaccines

- In general, Cancer Vaccines are not used to prevent cancer (except the HPV vaccine), but are used as **therapeutic** vaccines
- Cancer Vaccines is a method to induce anti-cancer immunity, especially **T-cell reactivity**
- In general, Cancer Vaccines has shown very **low toxicity**

Sli.do
#131525

The way to use Cancer Vaccines

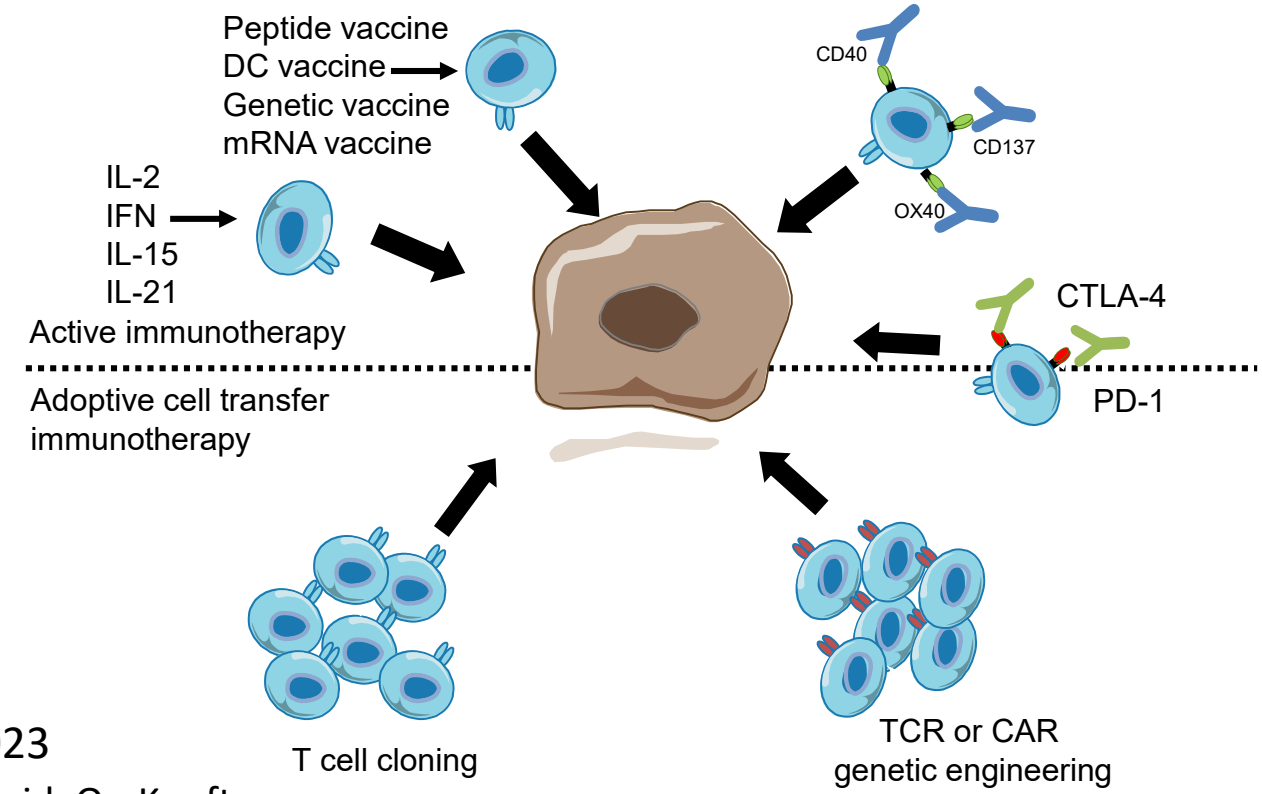
For many years therapeutic Cancer Vaccines were used as monotherapy in very late state cancers.

Cancer Vaccines work best as….

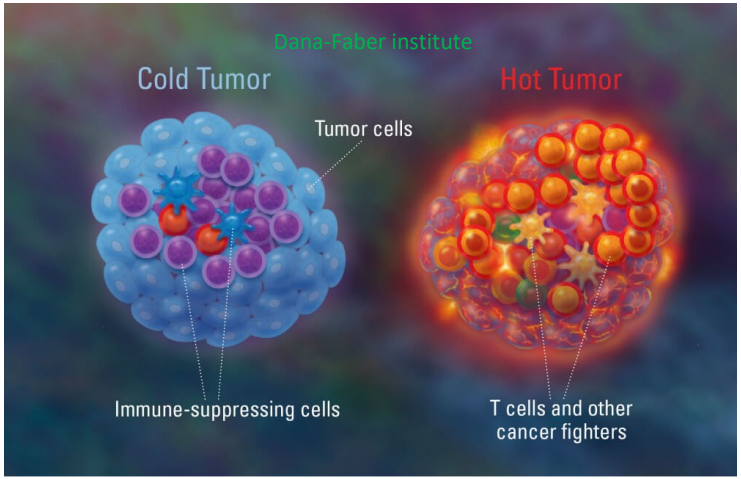
- **early as possible** in disease development

- **a combination agent** - for example (or obviously) with immune checkpoint molecules that works in patients harboring tumor reactive T cells.

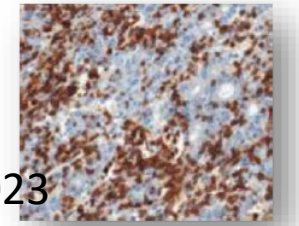
T-cells are involved in almost any form of cancer immunotherapy



Immuno-Cold versus Hot tumor

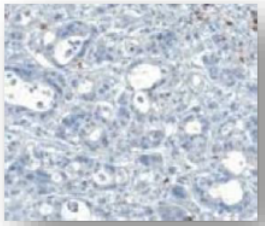


Inflamed



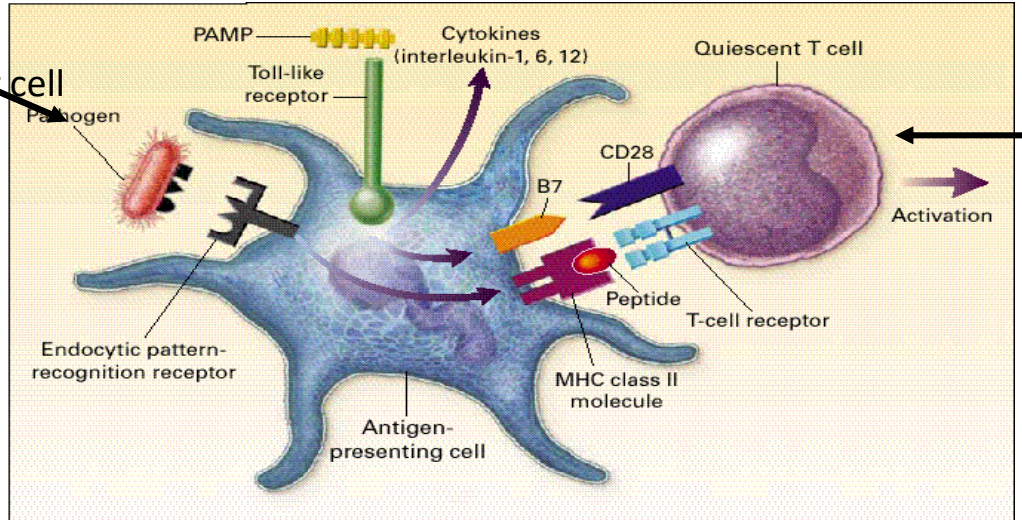
TILs
CD8+ T cells
IFN-γ gene signature
PDL1 expression
Pre-existing immunity

Non-inflamed



T-cell activation

Bacteria,
Vira, cancer cell
protein, ect



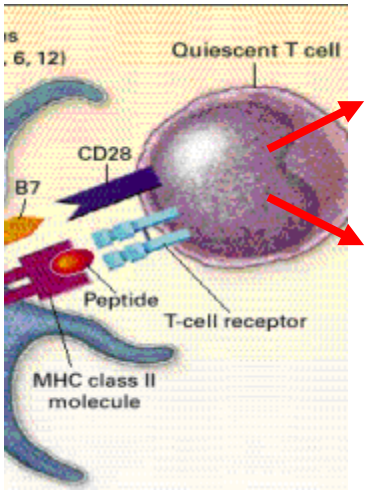
T-cell

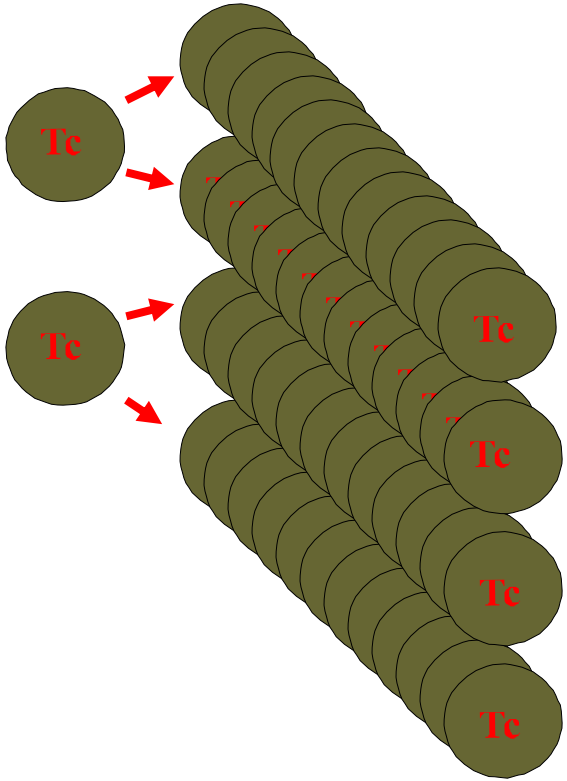
Immature DC: uptake of antigen

Mature DC: T-cell activation

Migration to lymph node:

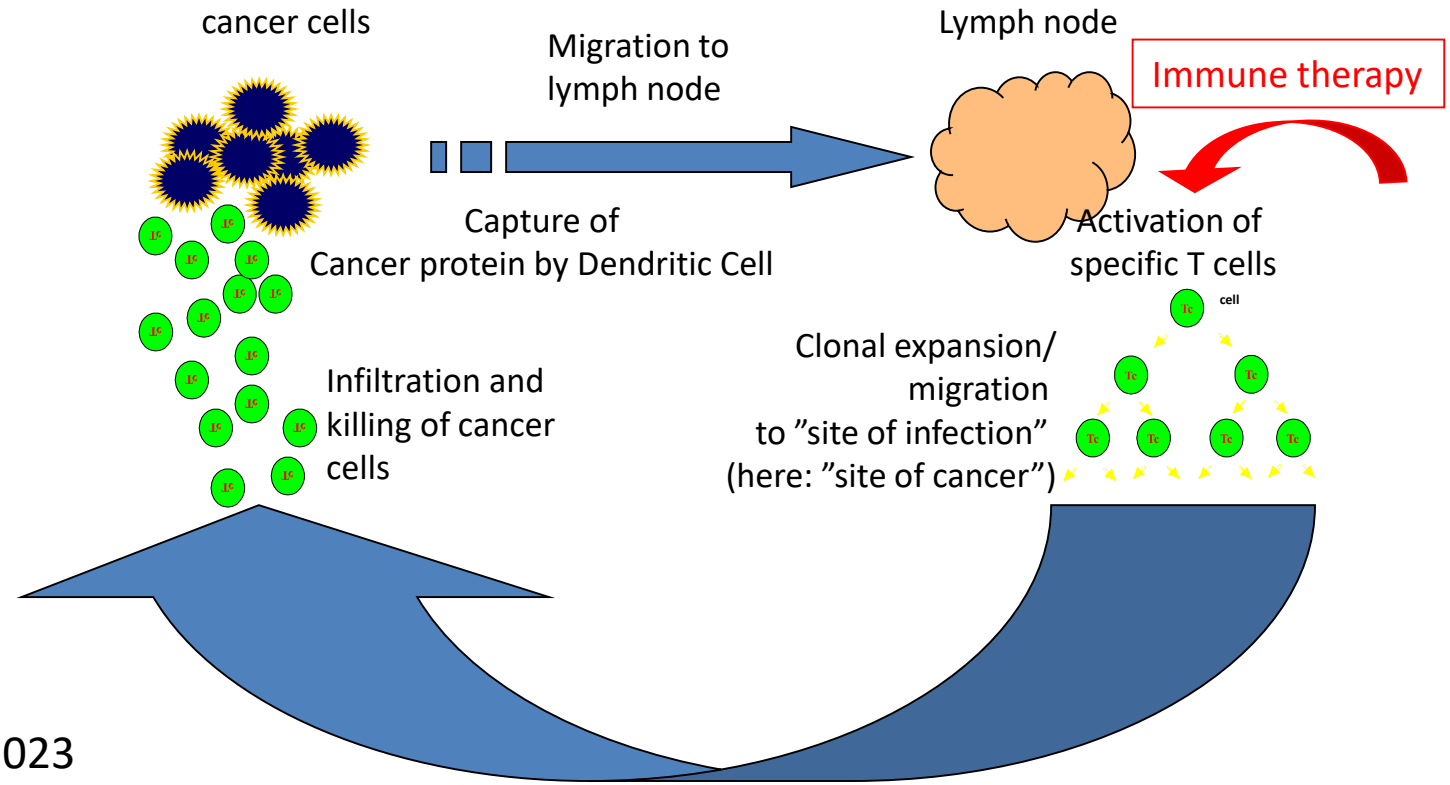
Proper activation leads to cell division





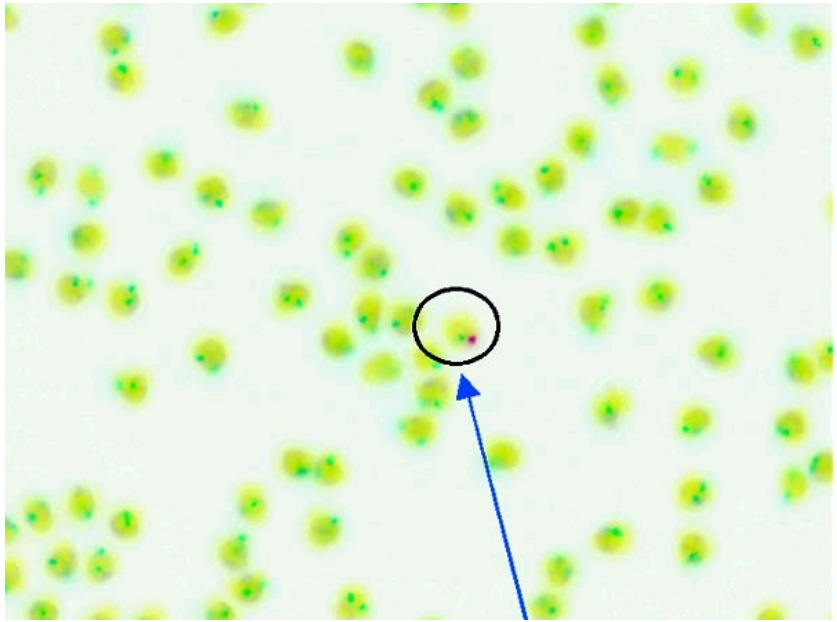
Circulate the body and kills cells presenting the same antigen on the cell surface

The Cancer Immunity Cycle



What is recognized by the immune system...

Cancer cells: genetic and epigenetic changes



….leading to some sort of ’non-self’

What is recognized by the immune system...

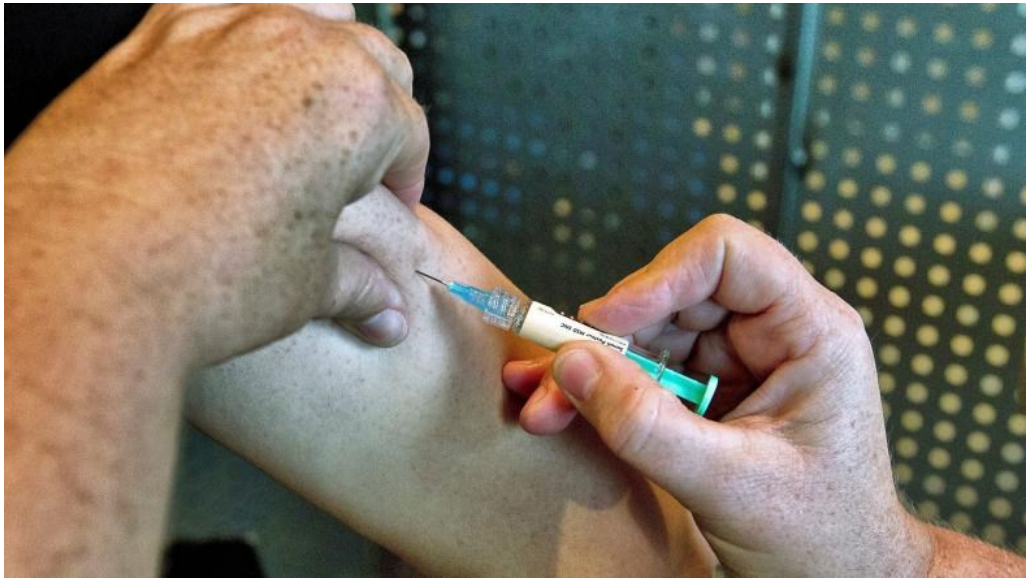
Tumor specific antigens (TSAs)
Group I. Viral antigens, e.g. HPV
Group II. Broadly expressed mutated antigens, e.g. ras, braf
Group III. *Patient specific mutated antigens*

Tumor associated antigens (TAAs)
Group IV. differentiation antigens, e.g. MART-1, gp100, PAP
Group V. Cancer-testis antigens, e.g. MAGE
Group VI. Overexpressed (including universal) tumor antigens, e.g. telomerase, survivin

….*new group:* ***Tumor microenvironment antigens (TMAs)***

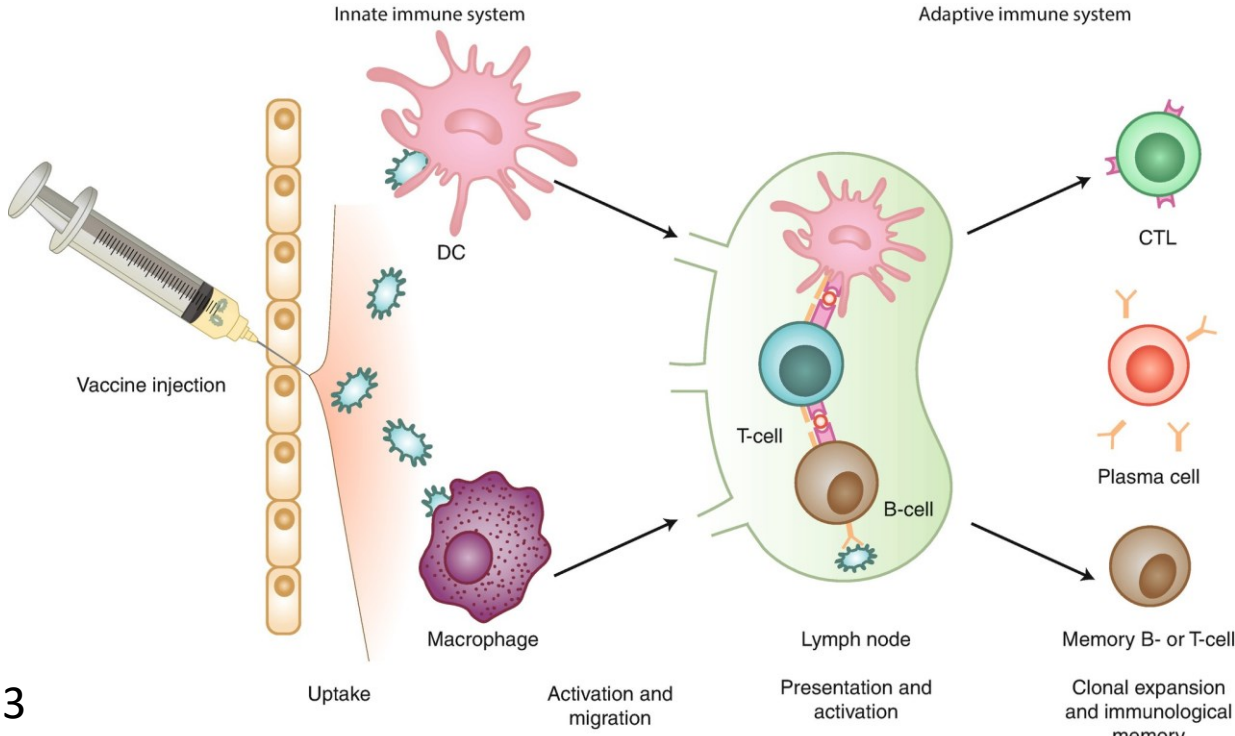
Cancer Vaccines

Consisting of a part that *activates* the immune system **= *adjuvant***
against something from the cancer cell = ***antigen***



Cancer Vaccines

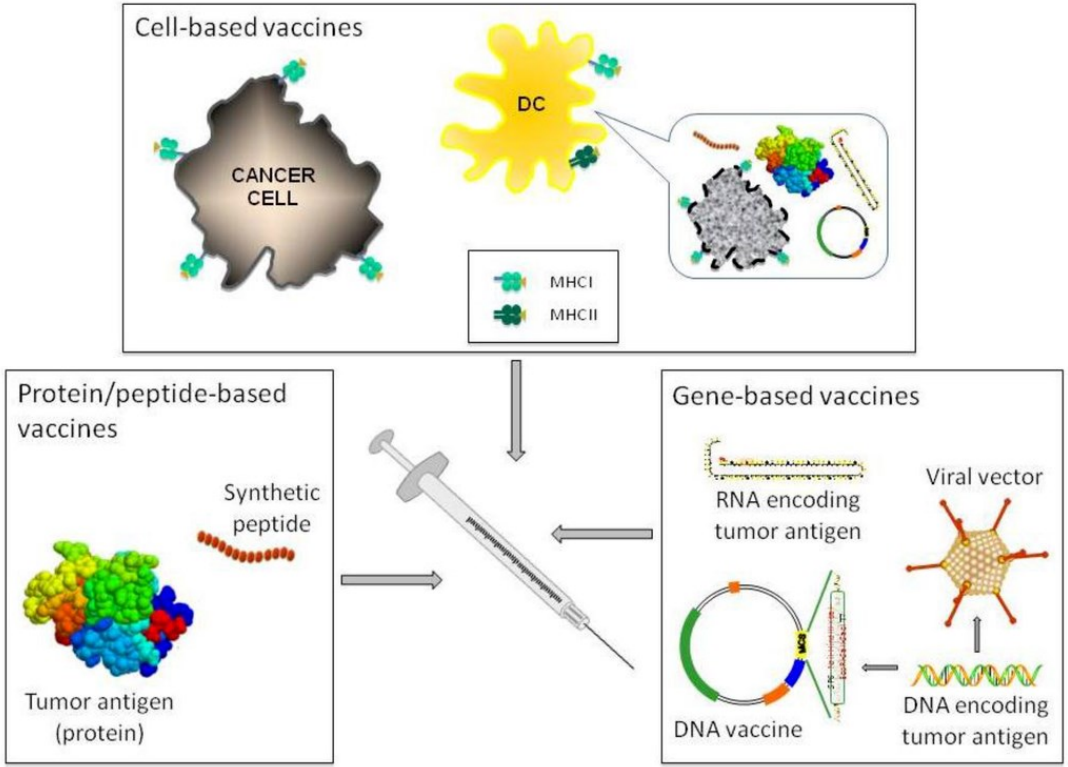
Consisting of a part that *activates* the immune system = ***adjuvant***
against something from the cancer cell = ***antigen***



Jiskoot et a,l Pharmaceutical Biotechnology 2019

Cancer Vaccines

Consisting of a part that *activates* the immune system = ***adjuvant***
against something from the cancer cell = ***antigen***



Lollini et al. Vaccines 2015

The long way to the Success Stories of Vaccines in Cancer

2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D., Jon M. Richards, M.D., Ph.D., Robert M. Conry, M.D., Donald M. Miller, M.D., Ph.D., Jonathan Treisman, M.D., Fawaz Gailani, M.D., Lee Riley, M.D., Ph.D., Kevin Conlon, M.D., Barbara Pockaj, M.D., Kari L. Kendra, M.D., Ph.D., Richard L. White, M.D., Rene Gonzalez, M.D., Timothy M. Kuzel, M.D., Brendan Curti, M.D., Phillip D. Leming, M.D., Eric D. Whitman, M.D., Jai Balkissoon, M.D., Douglas S. Reintgen, M.D., Howard Kaufman, M.D., Francesco M. Marincola, M.D., Maria J. Merino, M.D., Steven A. Rosenberg, M.D., Ph.D., Peter Choyke, M.D., Don Vena, B.S., and Patrick Hwu, M.D.

2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

2019

Original Investigation

ONLINE FIRST

September 27, 2018

Combining Immune Checkpoint Blockade and Tumor-Specific Vaccine for Patients With Incurable Human Papillomavirus 16-Related Cancer

A Phase 2 Clinical Trial

Erminia Massarelli, MD[1]; William William, MD[2]; Faye Johnson, MD, PhD[2]; et al

Author Affiliations

JAMA Oncol. Published online September 27, 2018. doi:10.1001/jamaoncol.2018.4051

#DKD2023

#SamarbejdeOmKræft

Sli.do

#131525

Moderna – personalized mRNA vaccines in development - Melanoma

ASCO 2023

Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial:

Melanoma patients in high risk for relaps after surgery treated with mRNA vaccines with up to 34 neoantigens + immune checkpoint inhibitors

18 months of follow-up: Pts who received the mRNA vaccine and immunotherapy had a **78.6%** rate of cancer-free survival vs **62.2%** in those who only received immunotherapy,

2 years of follow-up: **22%** of the patients who had received the combo treatment had died or relapsed vs **40%**.

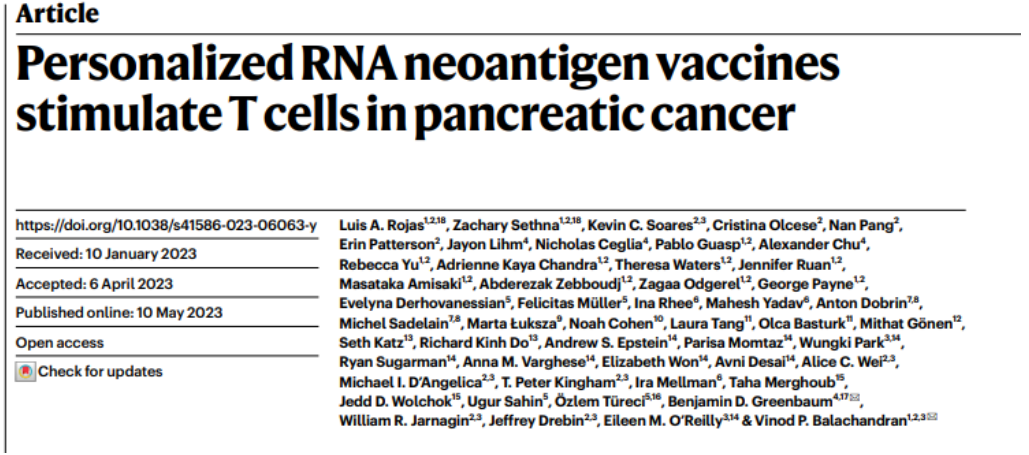
Moderna – personalized mRNA vaccines in development - Pancreas

- Pts with pancreatic cancer after surgery: Vaccination+anti-PDL1 antibody induced a **strong anti-tumor immune response in half the participants** in a small study.

- **At 18-month median follow-up**, patients (n=8) with vaccine-expanded T cells (responders) had a **longer median recurrence-free survival** (not reached) compared with patients (n=8) without vaccine-expanded T cells (non-responders; 13.4 months, *P* = 0.003)

- 16 out of 34 enrolled treated.

- Larger clinical trial ongoing



Article

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

https://doi.org/10.1038/s41586-023-06063-y

Received: 10 January 2023

Accepted: 6 April 2023

Published online: 10 May 2023

Open access

Check for updates

Luis A. Rojas[1,2,18], Zachary Sethna[1,2,18], Kevin C. Soares[2,3], Cristina Olcese[2], Nan Pang[2], Erin Patterson[2], Jayon Lihm[4], Nicholas Ceglia[4], Pablo Guasp[1,2], Alexander Chu[4], Rebecca Yu[1,2], Adrienne Kaya Chandra[1,2], Theresa Waters[1,2], Jennifer Ruan[1,2], Masataka Amisaki[1,2], Abderezak Zebboudj[1,2], Zagaa Odgerel[1,2], George Payne[1,2], Evelyna Derhovanessian[5], Felicitas Müller[5], Ina Rhee[6], Mahesh Yadav[6], Anton Dobrin[7,8], Michel Sadelain[7,8], Marta Łuksza[9], Noah Cohen[10], Laura Tang[11], Olca Basturk[11], Mithat Gönen[12], Seth Katz[13], Richard Kinh Do[13], Andrew S. Epstein[14], Parisa Momtaz[14], Wungki Park[3,14], Ryan Sugarman[14], Anna M. Varghese[14], Elizabeth Won[14], Avni Desai[14], Alice C. Wei[2,3], Michael I. D'Angelica[2,3], T. Peter Kingham[2,3], Ira Mellman[6], Taha Merghoub[15], Jedd D. Wolchok[15], Ugur Sahin[5], Özlem Türeci[5,16], Benjamin D. Greenbaum[4,17] ✉, William R. Jarnagin[2,3], Jeffrey Drebin[2,3], Eileen M. O'Reilly[3,14] & Vinod P. Balachandran[1,2,3] ✉

#DKD2023

#SamarbejdeOmKræft

Seminars in Immunopathology
https://doi.org/10.1007/s00281-022-00966-0

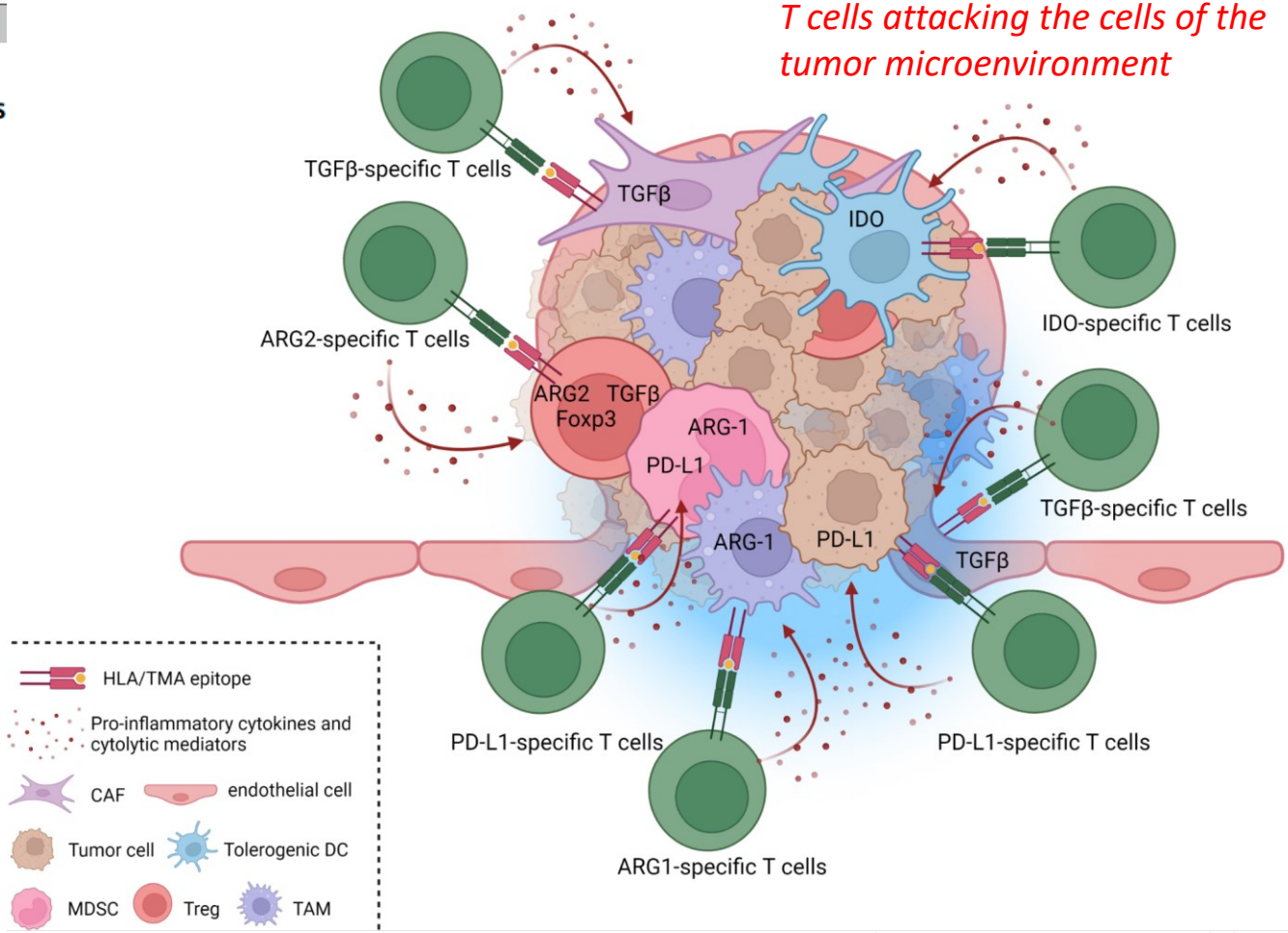
REVIEW

Tumor microenvironment antigens

Mads Hald Andersen[1,2]

Received: 7 July 2022 / Accepted: 16 September 2022

Take home message: Anti-regulatory T cells attacking the cells of the tumor microenvironment



#DKD2023
#SamarbejdeOmKræft

Andersen MH, *Seminars in immunopathology*, 2022

In the lab 10 years ago: First description of these T cells as CCIT-dk

OXFORD

JNCI J Natl Cancer Inst (2015) 107(9): djv154

doi:10.1093/jnci/djv154
First published online June 10, 2015
Commentary

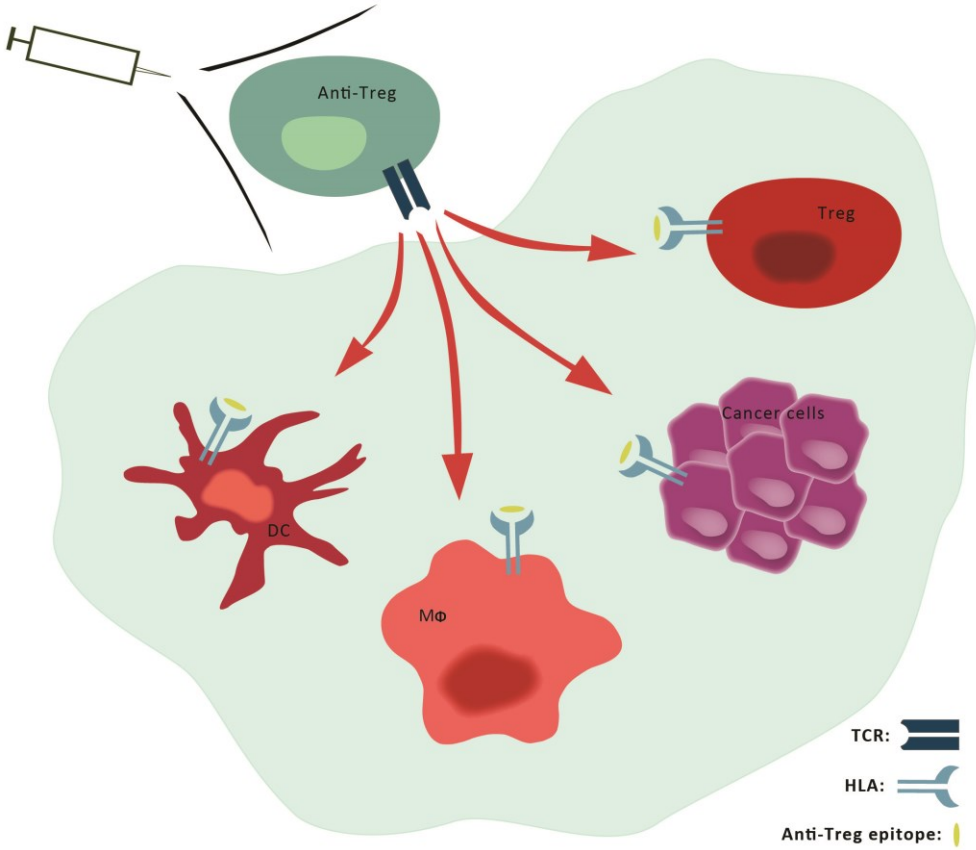
COMMENTARY

Immune Regulation by Self-Recognition: Novel Possibilities for Anticancer Immunotherapy

Mads Hald Andersen

Affiliation of author: Center for Cancer Immune Therapy (CCIT), Department of Hematology, Copenhagen University Hospital, Herlev, Denmark.

Correspondence to: Mads Hald Andersen, PhD, DScTech, Center for Cancer Immune Therapy (CCIT), Department of Hematology, Copenhagen University Hospital, Herlev, DK-2730 Herlev, Denmark (e-mail: mads.hald.andersen@regionh.dk).



IDO/PD-L1-peptide vaccine combined with nivolumab in first line melanoma

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01544-x

Check for updates

A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma

Julie Westerlin Kjeldsen[1,5], Cathrine Lund Lorentzen[1,5], Evelina Martinenaite[1,2], Eva Ellebaek[1], Marco Donia[1], Rikke Boedker Holmstroem[1], Tobias Wirenfeldt Klausen[1], Cecilie Oelvang Madsen[1], Shamaila Munir Ahmed[1], Stine Emilie Weis-Banke[1], Morten Orebo Holmström[1], Helle Westergren Hendel[3], Eva Ehrnrooth[2], Mai-Britt Zocca[2], Ayako Wakatsuki Pedersen[2], Mads Hald Andersen[1,4] and Inge Marie Svane[1]✉

Julie Westerlin Kjeldsen

Cathrine Lund Lorentzen

- The combination of IDO/PD-L1 peptide vaccine and nivolumab was safe with no additional systemic toxicity
- **An ORR of 80% was reached with 50 % reaching CR (as recently updated)**
- Median PFS reached 26 months and mOS was not reached (as recently updated)
- ORR was significantly higher than a matched historical control group, who had received anti-PD-1 monotherapy as standard of care.
- Vaccine specific T-cells were demonstrated in the Pts

Kjeldsen *et al. Nature Medicine* (2021)
Lorentzen et al. *J. Immunother. Cancer* (2023)

Immune modulating cancer vaccines

IO Biotech (CCIT-dk spin out company) is currently running IOB-013 / KN-D18 in **1st Line Melanoma**

- Phase 3 Trial - ONGOING
- Breakthrough Therapy Designation by FDA

Moderna *currently running mRNA-4359 that targets IDO and PD-L1 antigens in Phase 2 for Solid Tumors*

DANSKE KRÆFTFORSKNINGSDAGE 2023

mRNA eller peptid-baserede kræftvacciner i rivende udvikling

Vaccinerne er **veltolerede** og bivirkningerne er generelt håndterbare

Vaccinerne er **ikke smitsomme**, da de ikke er baseret på virale patogener

Vaccinerne aktiverer først og fremmest det **cellulære immunsystem**

Vaccinerne bør benyttes tidligt i forløbet, f.eks. adjuverende behandling

Virkelig lovende data i **kombination** med anden terapi, især immun-checkpoint blokerende antistoffer.

#DKD2023
#SamarbejdeOmKræft

Sli.do
#131525