Dendritische celtherapie bij melanoom

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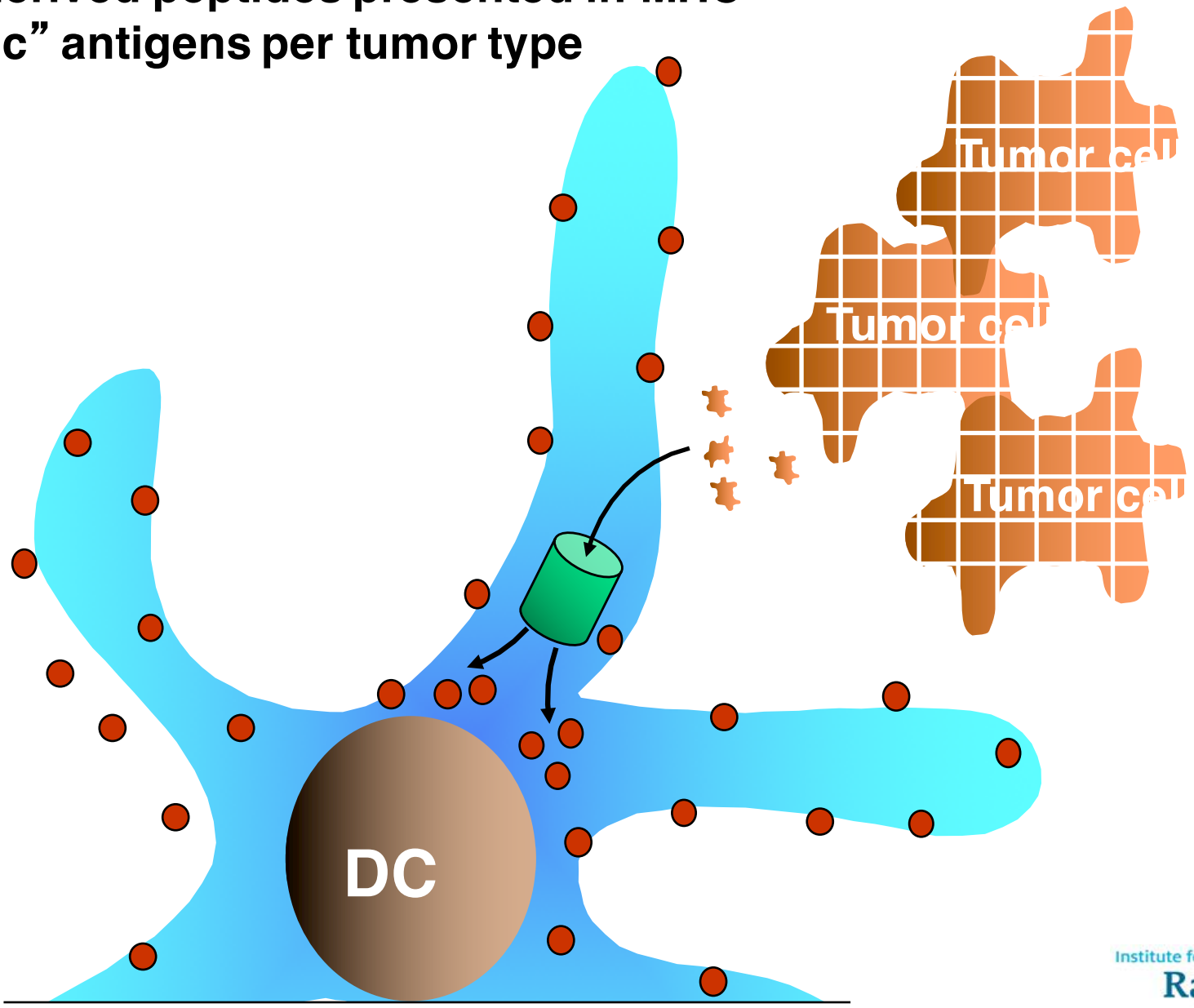
Dendritic cell vaccines

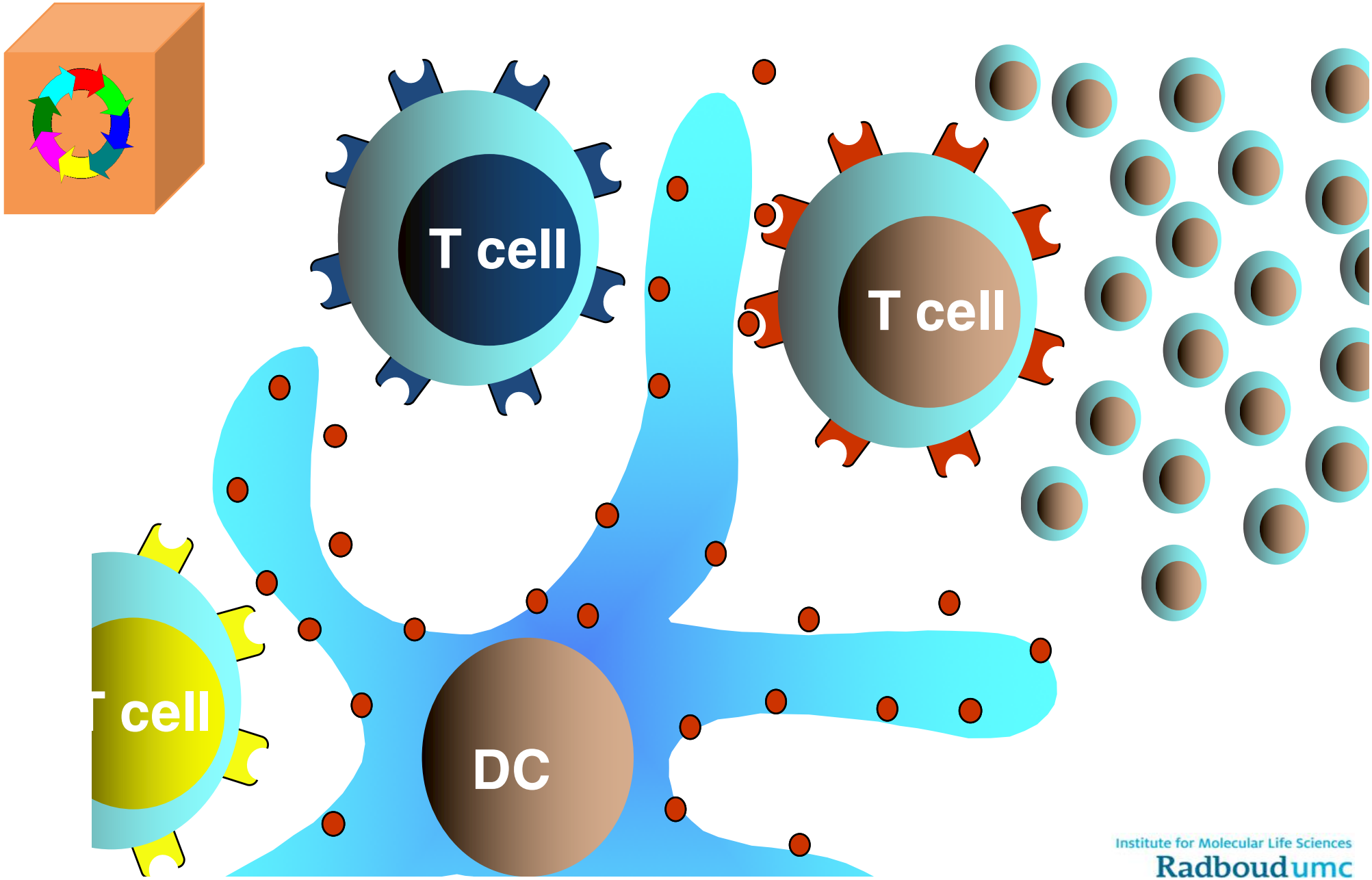
Why DC?

Dendritic cells digest tumor cells

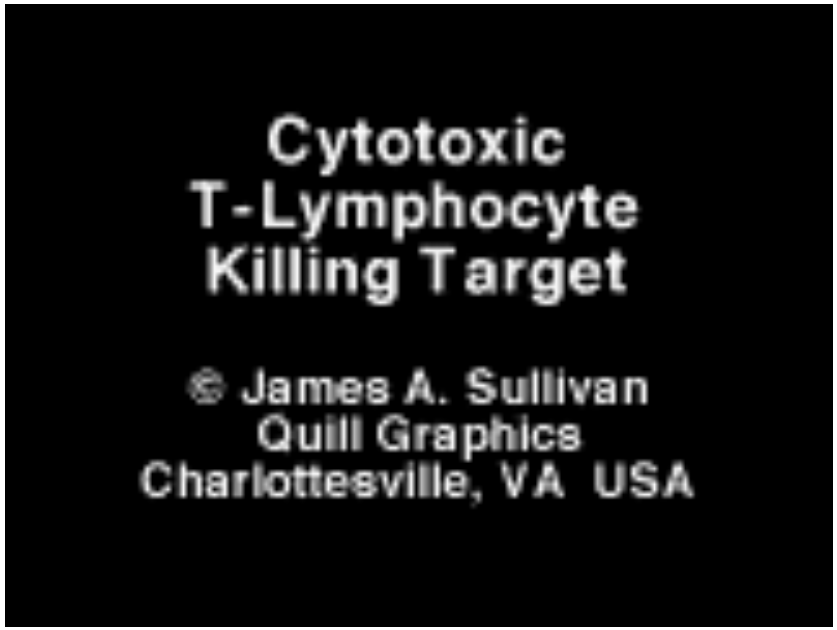
-tumor-derived peptides presented in MHC
-“specific” antigens per tumor type



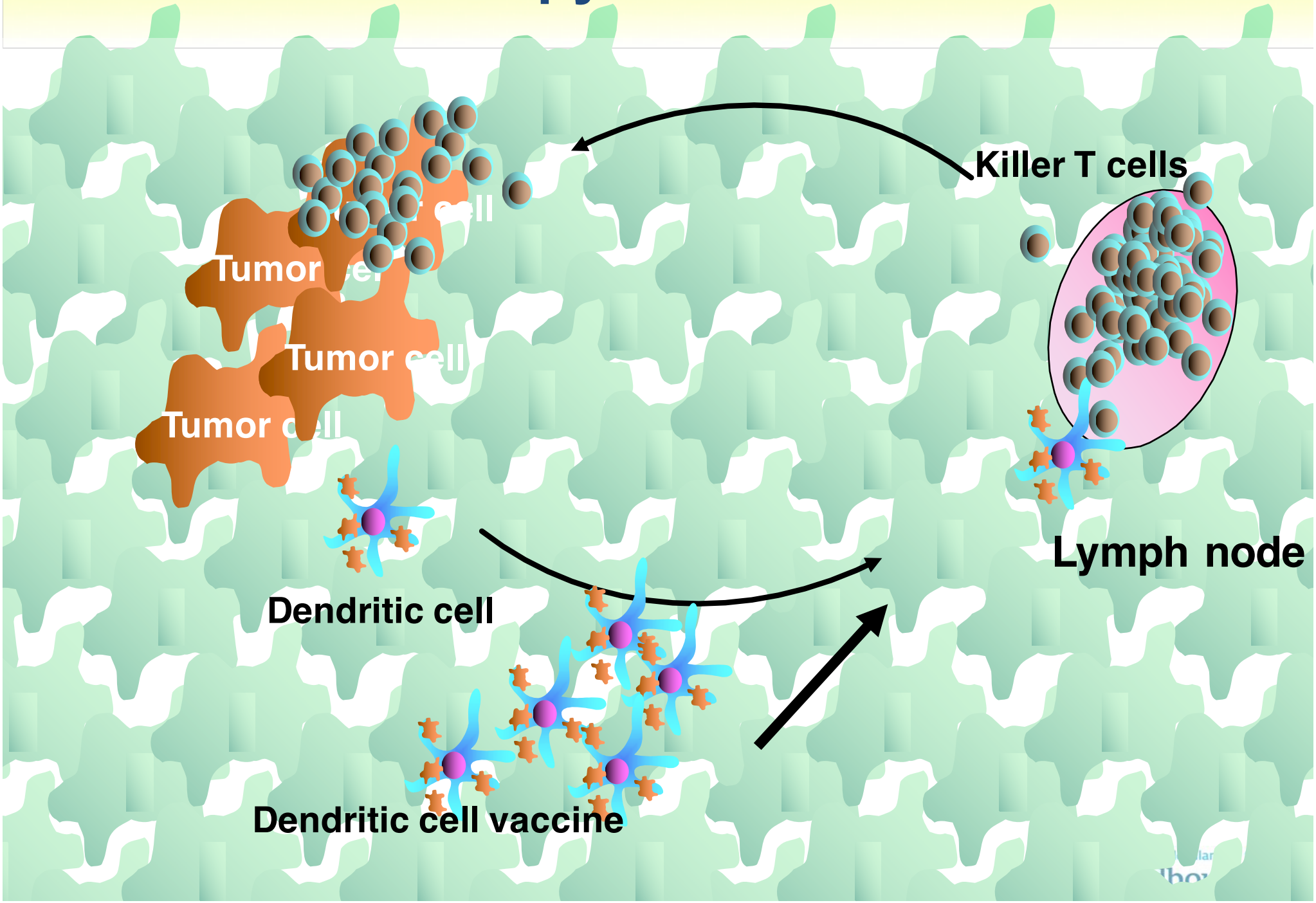
How DC stimulate T cells

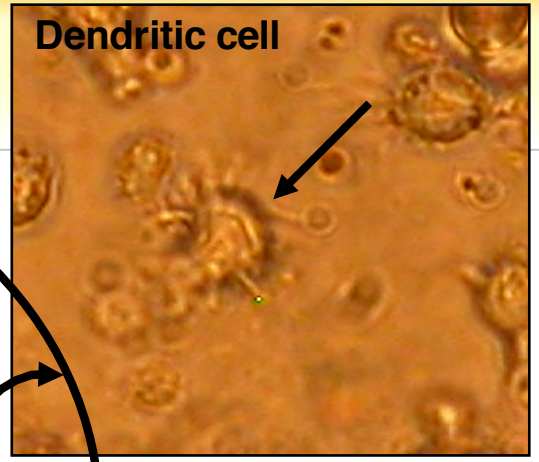


Killer T cells



Immunotherapy with dendritic cells





immature DC

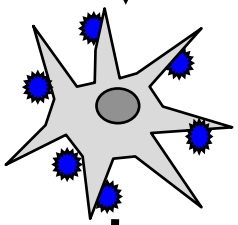
KLH

IL-4
GM-CSF

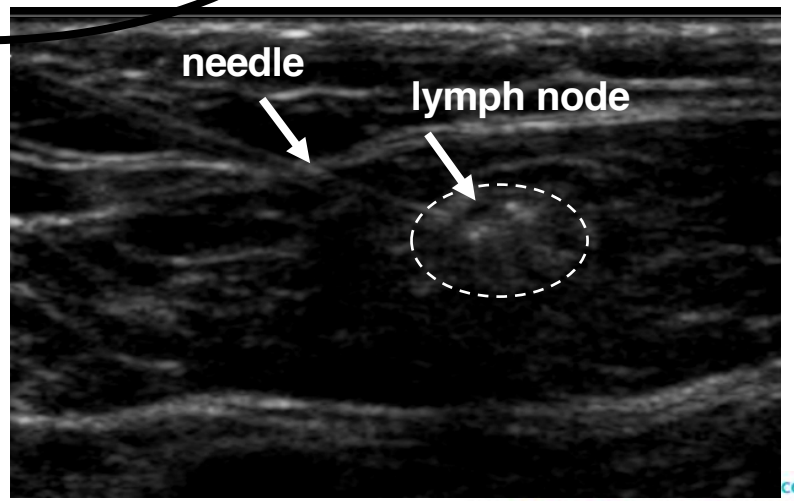
monocytes

TNFα
MCM
PGE_2

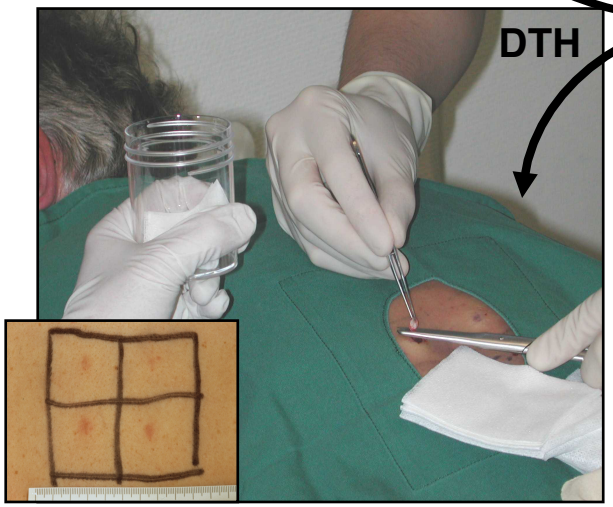
tumor-peptides or mRNA

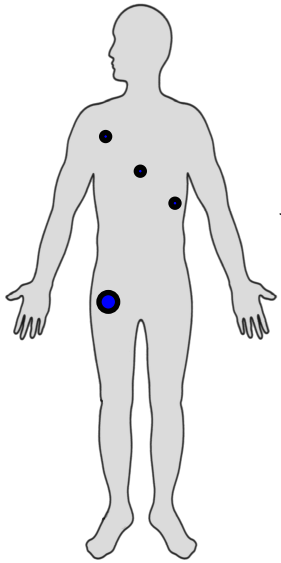


intranodal injection



afereses





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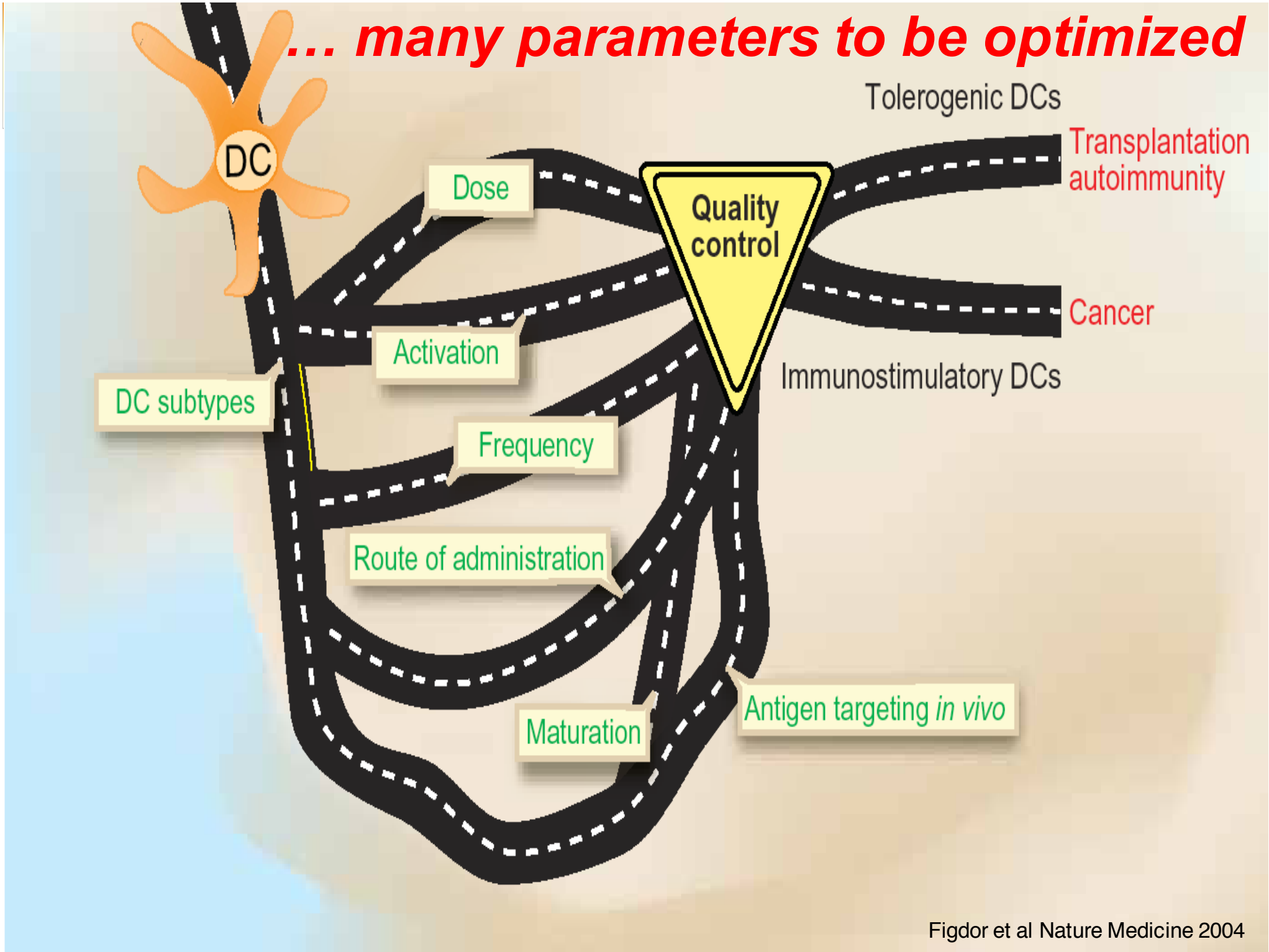
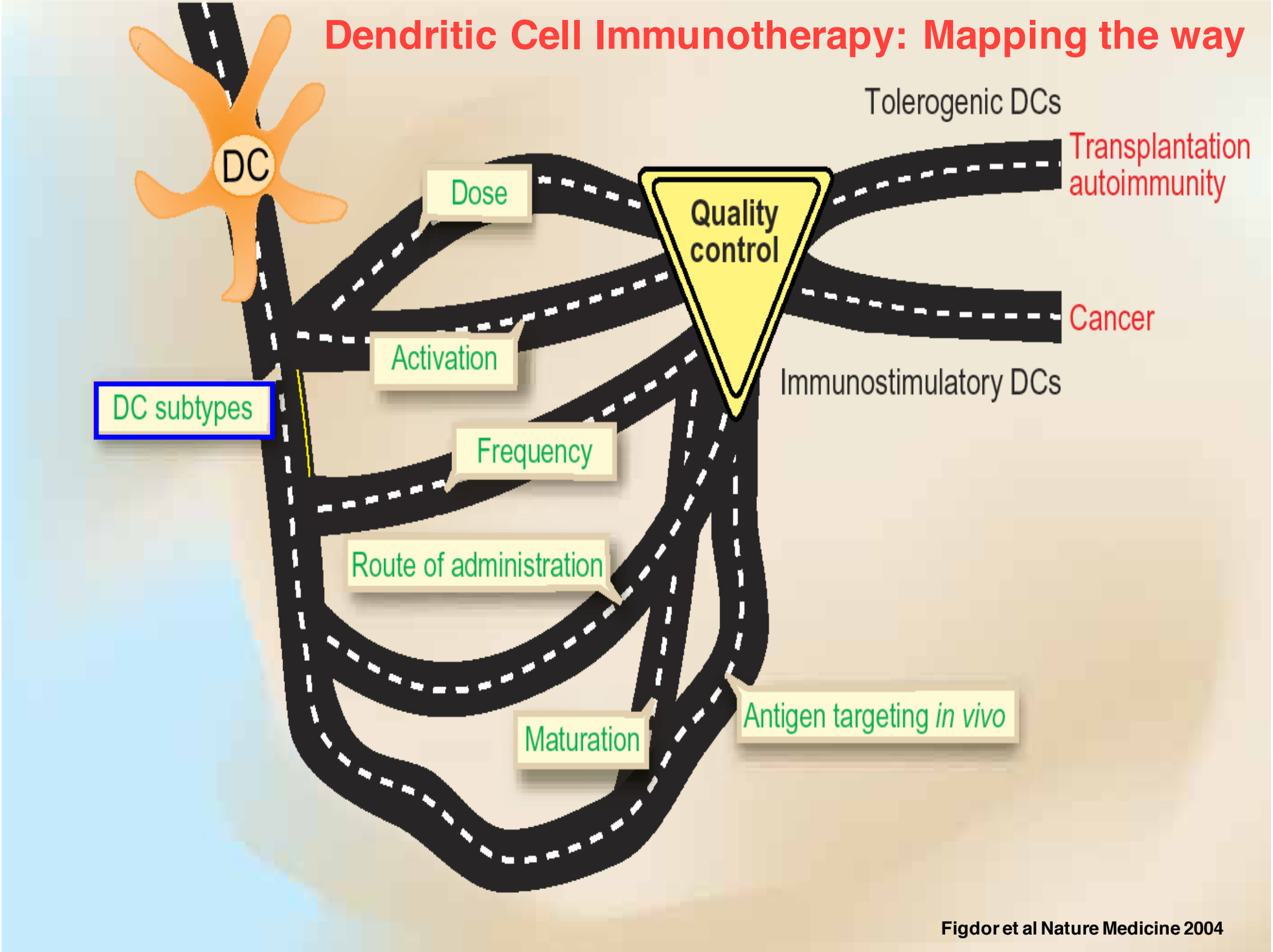
… many parameters to be optimized



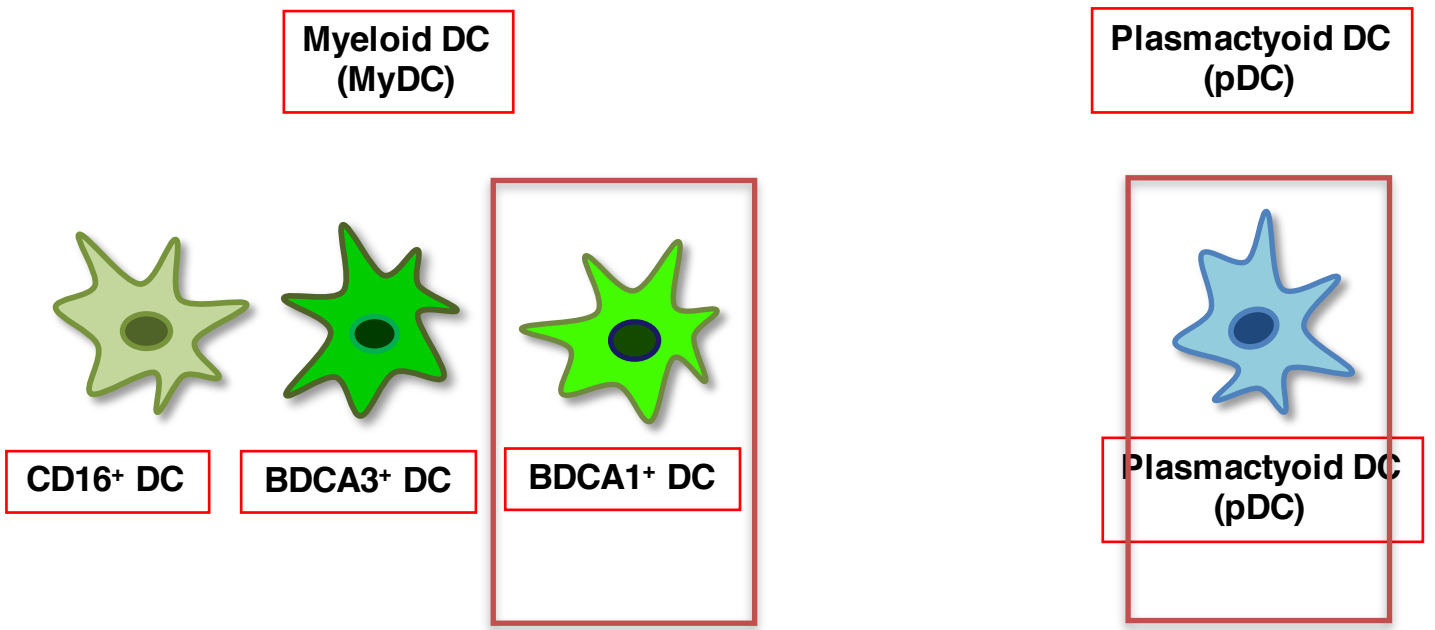
Figdor et al Nature Medicine 2004

Dendritic Cell Immunotherapy: Mapping the way



Figdor et al Nature Medicine 2004

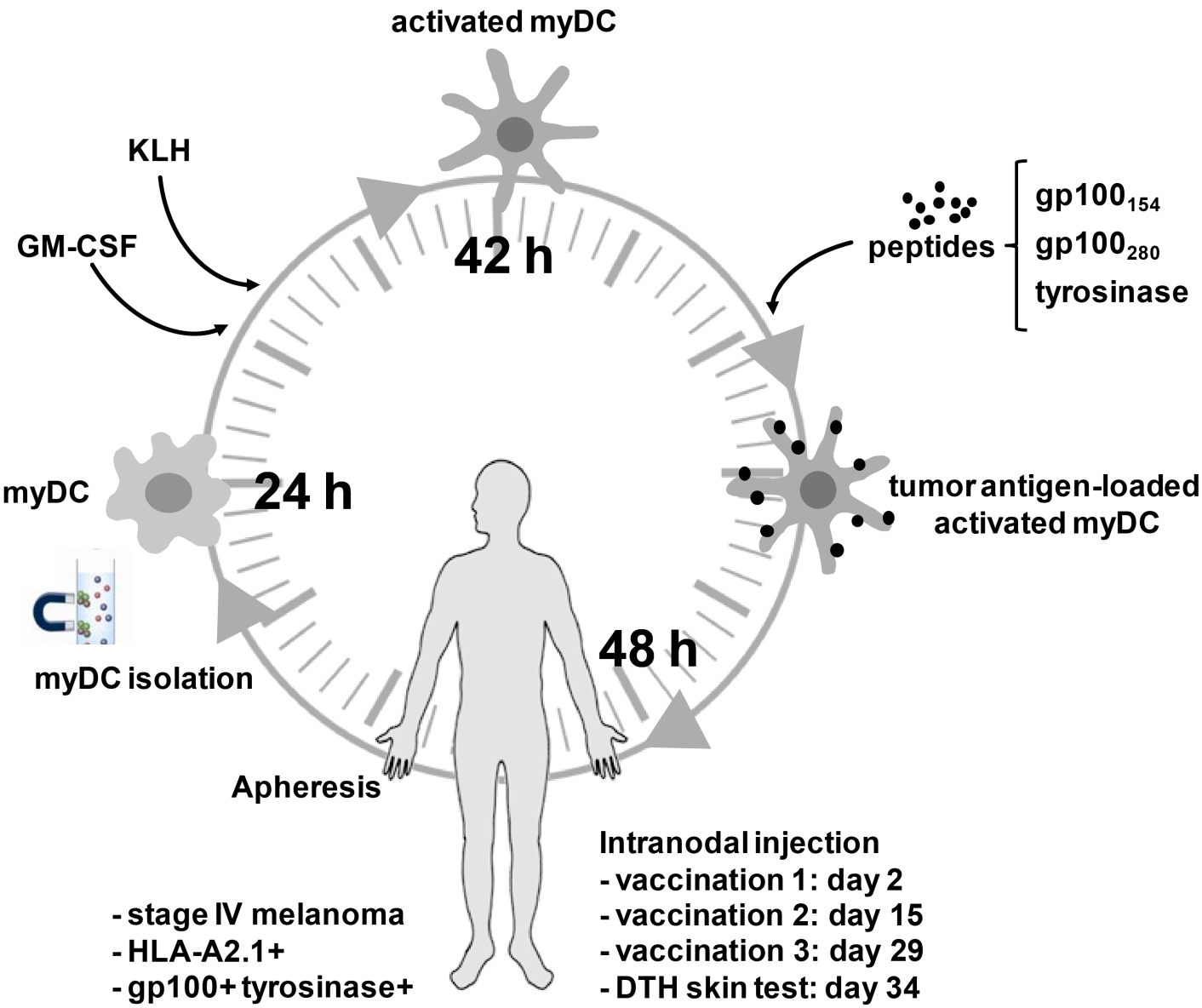
Primary blood DC subsets



Schreibelt et al
Clin Cancer Research 2016

Tel et al
Cancer Research 2013

Rapid BDCA-1+ myDC vaccine preparation



- stage IV melanoma
- HLA-A2.1+
- gp100+ tyrosinase+

Intranodal injection
- vaccination 1: day 2
- vaccination 2: day 15
- vaccination 3: day 29
- DTH skin test: day 34

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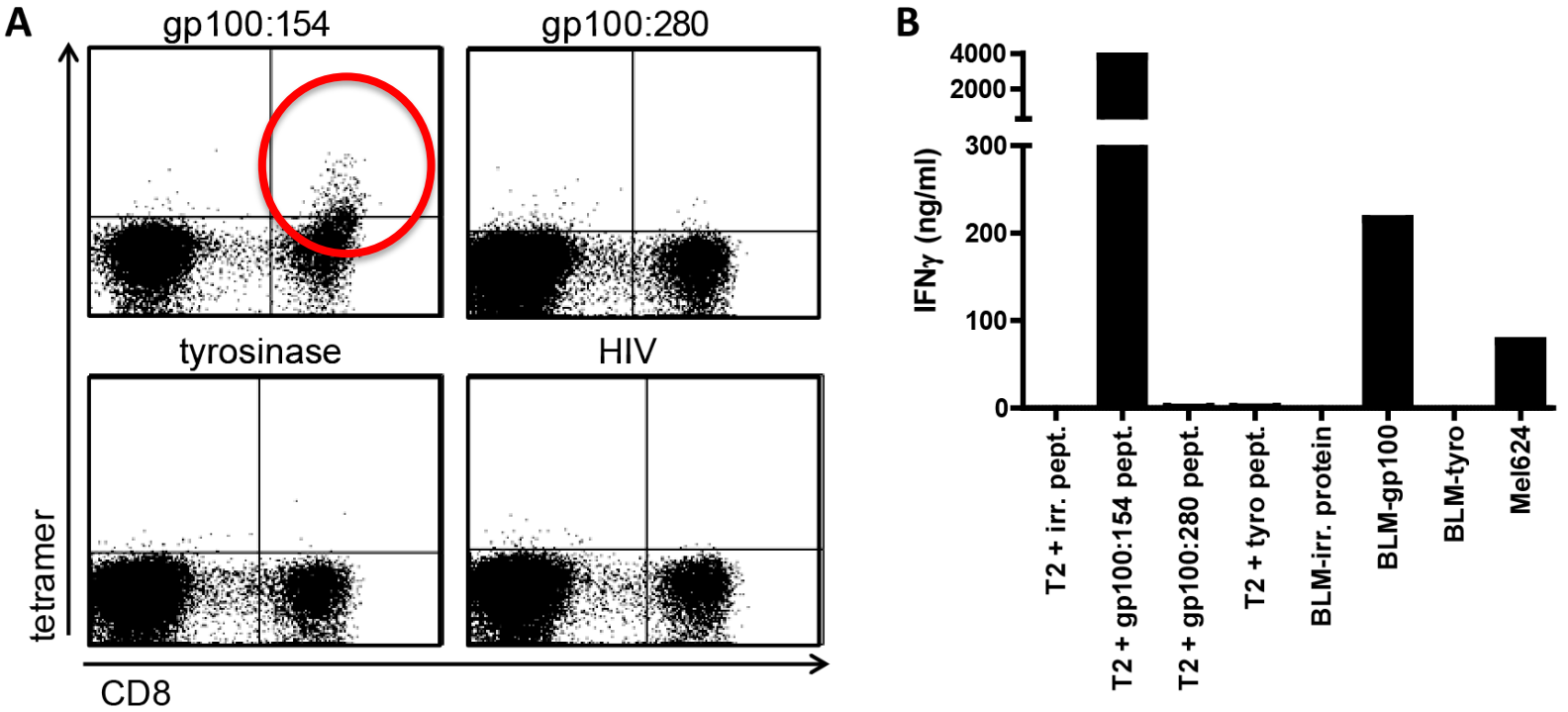
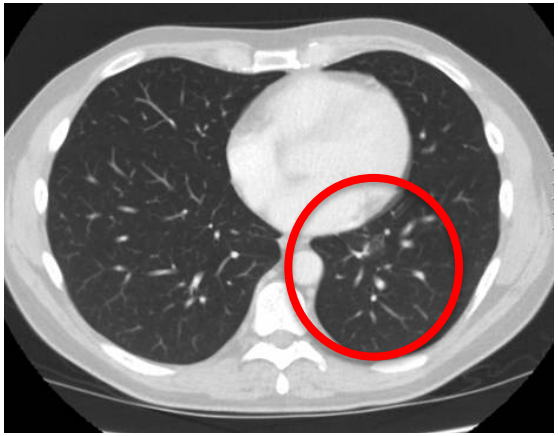
Complete remission

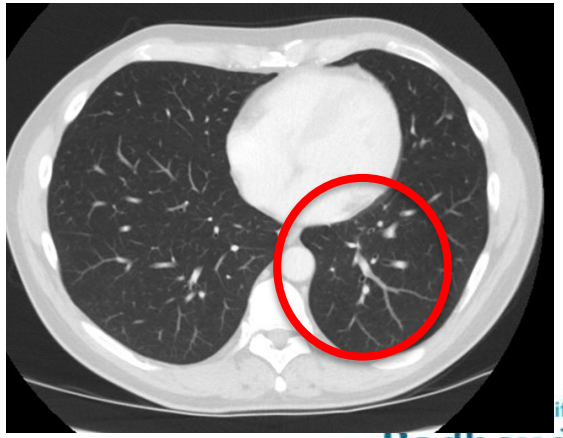


Before

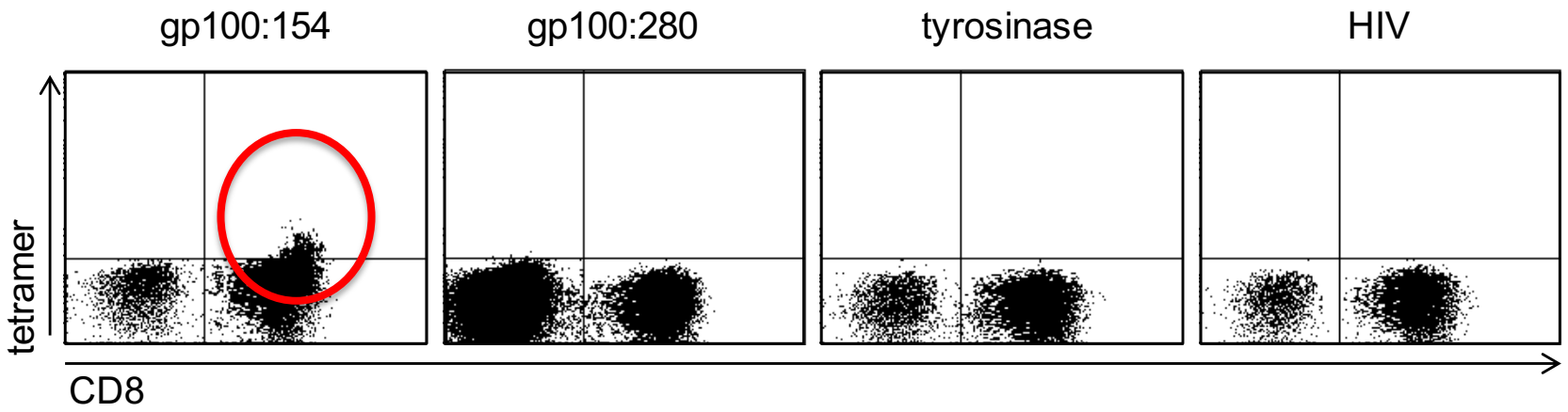
After 1st cycle

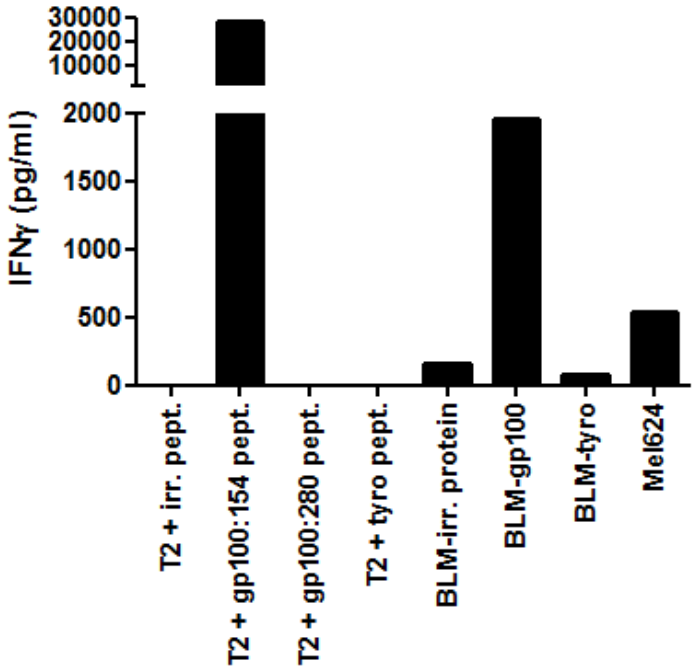


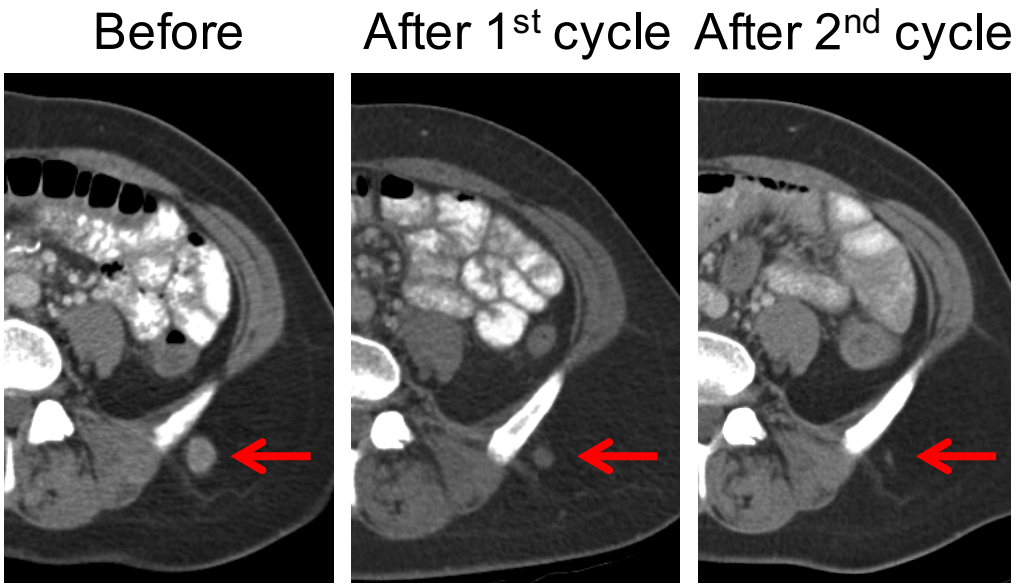
After 3rd cycle



Mixed response

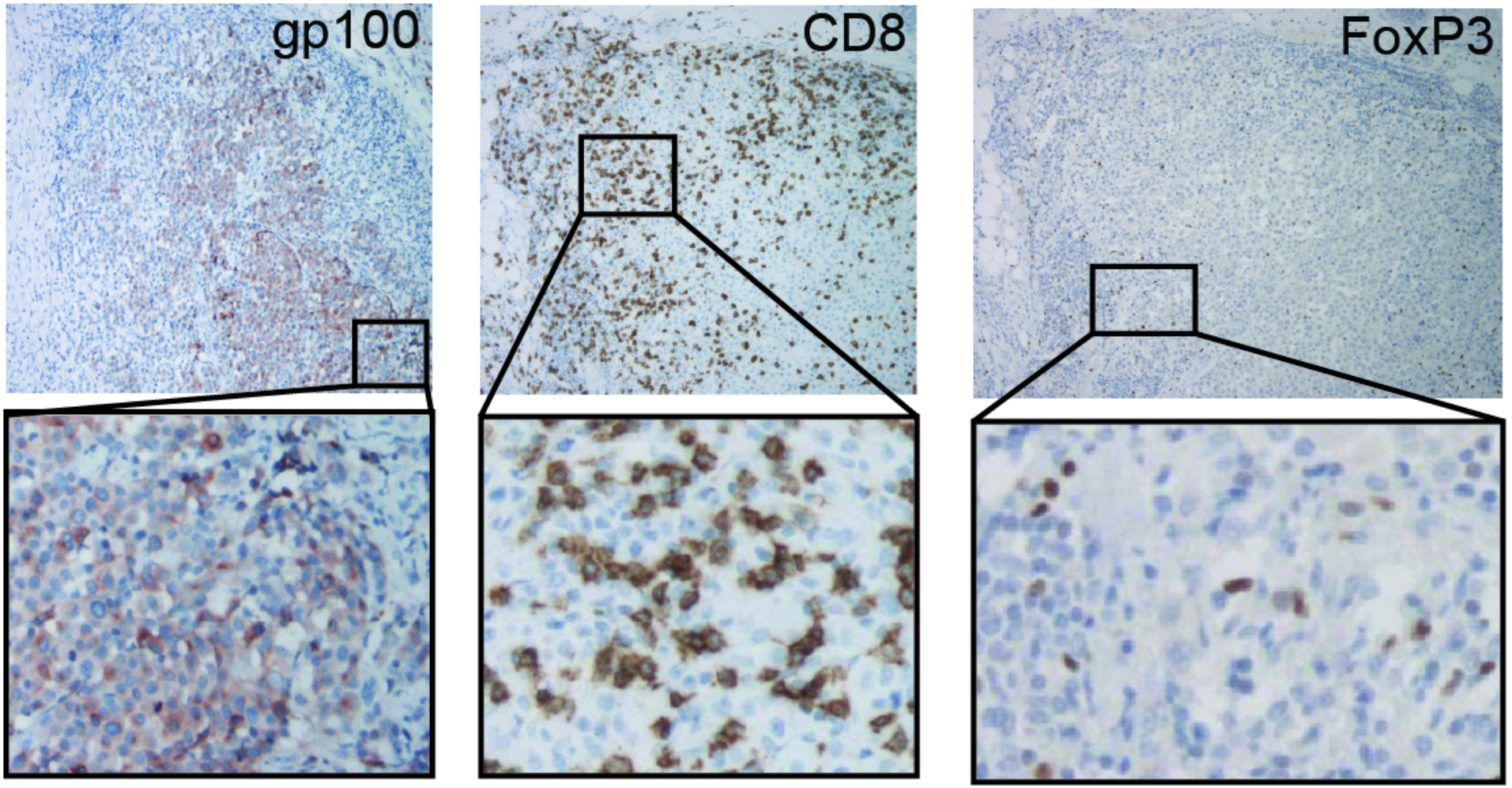






Histochemistry of progressive tumor

Tumor antigen | Cytotoxic T cells | Regulatory T cells



Patient VI-B-08

Patient VI-B-08

- myDC can induce anti-tumor responses in vivo
- Regulatory T cells may inhibit effective anti-tumor responses locally
- Is this the ideal candidate for checkpoint inhibitors like Ipilimumab or anti-PD-1/PD-L1?

  - no objective response to ipilimumab or vemurafenib

Clinical responses in stage IV melanoma patients after vaccination with primary CD1c+ myeloid DCs

Patient	clinical response	Progression free survival (months	Overall survival (months)	T cells blood	T cells biopties
VI-B-01	SD	18	22	+++	+++
VI-B-02	PD	<4	7	-	-
VI-B-03	SD	7	40	-	-
VI-B-04	PD	<4	3	n.a.	n.a.
VI-B-05	PD	<4	9	-	+
VI-B-06	SD	4	13	-	-
VI-B-07	PD	<4	11	-	-
VI-B-08	MR	15	29	+++	+++
VI-B-09	SD	12	15	-	-
VI-B-10	PD	<4	38	-	-
VI-B-11	PD	<4	6	+	-
VI-B-12	PD	<4	11	n.t.	-
VI-B-13	CR	35+	35+	+++	+++
VI-B-14	PD	<4	13	-	-

SD = stable disease
PD = progressive disease
CR = complete remission
MR = mixed response

\+ = antigen-specific T cells present
+++ = functional specific T cells

Schreibelt, Clinical Cancer Research accepted

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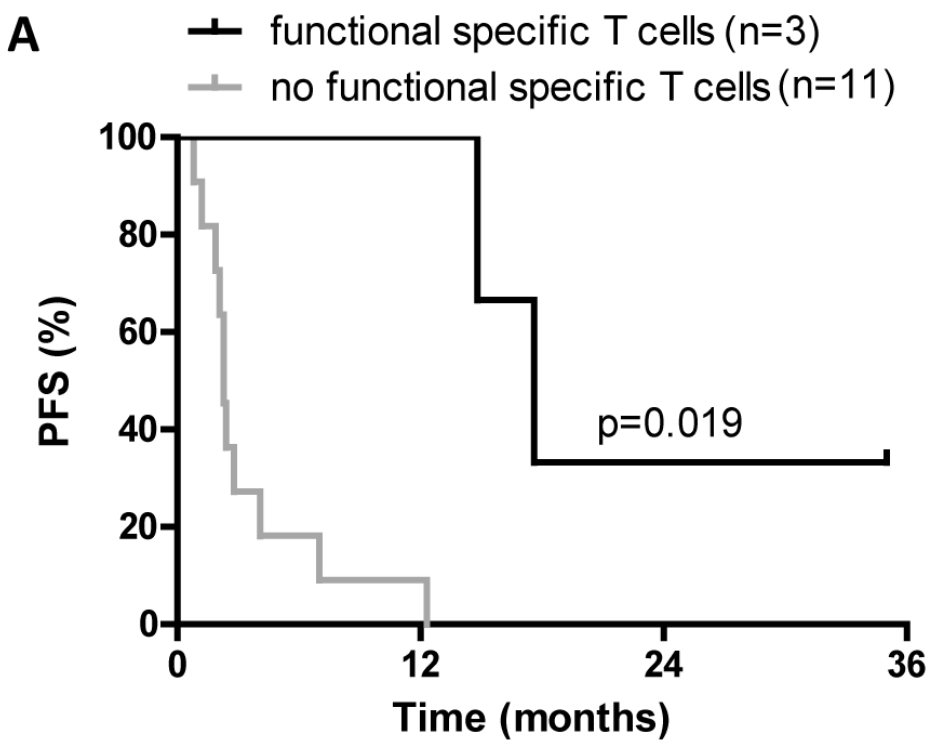
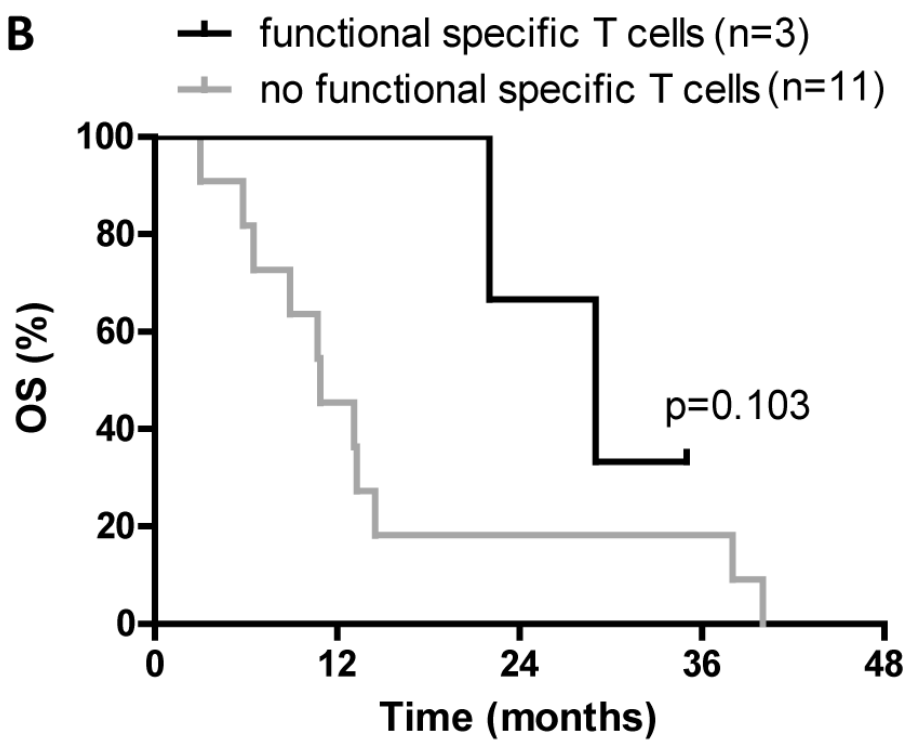
Clinical outcome and functional T cell response

Progression free survival



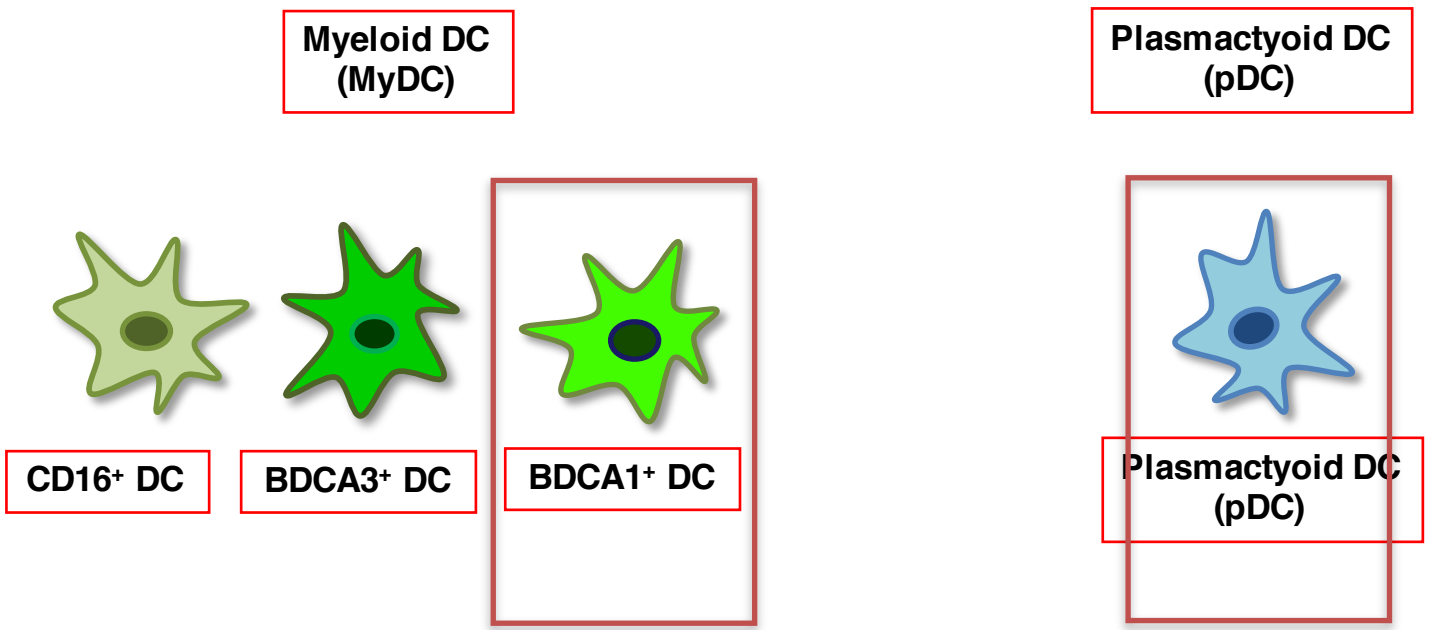
Overall survival



Summary

- Clinical trials with peptide-loaded primary BDCA1+ DCs are feasible and safe
- myDCs can induce strong de novo immune responses and objective clinical responses, even in advanced melanoma patients
- Clinical responses are associated with the presence of multifunctional tumor antigen-specific T cells in blood and DTH
- Next:
  - prove efficacy of DC vaccination with primary DC in a prospective randomized trial
  - combine myDC and pDC
  - combine primary blood DC with checkpoint inhibitors

Primary blood DC subsets



Schreibelt et al
Clin Cancer Research 2016

Tel et al
Cancer Research 2013

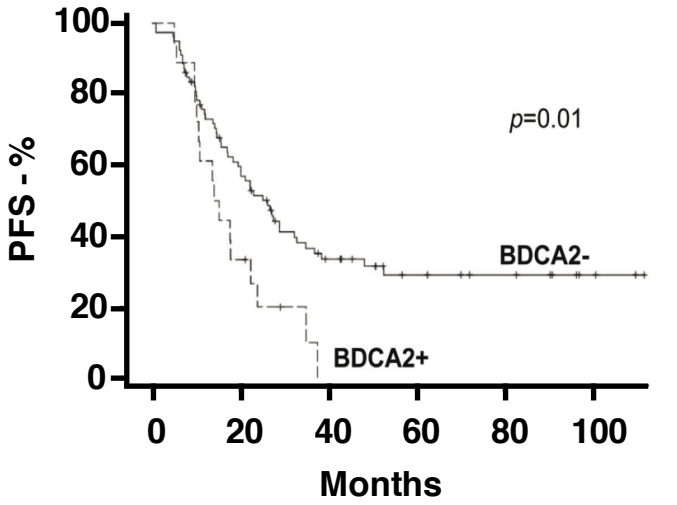
pDC infiltrate solid tumors

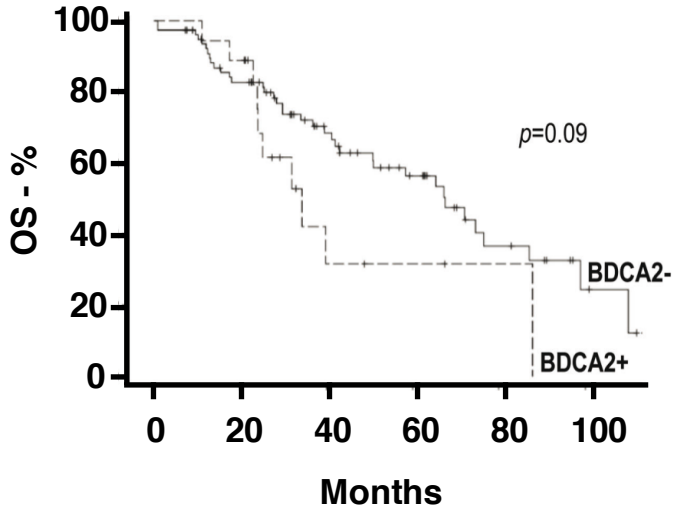
Breast cancer
Ovarian cancer
Head and neck cancer
Lung cancer
Skin cancer
Prostate cancer
Cervix cancer
Liver cancer

Cutaneous melanoma
Lymphomas

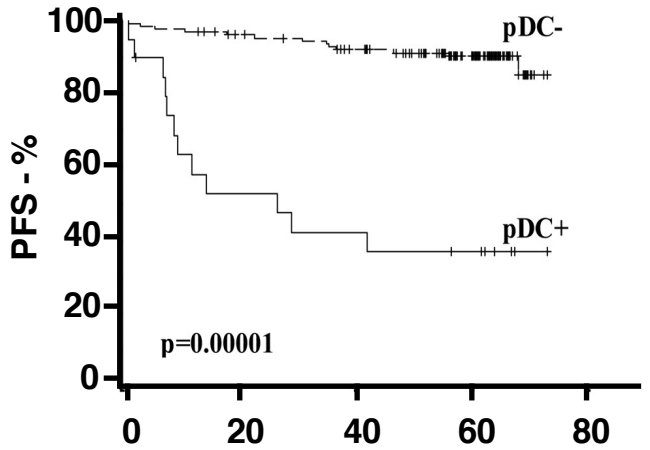
Tumor infiltrating pDC correlate with bad prognosis

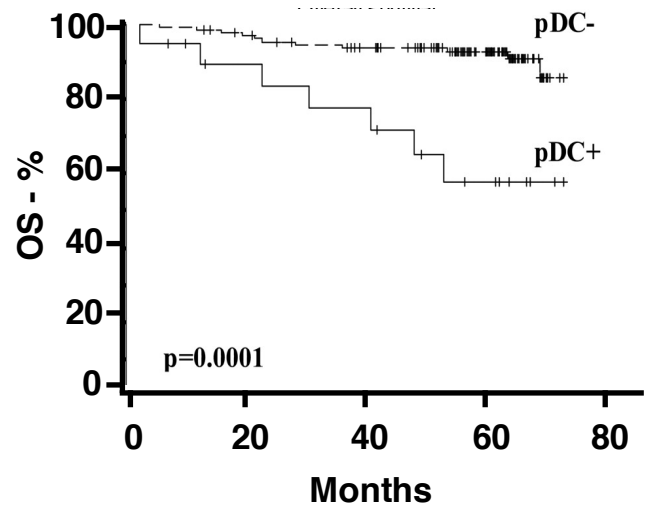
Ovarian Cancer





Breast Cancer





pDC infiltrate solid tumors

Summary studies:

- tumor infiltrating pDC are defective in IFNα production

- secrete immunosuppressive soluble factors

- responsible for tumor progression

Why pDC for cancer immuntherapy?

DC vaccination: pDC

- Type I IFN activates other cells of the (innate) immune system
- Type I IFN seems to yield more potent DC in terms of secretion of IL-12 and induction of tumor-specific CTL and Th1 *in vitro*
- pDC can promote the ability of mDC to cross-prime $CD8^+$ T cells
- pDC create the appropriate environment for efficient CTL response against viruses
- Activated and injected together with mDC, pDC may improve the anti-tumor responses

…TLR-ligand hurdle…

- **TLR 7/8 R848/ssRNA**
- **TLR 9 CpG-DNA**

For clinical studies we need GMP quality products.

These compounds mimic microbes (virus/bacteria)

Can we use "clinical grade virus/bacteria" to activate pDCs?

Commonly used preventive vaccines

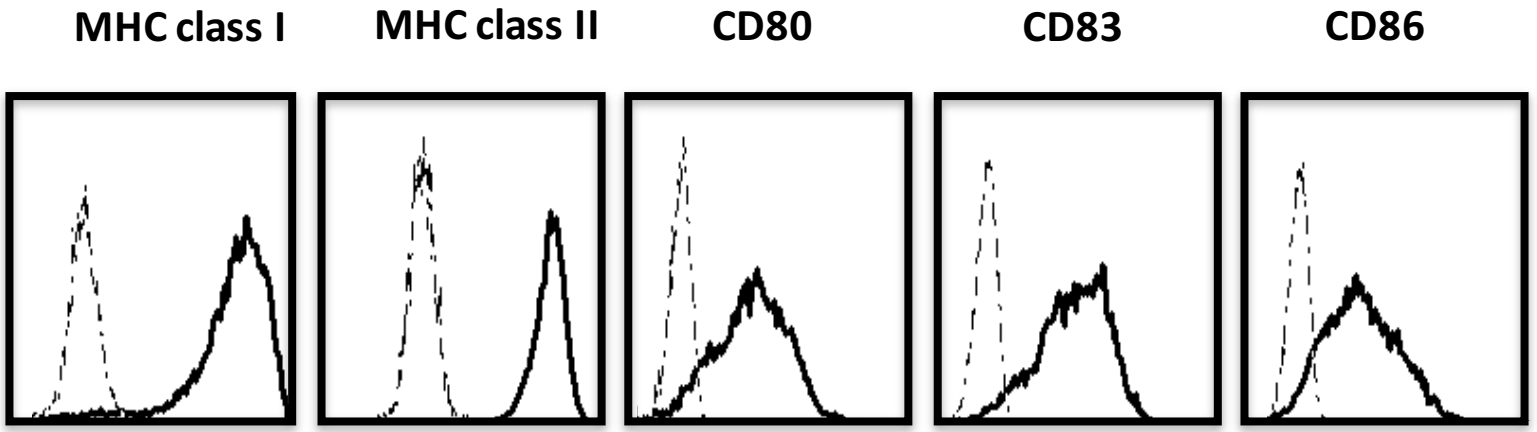
Vaccines tested for TLR-mediated DC stimulation

Infectious agent	Vaccine	Disease	Type of vaccine	Supplier	Adjuvant
bacteria					
Streptococcus pneumoniae	PREVENAR	Pneumonia, otitis media, meningitis	conjugated subunit	Wyeth	$AlPO_4$
Streptococcus pneumoniae	PNEUMO 23	Pneumonia, otitis media, meningitis	subunit	Aventis Pasteur	none
Clostridium tetani	Tetanus	Tetanus	subunit	NVI	$AlPO_4$, thiomersal
Salmonella typhi	TYPHIM Vi	Typhoid fever	subunit	Sanofi pasteur	none
Haemophilis influenzae type b	Act-HIB	Meningitis, epiglottitis, pneumonia type b	Conjugated subunit	Aventis Pasteur	Tetanus toxoid
Neisseria meningitidis	NEISVAC-C	Meningitis, sepsis	Conjugated subunit	Baxter	$Al(OH)_3$/Tetanus toxoid
Mycobacterium bovis	BCG	Tuberculosis	live attenuated	NVI	none
viruses					
Hepatitis A virus	HAVRIX	Liver disease, cancer	inactivated	Glaxo SmithKline	AlO(OH)
Hepatitis B virus	HBVAXPRO	Liver disease, cancer	Recombinant subunit	Sanofi Pasteur	$AlPO_4$
Tick-borne encephalitis virus	FSME	Tick-borne encephalitis	inactivated	Baxter	$Al(OH)_3$
Rabies virus	Rabies	Rabies	inactivated	Sanofi Pasteur	Neomycin
Yellow fever virus	STAMARIL	Jaundice, kidney and liver failure	Live attenuated	Sanofi Pasteur	none
Measles virus Mumps virus Rubella virus	BMR	German measles, Respiratory tract infection, mumps, meningitis, orchitis	Live attenuated	NVI	none
Corynebacterium diphtheriae *Clostridium tetani* *Bortella pertussis* Poliovirus *Haemophilis influenzae* type b	INFANRIX-IPV +HIB	Difteria Tetanus Pertussis Poliomyelitis, paralysis Meningitis, epiglottitis, pneumonia type b	subunit, inactivated, conjugated	Glaxo SmithKline	$AlPO_4$, AlO(OH), Tetanus toxoid
Influenzavirus A Influenzavirus B	INFLUVAC 2006-2007, INFLUVAC 2007-2008	Flu, respiratory diseases	Inactivated subunit	Solvay Pharma	none

Stimulation of pDC by preventive vaccines

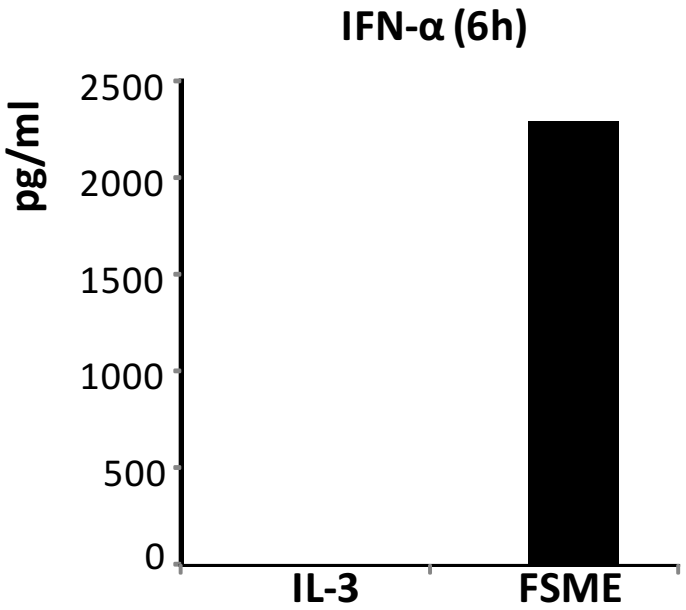
Infectious agent	Vaccine	pDC survival	IFN-α by pDC	Maturation of pDC
bacteria				
Streptococcus pneumoniae	PREVENAR	-	-	-
Streptococcus pneumoniae	PNEUMO 23	-	-	-
Clostridium tetani	Tetanus	-	-	-
Salmonella typhi	TYPHIM Vi	+	-	-
Haemophilis influenzae type b	Act-HIB	+	-	+
Neisseria meningitidis	NEISVAC-C	-	-	-
Mycobacterium bovis	BCG	+	-	+
viruses			-	-
Hepatitis A virus	HAVRIX	-	-	-
Hepatitis B virus	HBVAXPRO	-	-	-
Tick-borne encephalitis virus	FSME	+	+	+
Rabies virus	Rabies	+	+	-
Yellow fever virus	STAMARIL	+	-	-
Measles virus Mumps virus Rubella virus	BMR	+	+	-
Corynebacterium diphtheriae *Clostridium tetani* *Bortella pertussis* Poliovirus *Haemophilis influenzae* type b	INFANRIX-IPV+HIB	-	-	-
Influenzavirus A Influenzavirus B	INFLUVAC 2006-2007,	-	-	-

Maturation of pDC by FSME

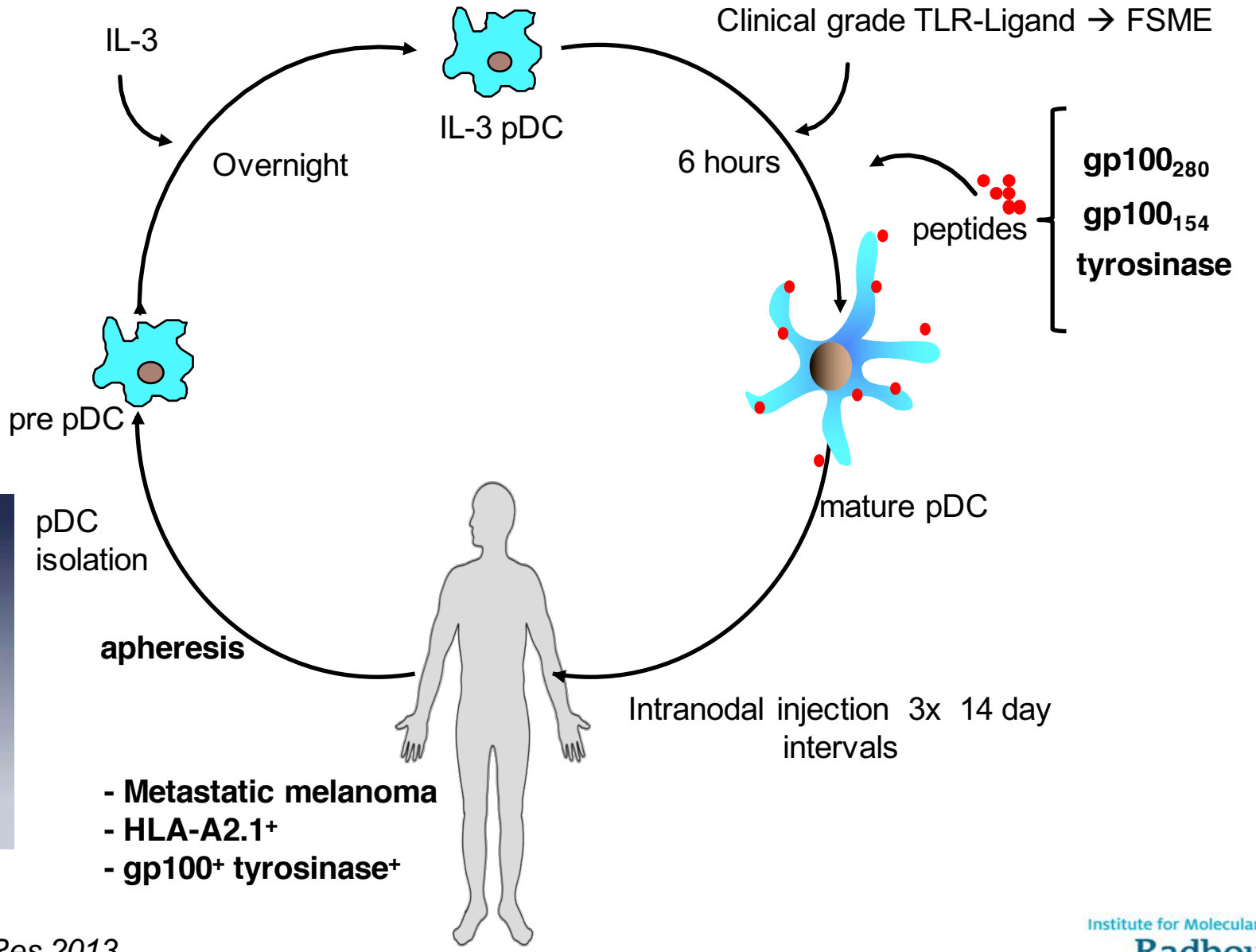


Fresh pDC

6 hours FSME



Vaccination & culture strategy



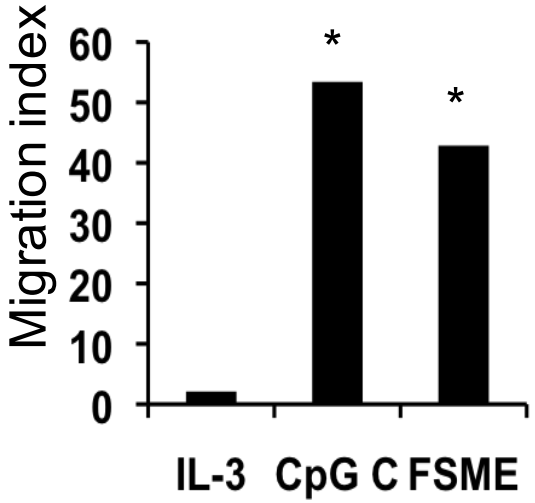
Tel et al Cancer Res 2013

What is the mechanism?

Migration of plasmacytoid DC

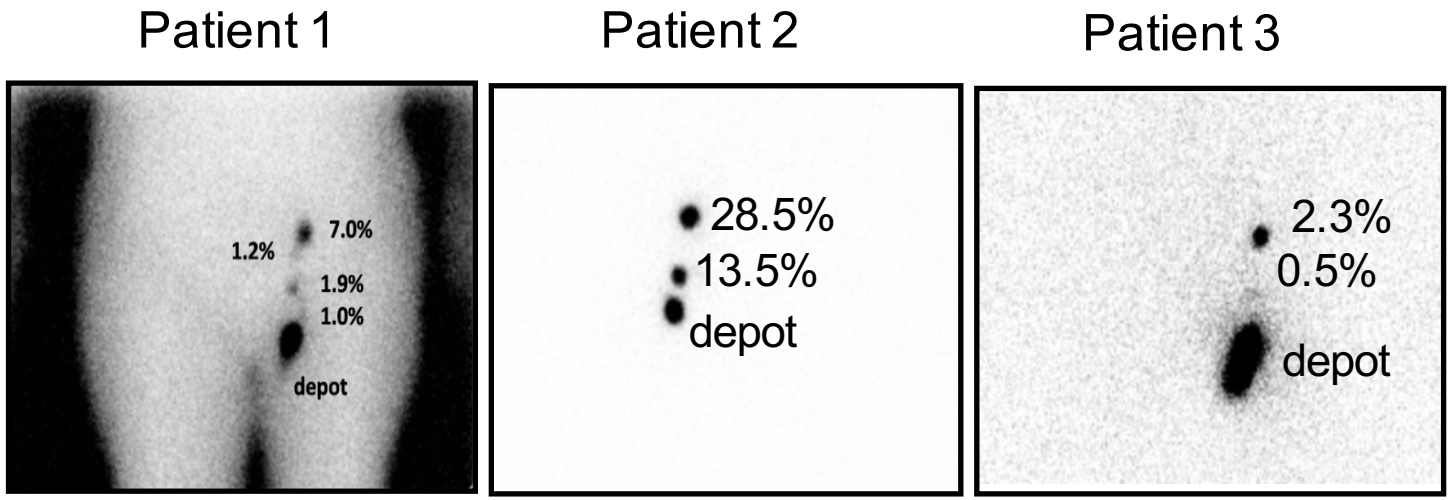
In vitro

towards CCL21



In vivo

after intranodal injection



l et al Cancer Res 2013, Aarntzen et al Clin Cancer Res 2013

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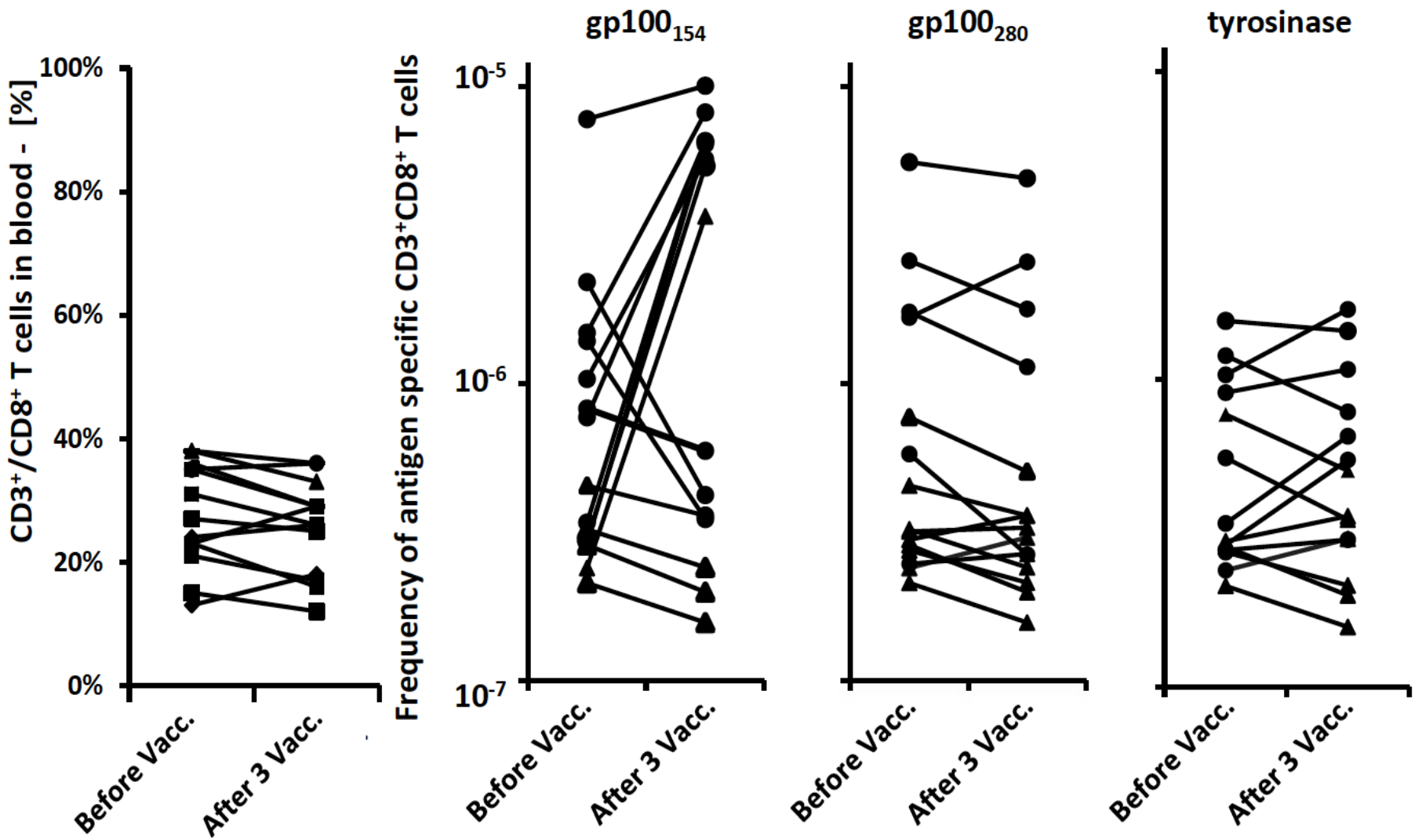
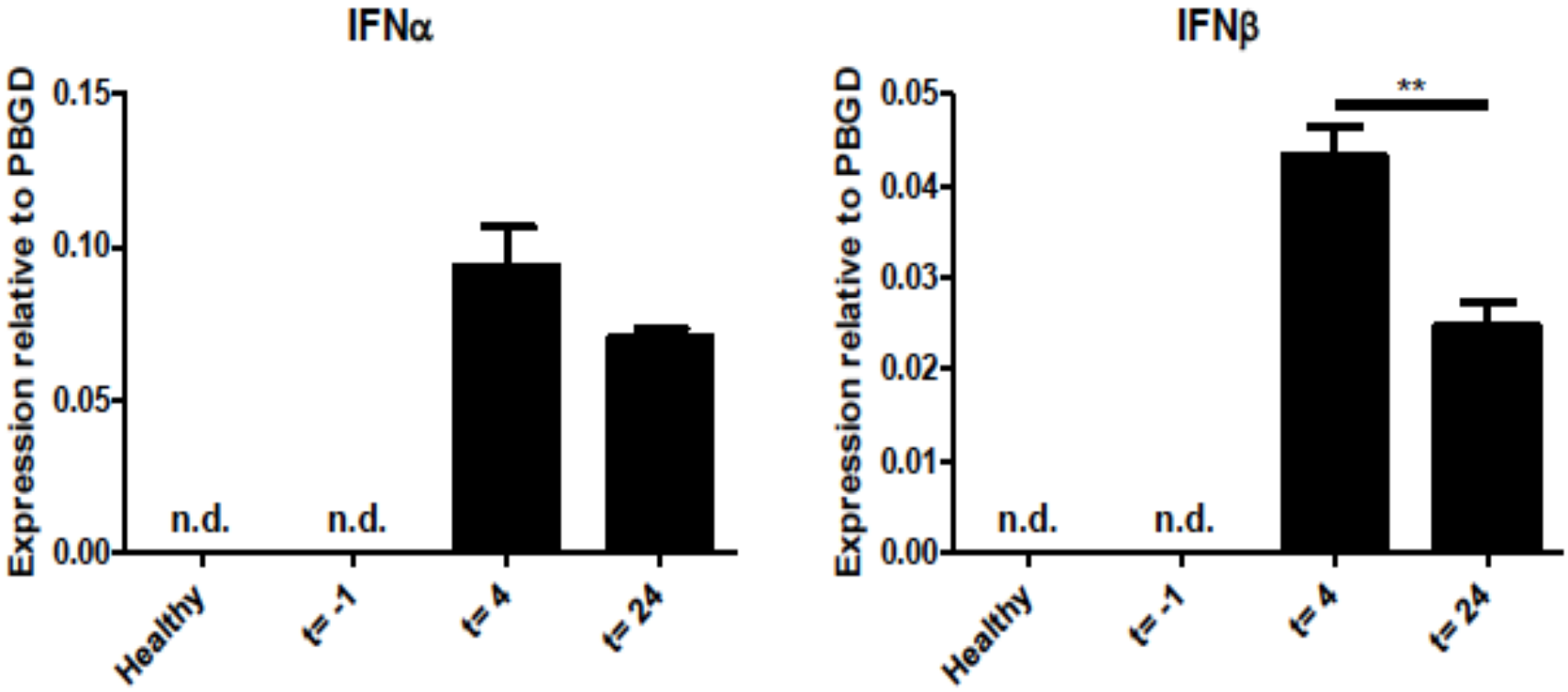
Frequency of precursor T cells in PBMC



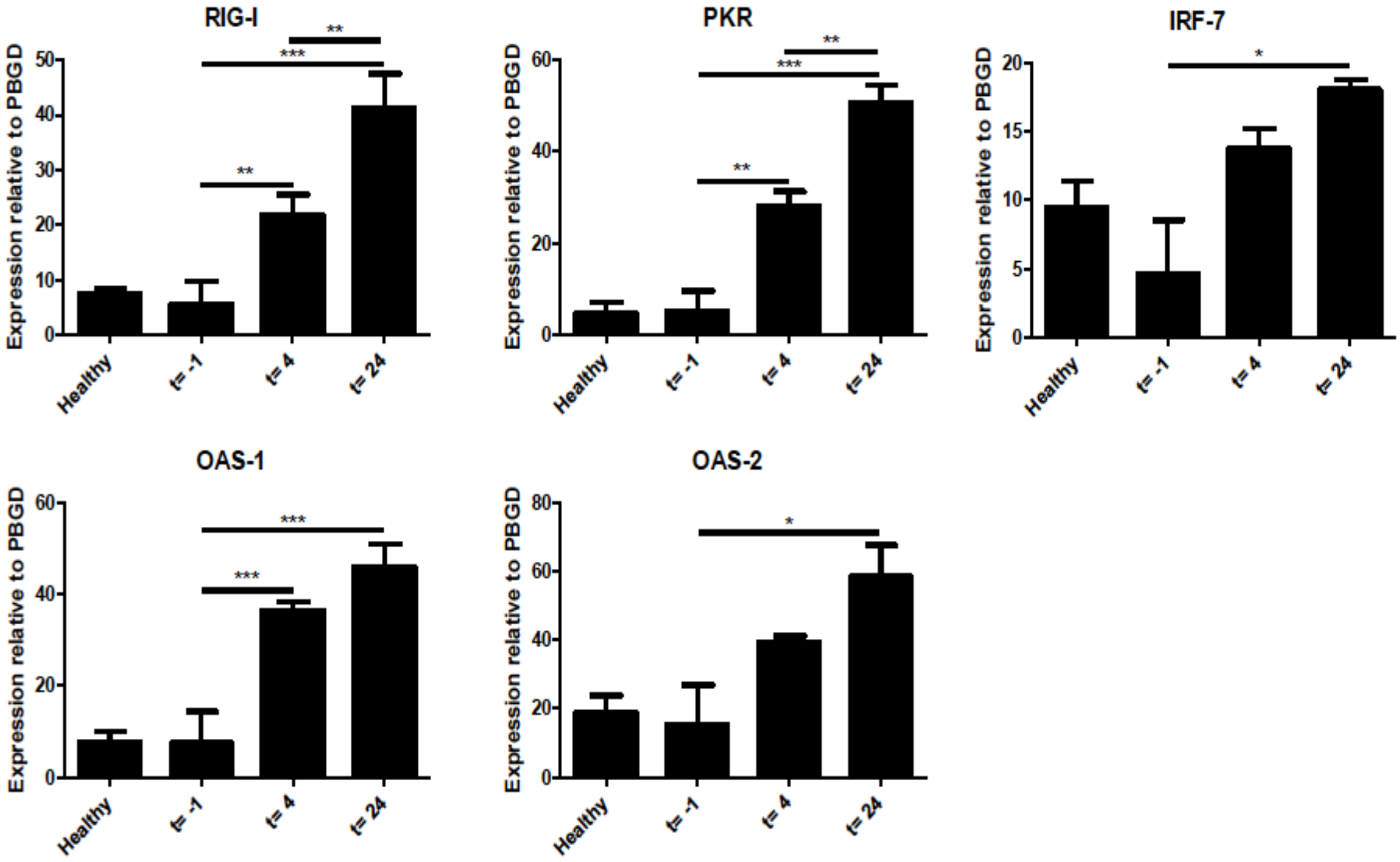
Tel, Cancer Research 2013

mRNA expression of Interferons in blood



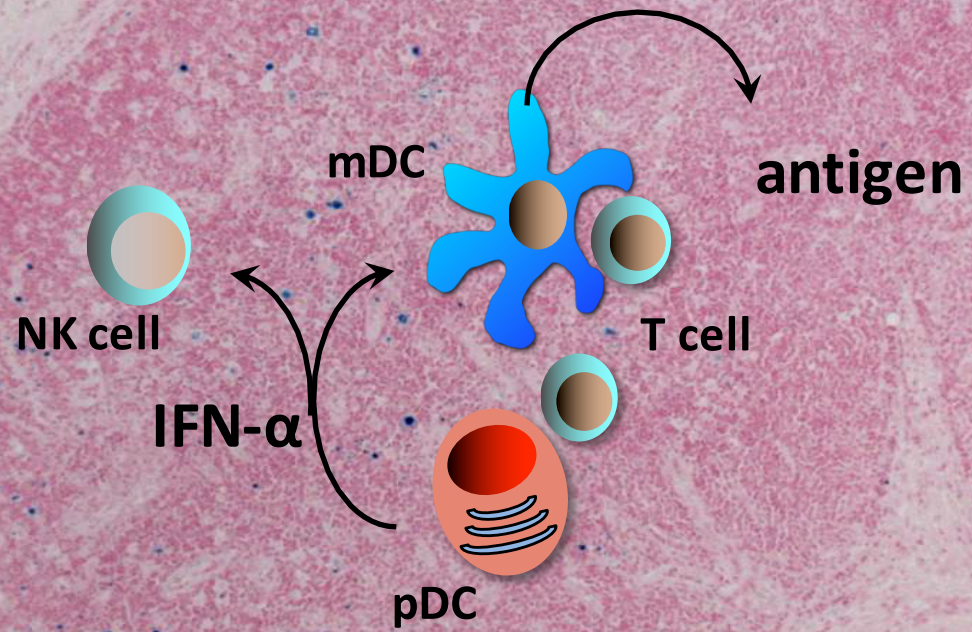
Tel, Cancer Research 2013

mRNA expression of IFN-regulated genes in blood



Tel, Cancer Research 2013

Mechanism?



Is it the IFN-α that activates cells of the innate immune system, such as NK cells?

Does it lead to activation of local mDC and presentation of endogenous antigens?

Is it better presentation of the tumor antigens loaded onto the pDC?

Is the massive FSME response the driving factor?

Is it reactivation of dormant effector T cells?

Summary pDC vaccination

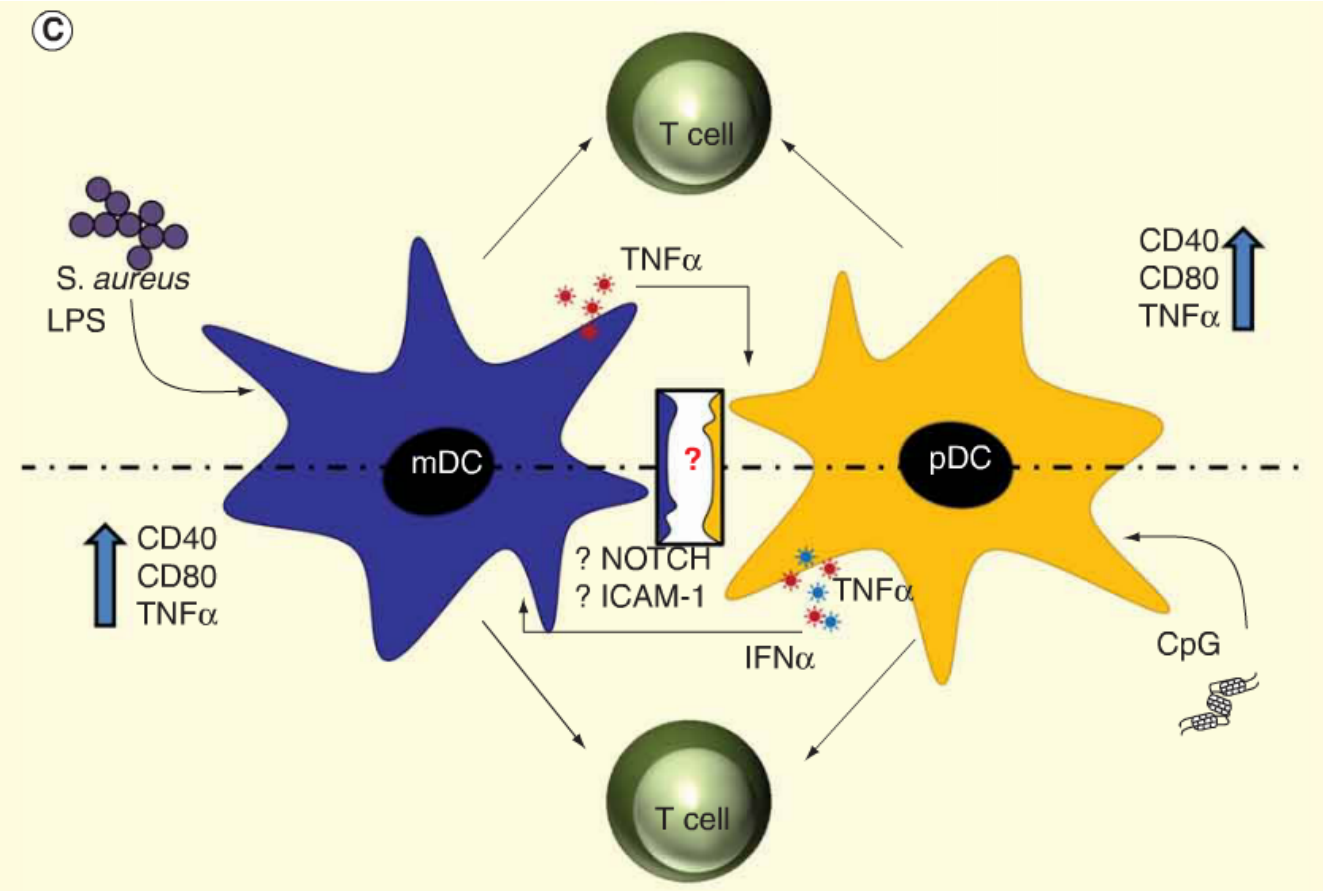
- **Clinical trials with peptide-loaded pDC are feasible**
- **No severe side effects nor toxicity has been observed**
- **Preliminary findings indicate that even small numbers of pDC can induce an immune response in cancer patients**
- **A first phase I/II study demonstrates significant increase in overall survival of stage IV melanoma patients**

Conclusions

- Clinical trials with pDC and myDC are feasible
- Vaccines are rapidly produced
- No severe side effects nor toxicity has been observed
- Preliminary findings indicate that even small numbers of pDC or myDC can induce a response in cancer patients
- Increased overall survival correlates with Ag specific multifunctional T cells and SKILs
- Results primary DC are much better than with moDC
- PDC and myDC seem to exploit different mechanisms and a synergistic effect might be achieved if they are combined

Combine myDC and pDC

- **pDC-myDC cross-talk**
- **Synergy in anti-pathogen and anti-tumor responses**



Bakdash et al, *Expert Rev. Clin. Immunol.* 2014

Future perspectives

- **Vaccination with primary DC subsets is a serious and non-toxic treatment option in melanoma.**

- **We need larger scale DC vaccination studies! A multicentre randomized phase II/III combined pDC and mDC trial is planned (210 pts), for the first time sponsored by the Dutch health authorities.**

- **Standardized vaccine production by fully automated Prodigy (Miltenyi) will greatly facilitate multicentre trials.**

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