

Dendritische cel vaccinatie bij gemetastaseerd melanoom

I. Jolanda M. de Vries
Department of Tumor Immunology

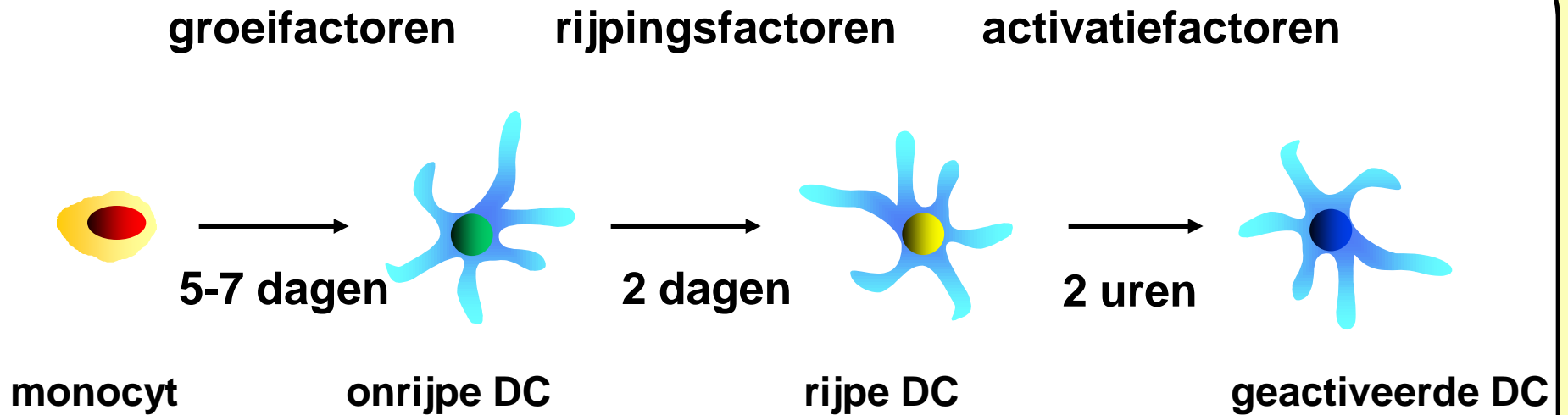
Nijmegen Centre for Molecular Life Sciences
Radboud University Nijmegen Medical Centre

Email: j.devries@ncmls.ru.nl



Wat is een Dendritische Cel?

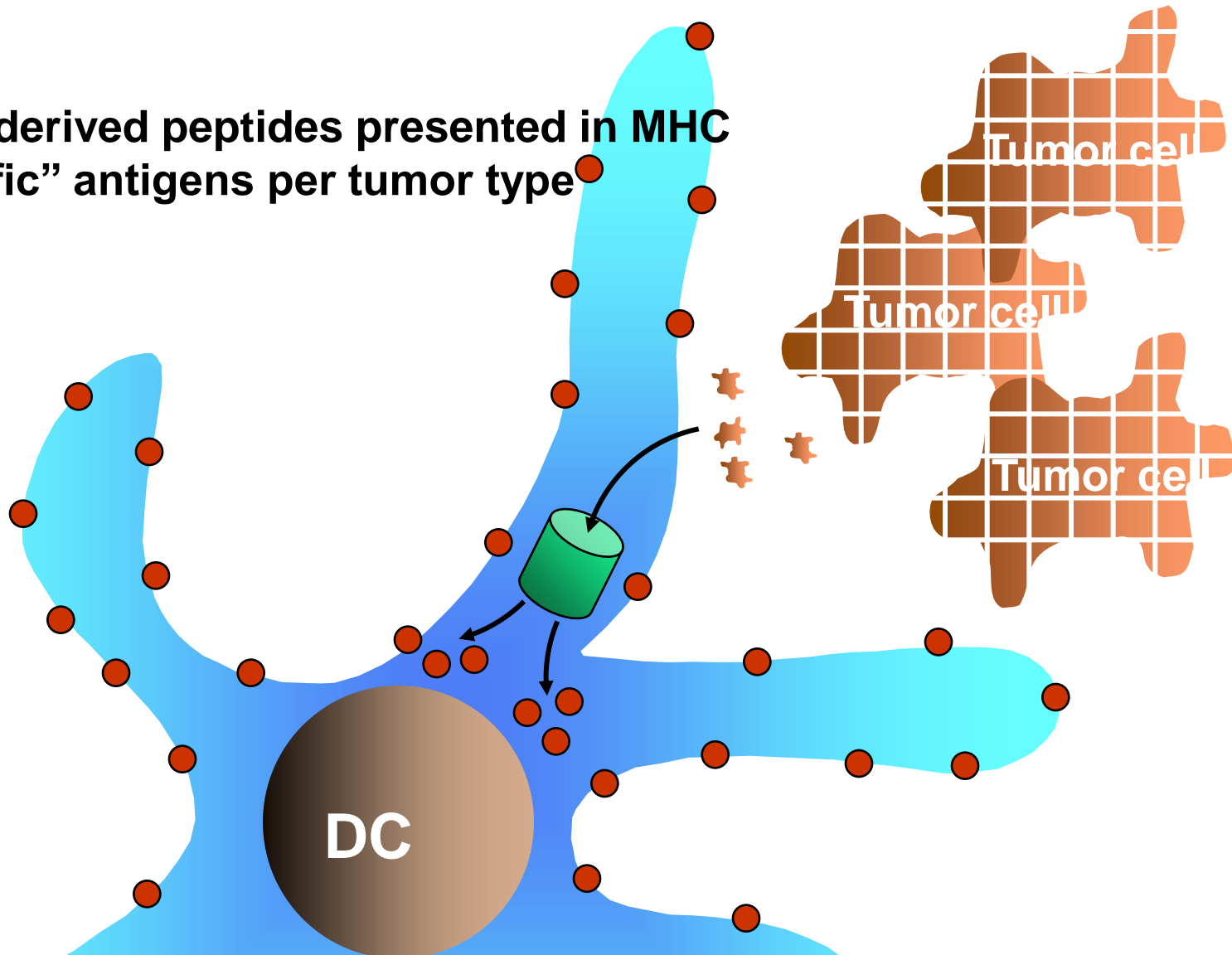
Uitrijpen van dendritische cellen (DC) in het celweek laboratorium duurt 9 dagen



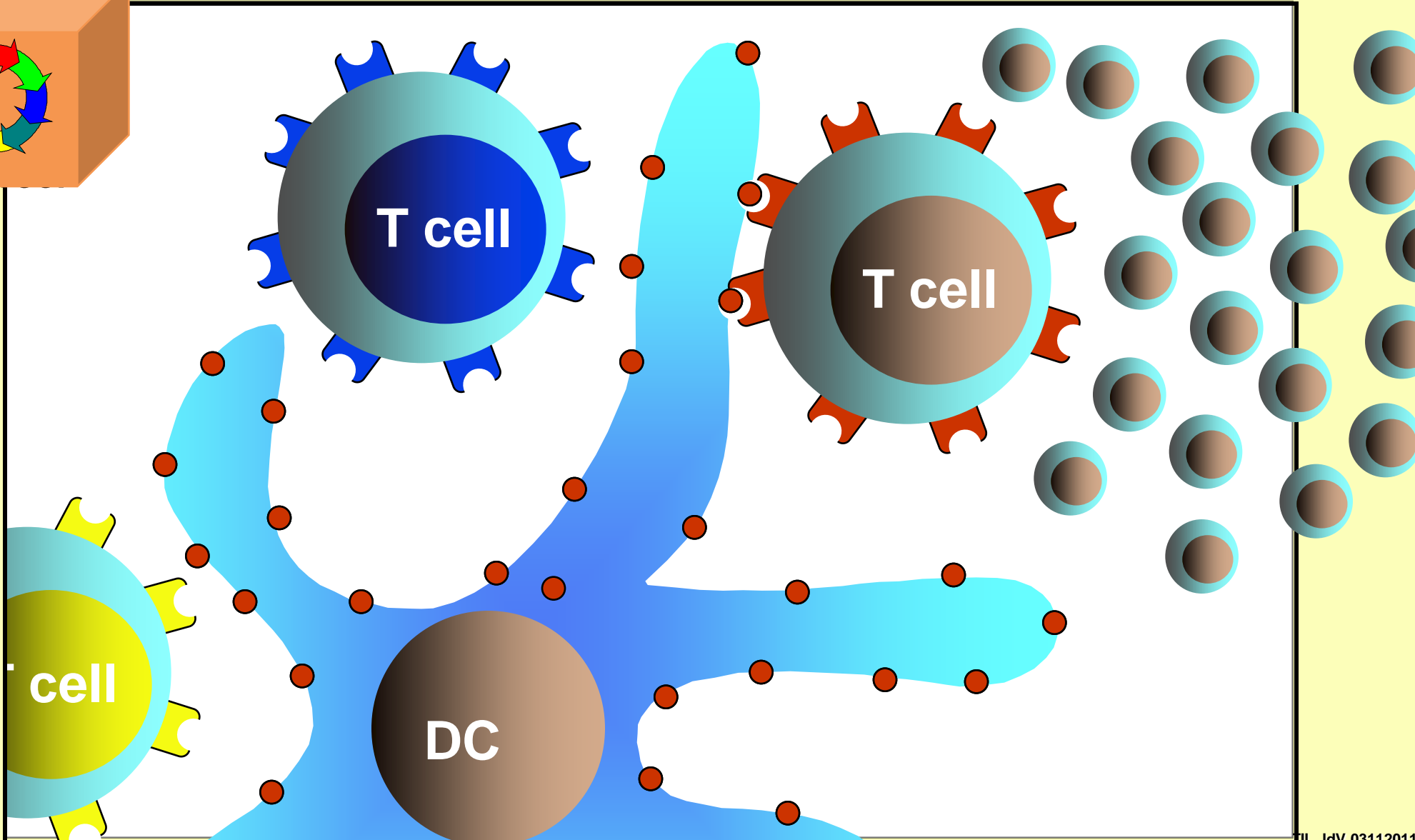
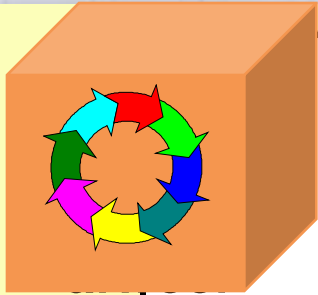
Waarom DC?

Dendritic cells digest tumor cells

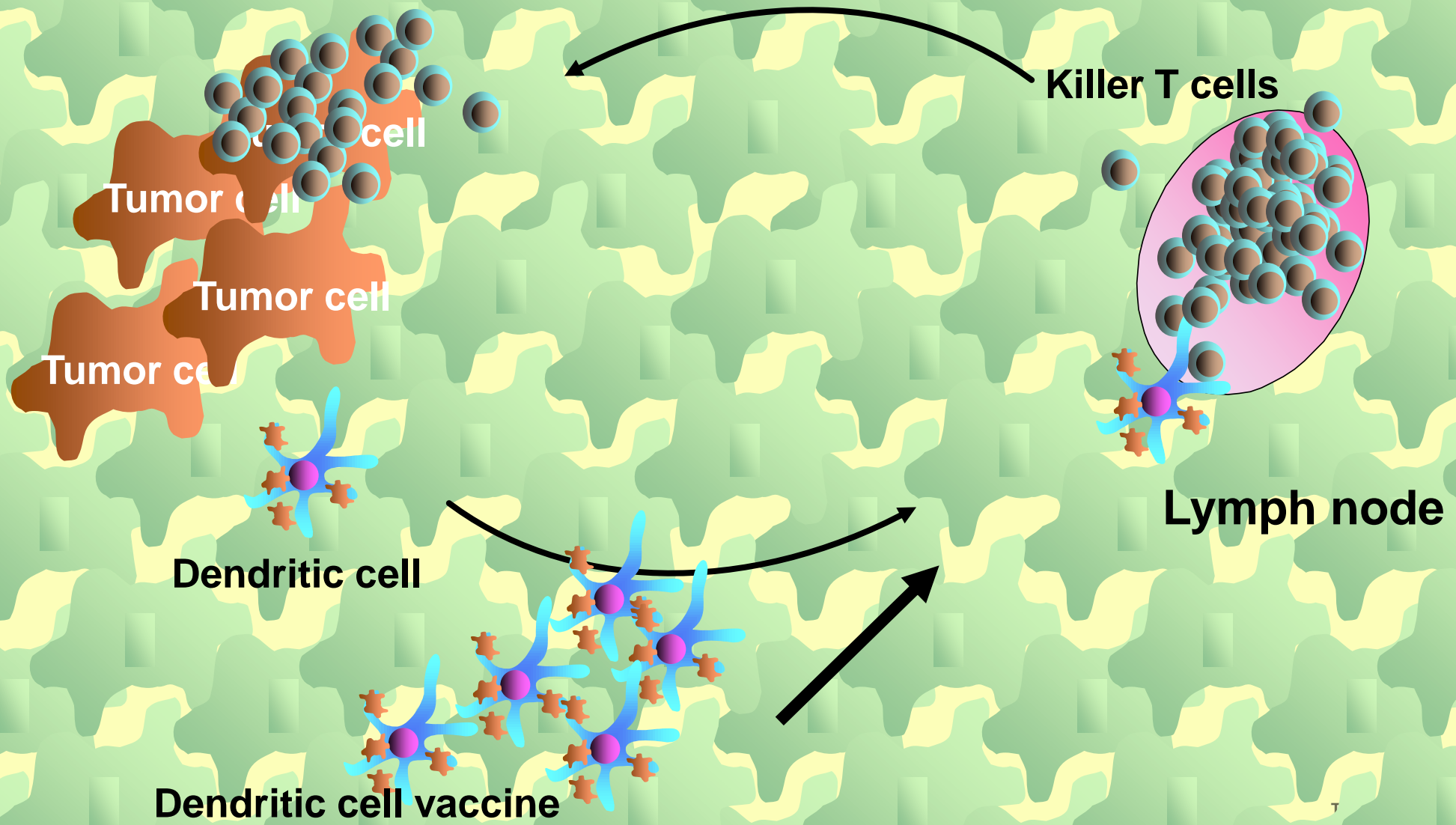
- tumor-derived peptides presented in MHC
- “specific” antigens per tumor type

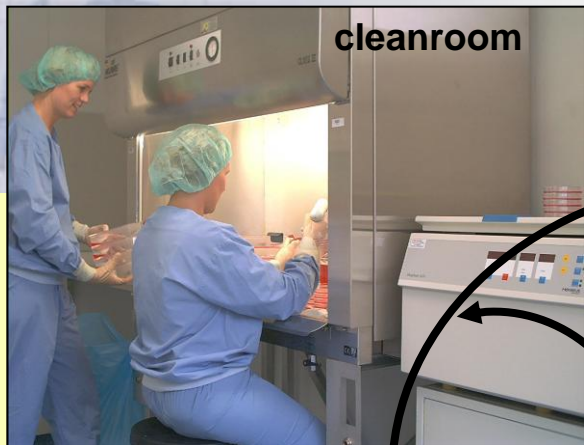


How DC stimulate T cells

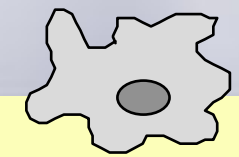


Immunotherapy with dendritic cells





cleanroom



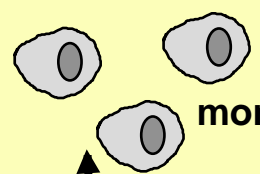
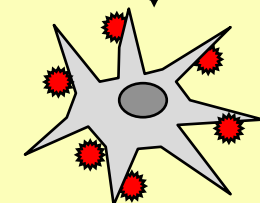
immature DC

TNF α
MCM
PGE $_2$



Dendritische cel

tumor-peptiden of mRNA



monocyten

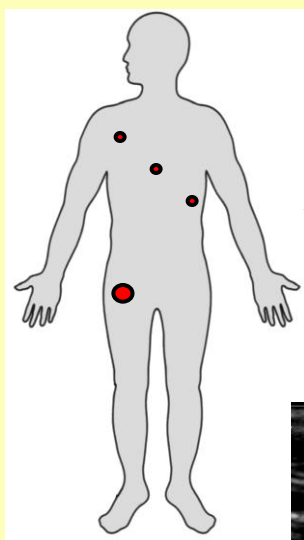
IL-4
GM-CSF

KLH

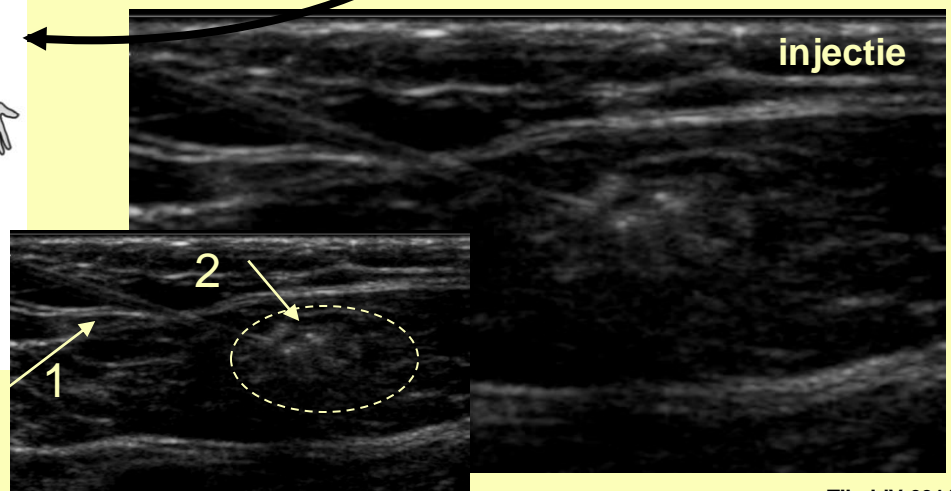
aferese



DTH



intranodale injectie



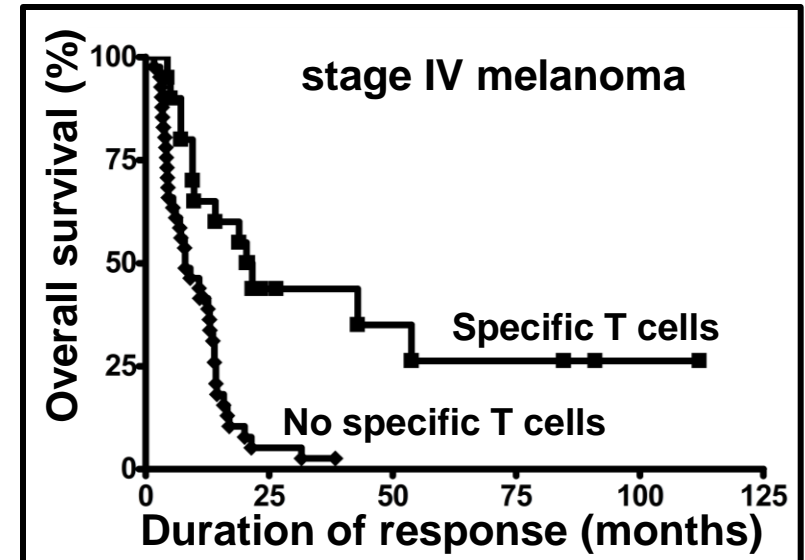
injectie

DC vaccination: status

After 10 years of DC vaccination:

- We can now induce an immune response in 40% of stage IV melanoma patients

- Patients with immune responses show increased progression free survival, but long-term clinical responses are still limited (25%)



- Monocyte derived DC vaccines are not yet optimal: limited survival, migration, co-stimulation, Ag presentation

- Most patients treated are late stage cancer patients

DC vaccination: issues

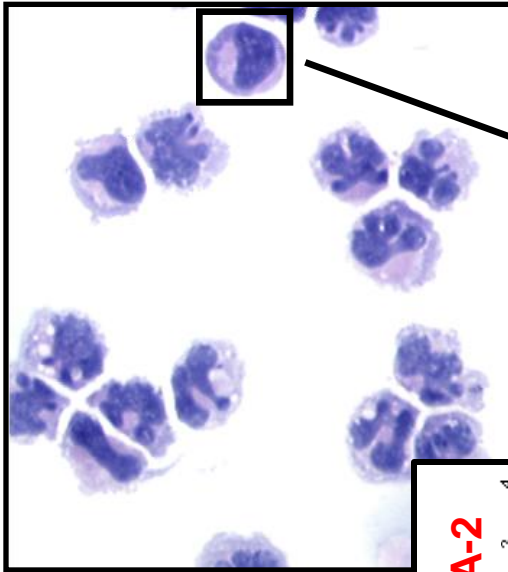
- Perform vaccination studies at much **earlier stages of disease**, -> long follow-up
- **Optimize monocyte derived DC vaccines**: RNA can be used to extend expression of whole tumor antigens, but also allows manipulation of DC function!
- We must try to **manipulate immunosuppression** (Tregs, MDSC, tumor-microenvironment)
- **In vivo targeting of DC** is an interesting opportunity, also to reach resident DC
- Exploit different (combinations of) **naturally occurring DC subsets**, such as blood derived MDC and PDC

DC vaccination: why pDCs?

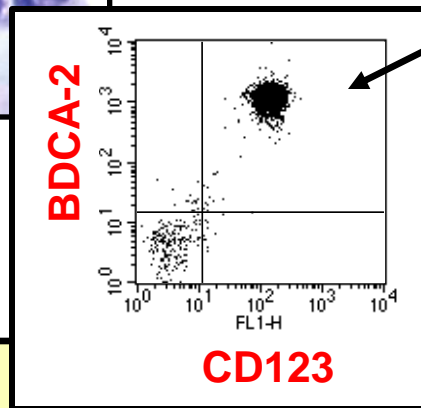
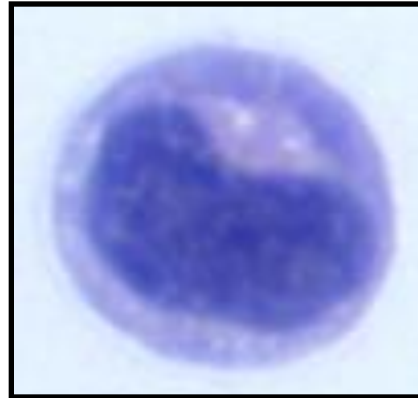
- Immature pDCs infiltrate solid tumors
- Type I IFN activates other cells of the (innate) immune system.
- Type I IFN seems to yield more potent DCs in terms of secretion of IL-12 and induction of tumor-specific CTLs and Th1 *in vitro*
- pDCs can promote the ability of mDCs to cross-prime CD8⁺ T cells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

Plasmacytoid DCs are major type I IFN producers

Myeloid and plasmacytoid DCs



Plasmacytoid DC



Plasmacytoid DCs are

- antigen-presenting cells
- scarce (less than 0,1% of peripheral blood leukocytes).
- the major **type I IFN** producers
- **critical** for **anti-viral** immunity
- **not yet** well understood

...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

Optimizing a cancer vaccine

The health achievement of the 20th century:

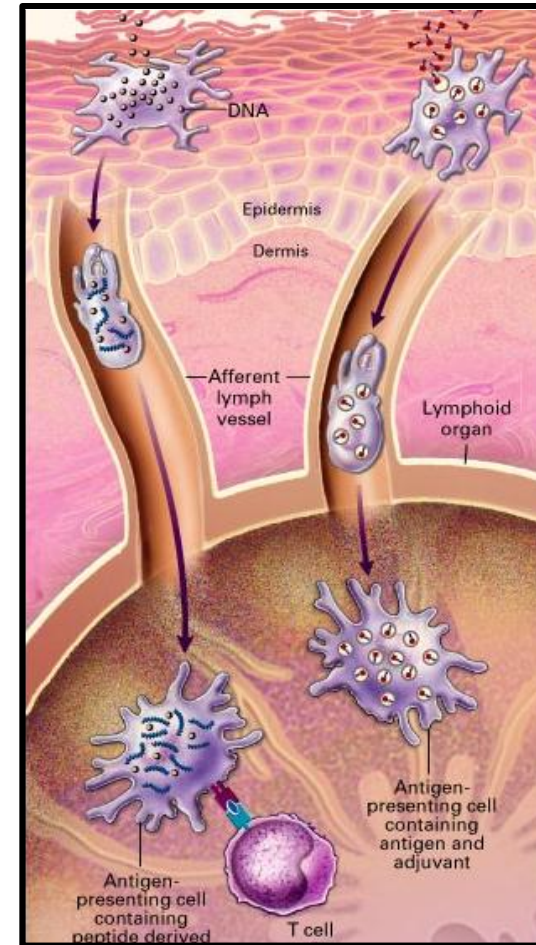
Preventive vaccines

Control & elimination of infectious diseases.
Are safe, have been used over 50 years

Two types of successful vaccines

- Live attenuated vaccines
- Non-replicating vaccines

DC sense microbial components within the vaccines



Gordon Ada, NEJM, 2001

Preventive vaccines contain TLR ligand

TLR-stimulating preventive vaccines:

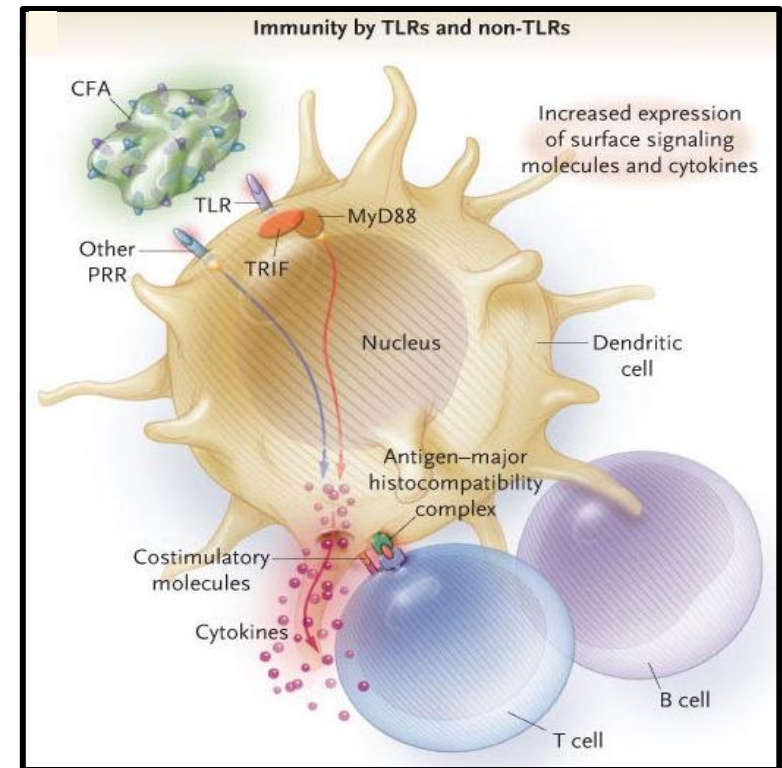
In vivo first target is the DC

1. Maturation

2. Migratory phenotype

New opportunity:

cultured DC “matured” with vaccines



Vaccines tested for TLR mediated DC stimulation

Infectious agent	Vaccine	Disease	Type of vaccine	Supplier	Adjuvant
bacteria					
<i>Streptococcus pneumoniae</i>	PREVENAR	Pneumonia, otitis media, meningitis	conjugated subunit	Wyeth	AlPO ₄
<i>Streptococcus pneumoniae</i>	PNEUMO 23	Pneumonia, otitis media, meningitis	subunit	Aventis Pasteur	none
<i>Clostridium tetani</i>	Tetanus	Tetanus	subunit	NVI	AlPO ₄ , thiomersal
<i>Salmonella typhi</i>	TYPHIM VI	Typhoid fever	subunit	Sanofi pasteur	none
<i>Haemophilis influenzae</i> type b	Act-HIB	Meningitis, epiglottitis, pneumonia type b	Conjugated subunit	Aventis Pasteur	Tetanus toxoid
<i>Neisseria meningitidis</i>	NEISVAC-C	Meningitis, sepsis	Conjugated subunit	Baxter	Al(OH) ₃ /Tetanus toxoid
<i>Mycobacterium bovis</i>	BCG	Tuberculosis	live attenuated	NVI	none
viruses					
Hepatitis A virus	HAVRIX	Liver disease, cancer	inactivated	Glaxo SmithKline	Al(OH) ₃
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	BMR	German measles, Respiratory tract infection, mumps, meningitis, orchitis	Live attenuated	NVI	none
Mumps virus					
Rubella virus					
<i>Corynebacterium diphtheriae</i>	INFANRIX-IPV	Difteria	subunit, inactivated,	Glaxo SmithKline	AlPO ₄ , Al(OH) ₃ ,
<i>Clostridium tetani</i>	+HIB	Tetanus	conjugated		Tetanus toxoid
<i>Bordetella pertussis</i>		Pertussis			
Poliovirus		Polio			
<i>Haemophilis influenzae</i> type b		Meningitis, epiglottitis, pneumonia type b			
Influenzavirus A	INFLUVAC	Flu, respiratory diseases	Inactivated subunit	Solvay Pharma	none
Influenzavirus B	2006-2007, INFLUVAC 2007-2008				

Preventive vaccines and pDC

- pDC express selected TLR ligands: TLR7 and TLR9
- Test preventive vaccines: IFN- α production or maturation

Select most appropriate preventive vaccine for pDC maturation

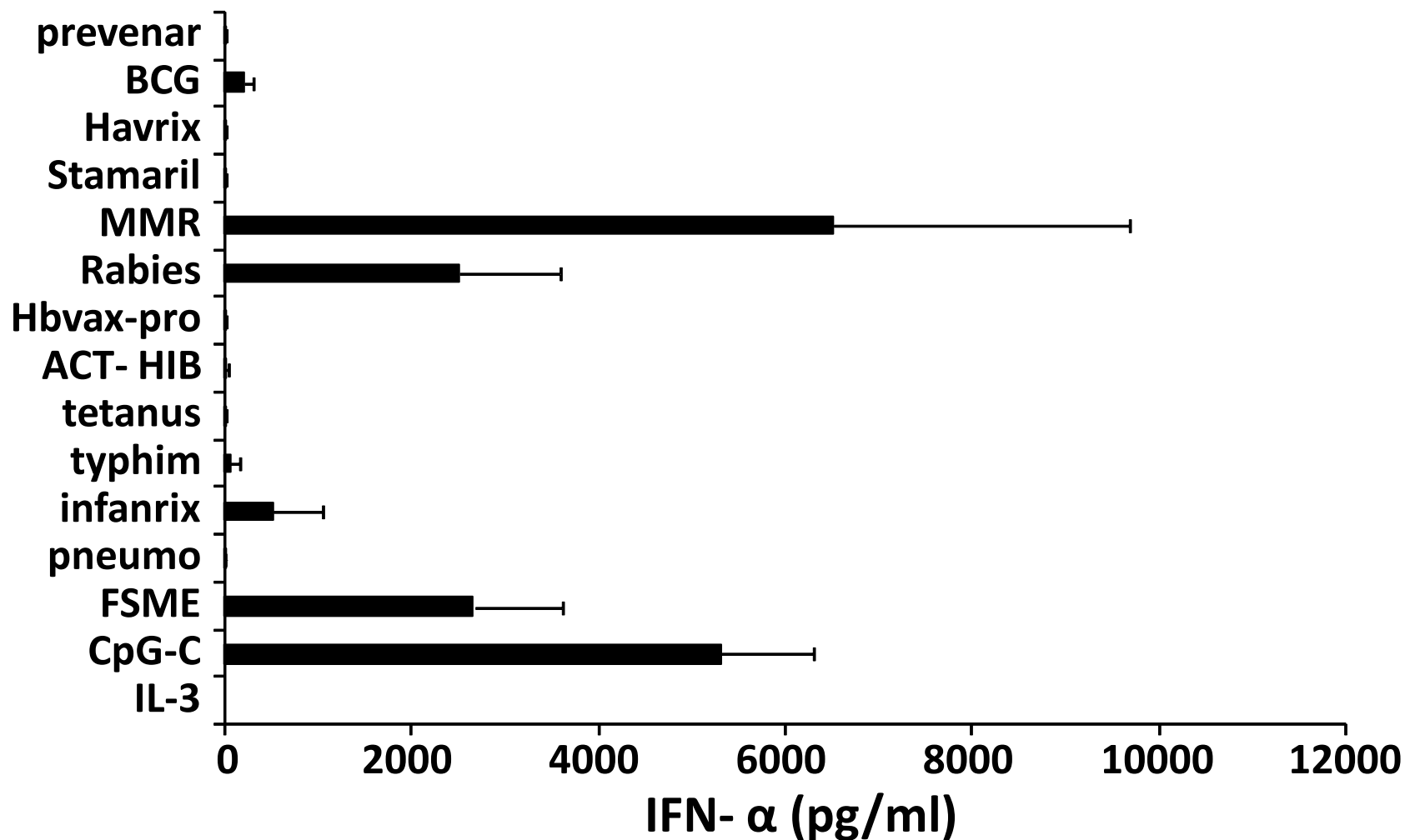


pDC/IPC:
professional type I IFN-producing cell



pDC-derived DC:
professional Ag-presenting cell

IFN- α production by pDC



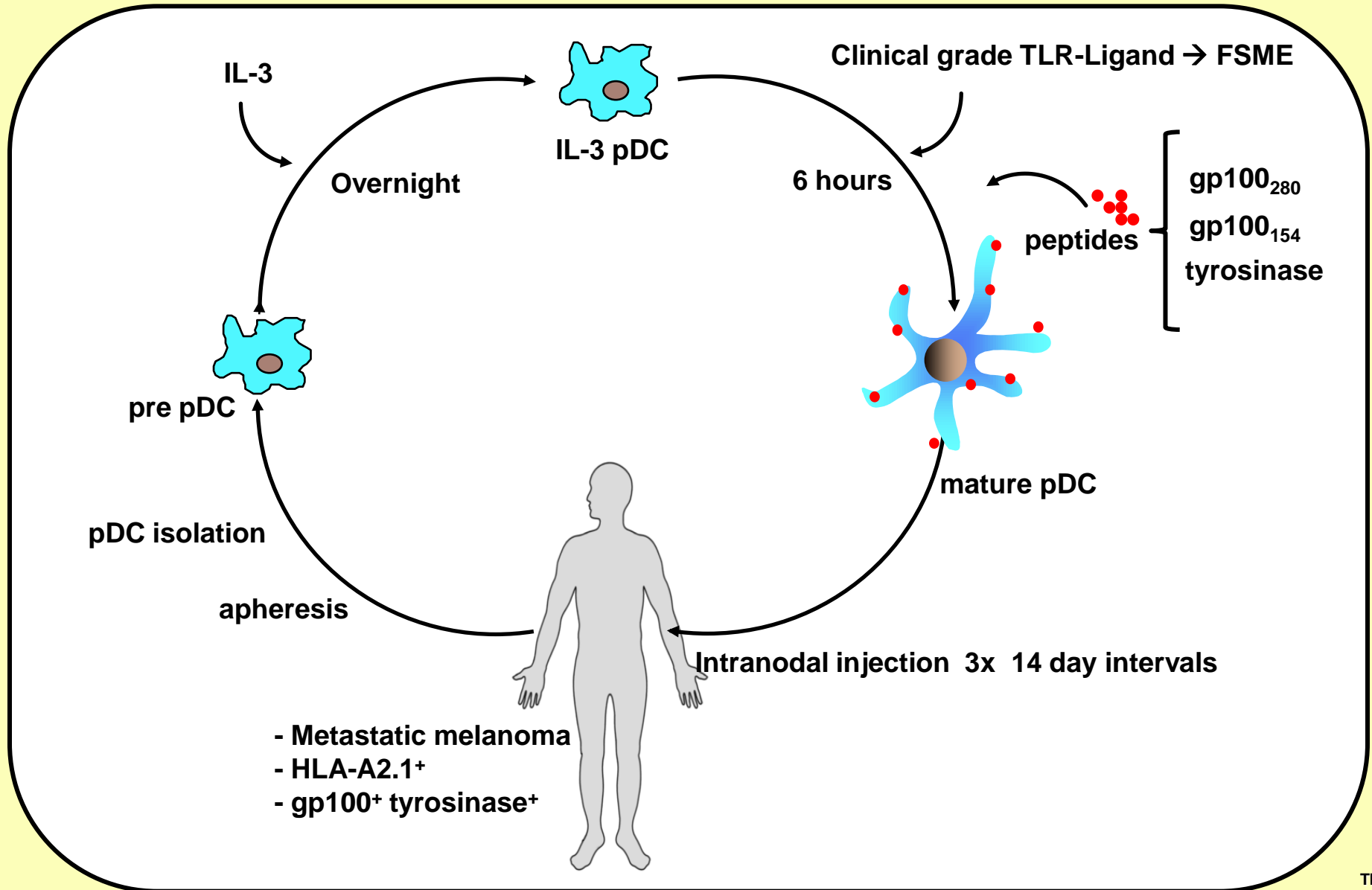
Stimulation of pDC by preventive vaccines

summary

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

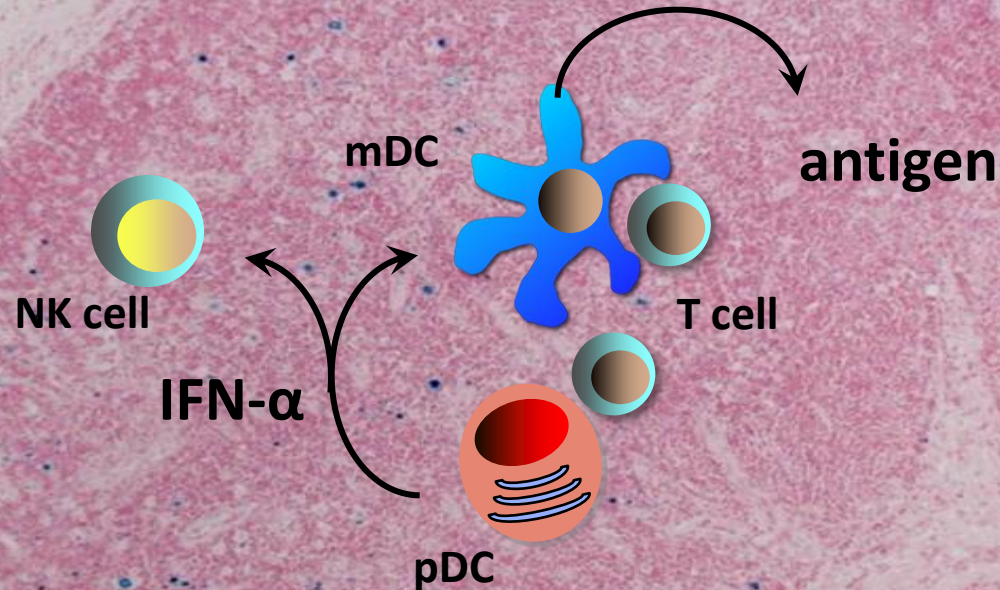
- **Vaccine against tick-borne encephalitis virus**
 - Neudörfl-strain
 - disease involving the Central Nervous System
- **Inactivated**
- **Adjuvant AIOH**

Vaccination & culture strategy



Conclusions

- **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**
- **pDC migrate in vivo**
- **A first phase I/II study demonstrates significant increase in overall survival of stage IV melanoma patients.**
- **Next:**
 - randomized phase II study
 - Combine pDC with naturally occurring myeloid DC



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?

Acknowledgements



Department of Tumor Immunology

**Mangala Srinivas
Gerty Schreibelt
Jurjen Tel
Daniel Benitez-Ribas**

**Annemiek de Boer
Tjitske Duiveman
Mandy van de Rakt
Nicole Scharenborg**

**Gosse Adema
Carl Figdor**

Department of Medical Oncology

**Erik Aarntzen
Kees Punt**

Department of Nuclear Medicine

**Otto Boerman
Wim Oyen**

Miltenyi Biotec

**Katja Petry
Gregor Winkels**

