ΔΕΝΤΡΙΤΙΚΑ ΚΥΤΤΑΡΑ ΚΑΙ ΕΜΒΟΛΙΑ ΓΙΑ ΤΟΝ ΚΑΡΚΙΝΟ

DENDRITIC CELLS AND CANCER VACCINES

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Τμήμα Ιατρικής – Πανεπιστήμιο Θεσσαλίας

David Hunt. Cell Systems Initiative, U. of Washington.

Lecture Outline

- ✓Dendritic cells (DC)
  - -Subtypes (immature vs mature) & function
  - -Interaction with T cells
- ✓Tumour Immunology
  - -Milestones
  - -Current efforts
- ✓Dendritic Cell Immunotherapy
  - -Considerations
  - -Clinical Trials

Dendritic Cells

“The cell”

Paul Langerhans
1868

‘peculiar cells within the skin epithelium’

Steinman & Cohn

‘Identification of a novel cell type in peripheral lymphoid organs of mice. Morphology, quantitation, tissue distribution’

J Exp Med. 1973;137: 1142–62

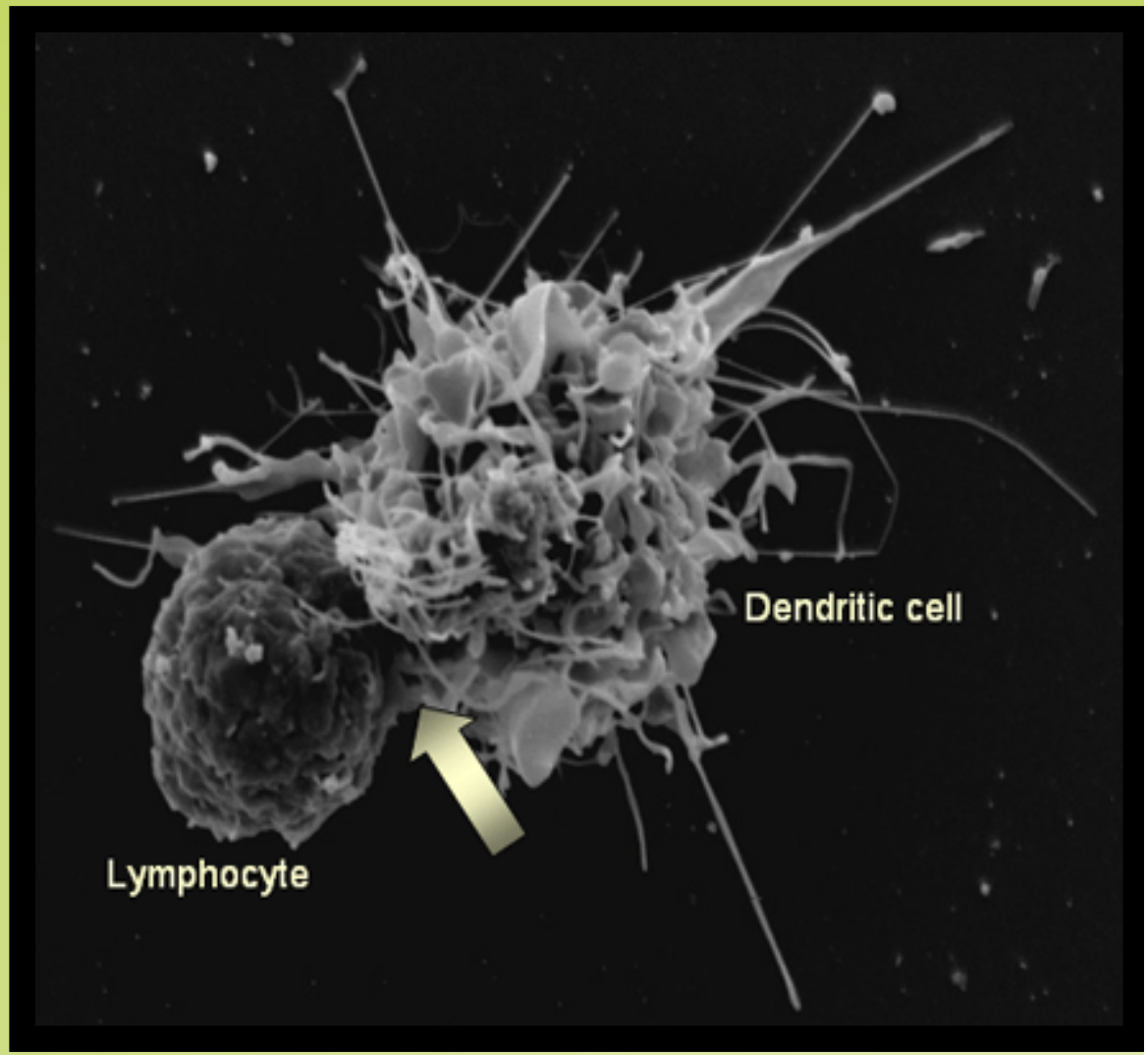
DC

‘The most professional cell of the immune system’

Dendritic Cells

Description-Function

- originate in the BM
- unique cytoplasmic extensions arranged as dendrites of varying length, width, form and number
- function as antigen presenting cells (APC)
- found in: lymphoid organs, bloodstream and other tissues
- capture antigen or bring it to the lymphoid organs where an immune response is initiated



Dendritic Cells

Function (immunity and tolerance)

Steady state

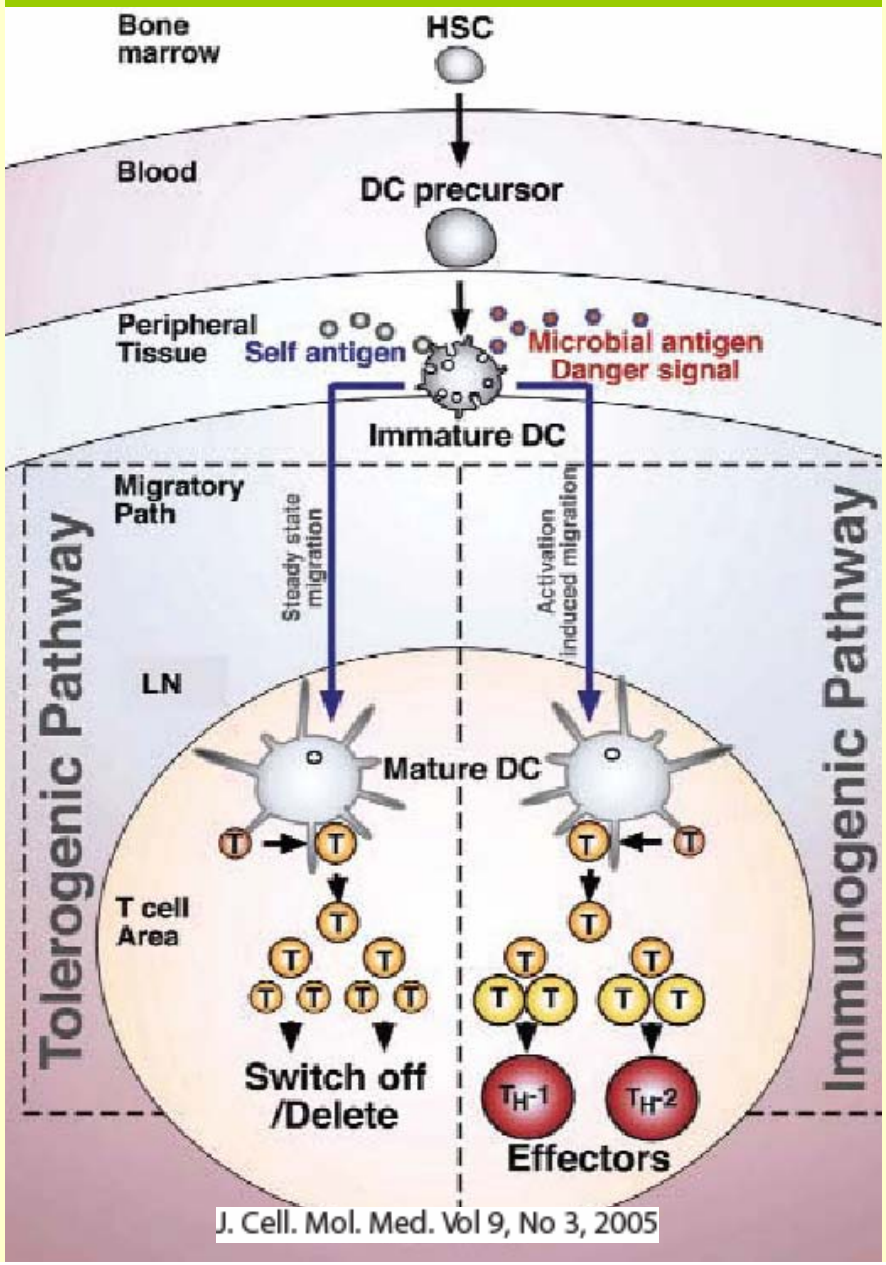
iDCs take up protein

express TLRs (2, 3, 4, 5, 8, 9), MR, DEC205, DC-SIGN, FcγII/IIIR, CD36

iDC may enter regional LN (lack of inflammatory signals)

T cells encounter self-Ag on iDCs and become regulatory rather than effector T cells

internalized proteins can accumulate in MIIC for up to 60hr



Immune induction

iDCs mature with danger signals

within 3-4hrs Ag is complexed with MHC

endocytic capacity is reduced

increased expression of MHC, CD80, CD86, CD40

expression of CD2, CD11a, CD54 (ICAM1), CD58 (LFA-3), integrins

mDCs migrate to regional LNs and prime naive CD4 or CD8 T cells

mDC may polarize CD4 cells toward a Th1 or Th2 phenotype

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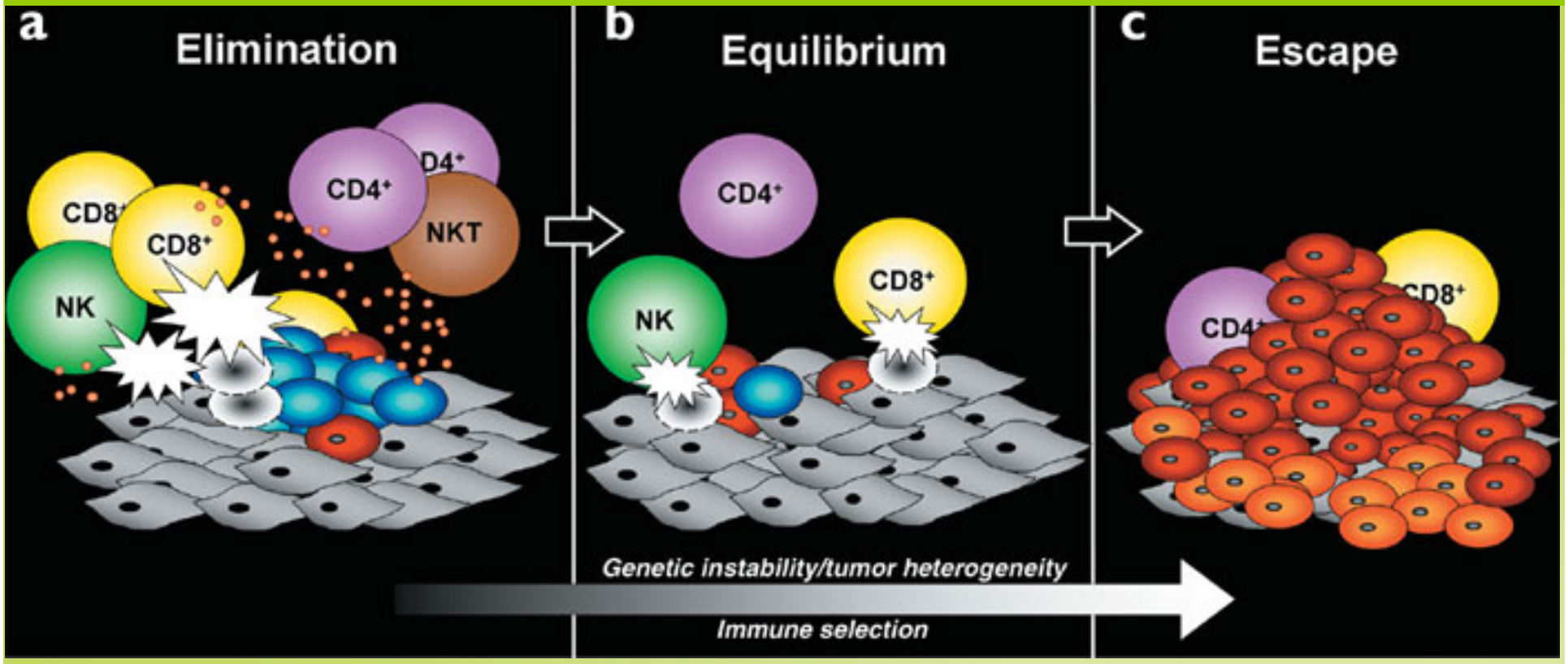
Tumour Immunology

The Eras of Tumor immunology

1970s	**Tumour cells are recognized and killed by immune cells**
1980s	**Tumour cells express a plethora of immunogenic peptides and at the same time generate antigen-loss variants**
1990s	**Several potential cancer vaccines are tested**
2000s	**Evaluation and Reflection**
Today	**Search for new immunotherapeutic modalities**

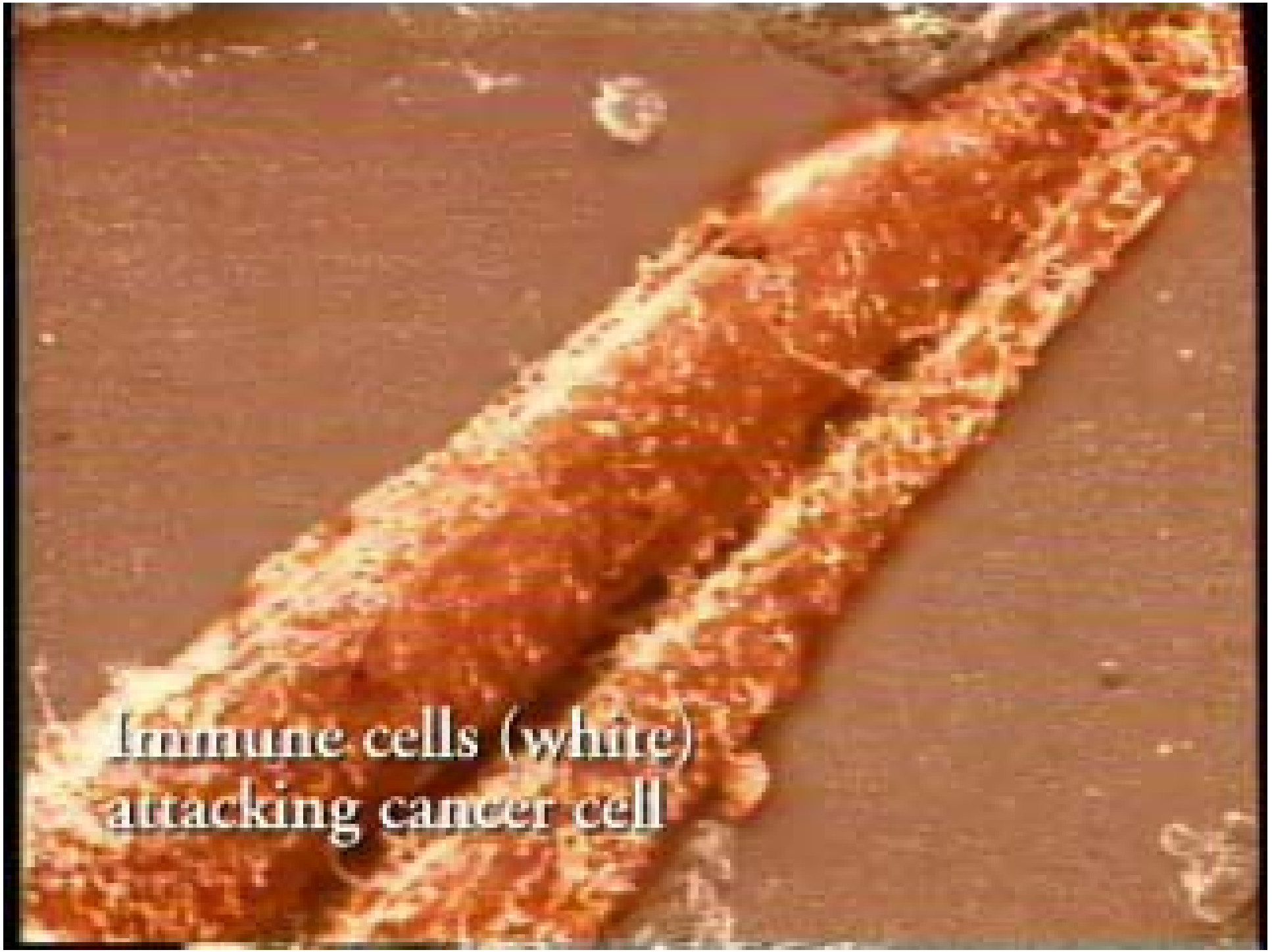
Tumour Immunology

Milestones



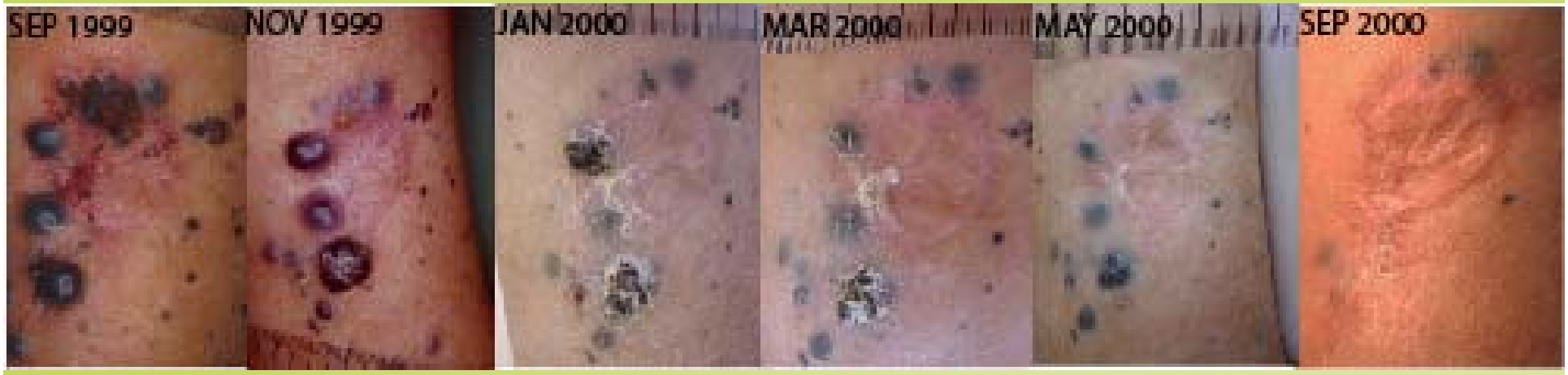
Constant balance between

Immunosurveillance & Immunoediting


Immune cells (white)
attacking cancer cell

Tumour Immunology

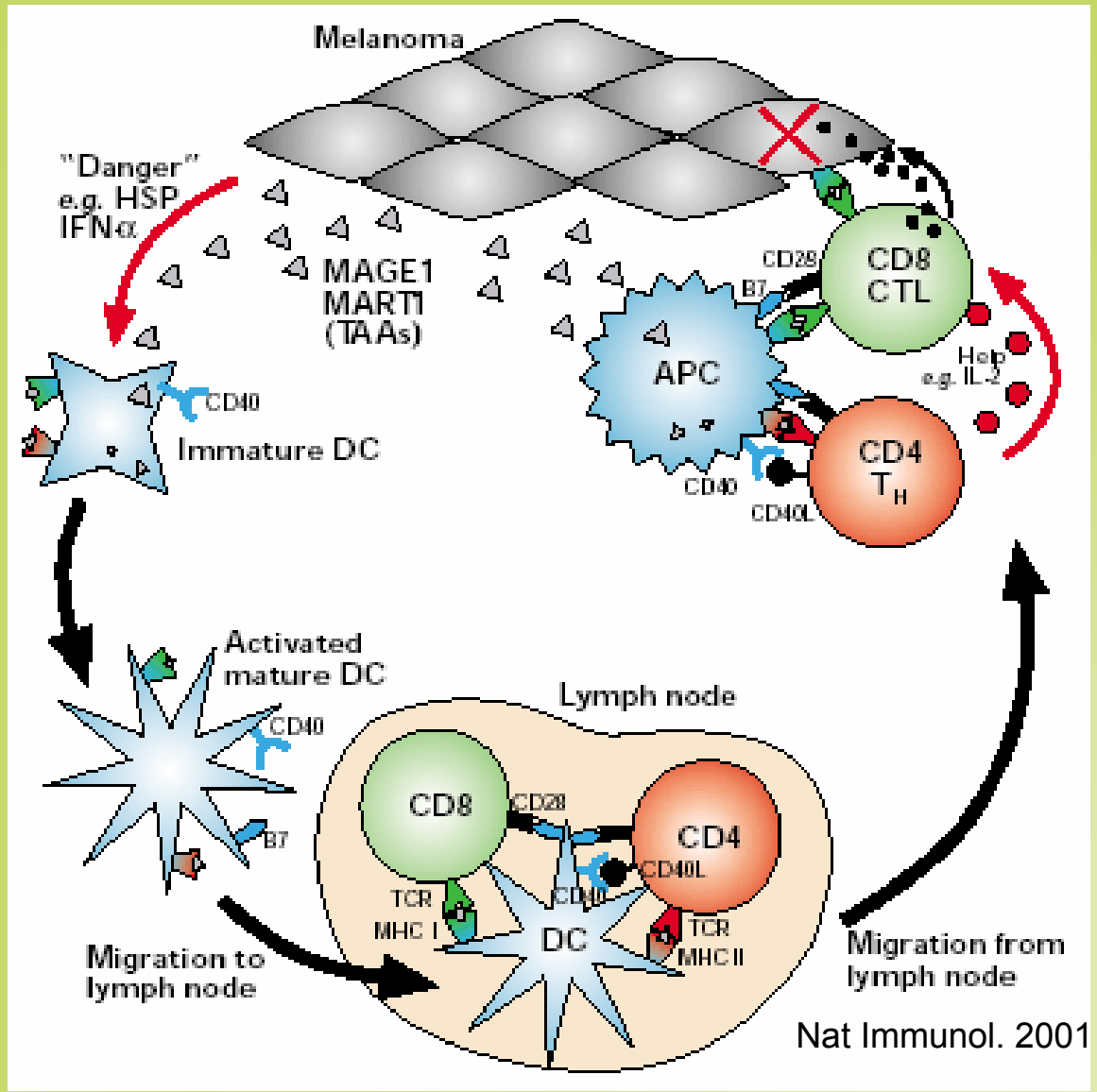
Milestones



Tumour antigen vaccination

Tumour Immunology

Current efforts:
Understanding DC-T cell activation



Nat Immunol. 2001

Cancer Immunotherapy Outcomes over the last 20 years

	Clinical	Immunological
Group A	+	+
Group B	-	-
Group C	+	-
Group D	-	+

All trials

(irrespective of immunogens, Ag, adjuvants, sex, age etc)

<5% clinical response rate

Improved quality of life

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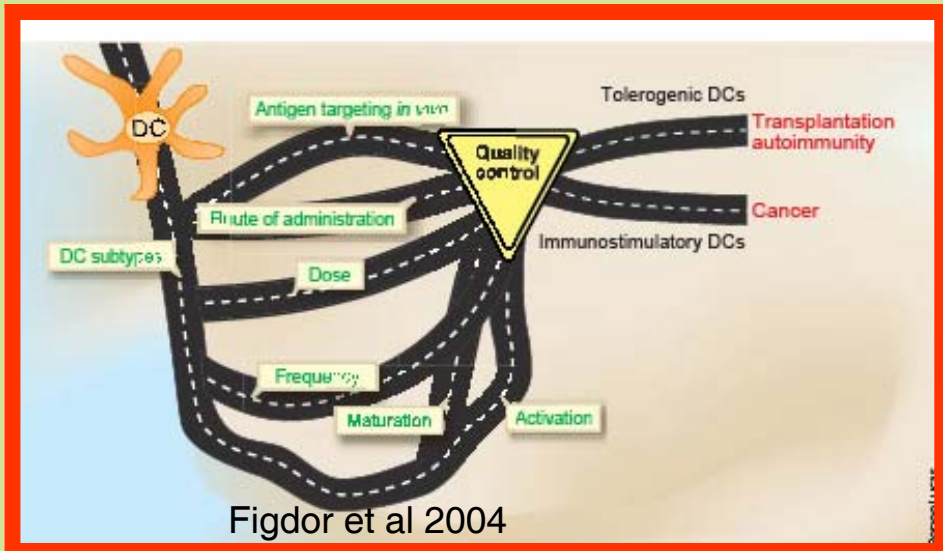
  - **-Considerations**
  - **-Clinical Trials**

DC Immunotherapy

Clinical Trials-Considerations

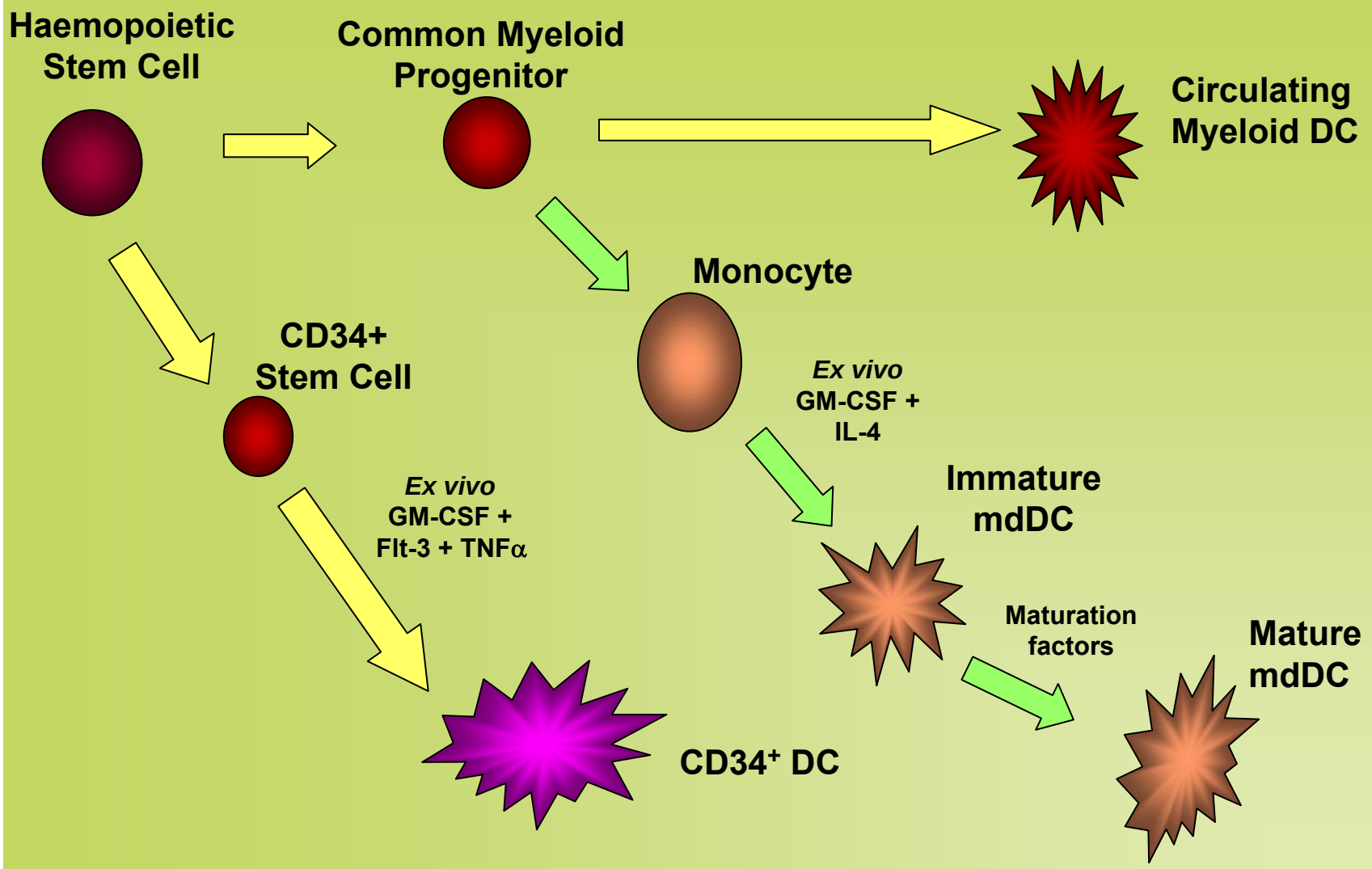
- **Source/Type of DC**
- **Maturation** (pathogens etc)
- **Phenotype**
- **Tu Ag choice/loading** (peptides, proteins, viruses, Tumour lysates)
- **Dose** (1-50x10^6 cells/site), n sites
- **Route** (IV, IN, SQ, ID)
- **Frequency** (monthly x 3) x 3 cycles
- **Monitoring T cell responses**



Figdor et al 2004

DC Immunotherapy

DC sources



Blood DC ----------> Density gradient
Mo-DCs ---------> Adherent CD14
Stem cell DC ---------> Immuno-selected CD34

Copland *et al* (2005)

DC Immunotherapy

DC isolation

Collection of cells ----------> isolation of cells

DC Immunotherapy

Maturation agents

- **Pathogens**

  (LPS, virus, CpG)

- **T cell derived stimulation**

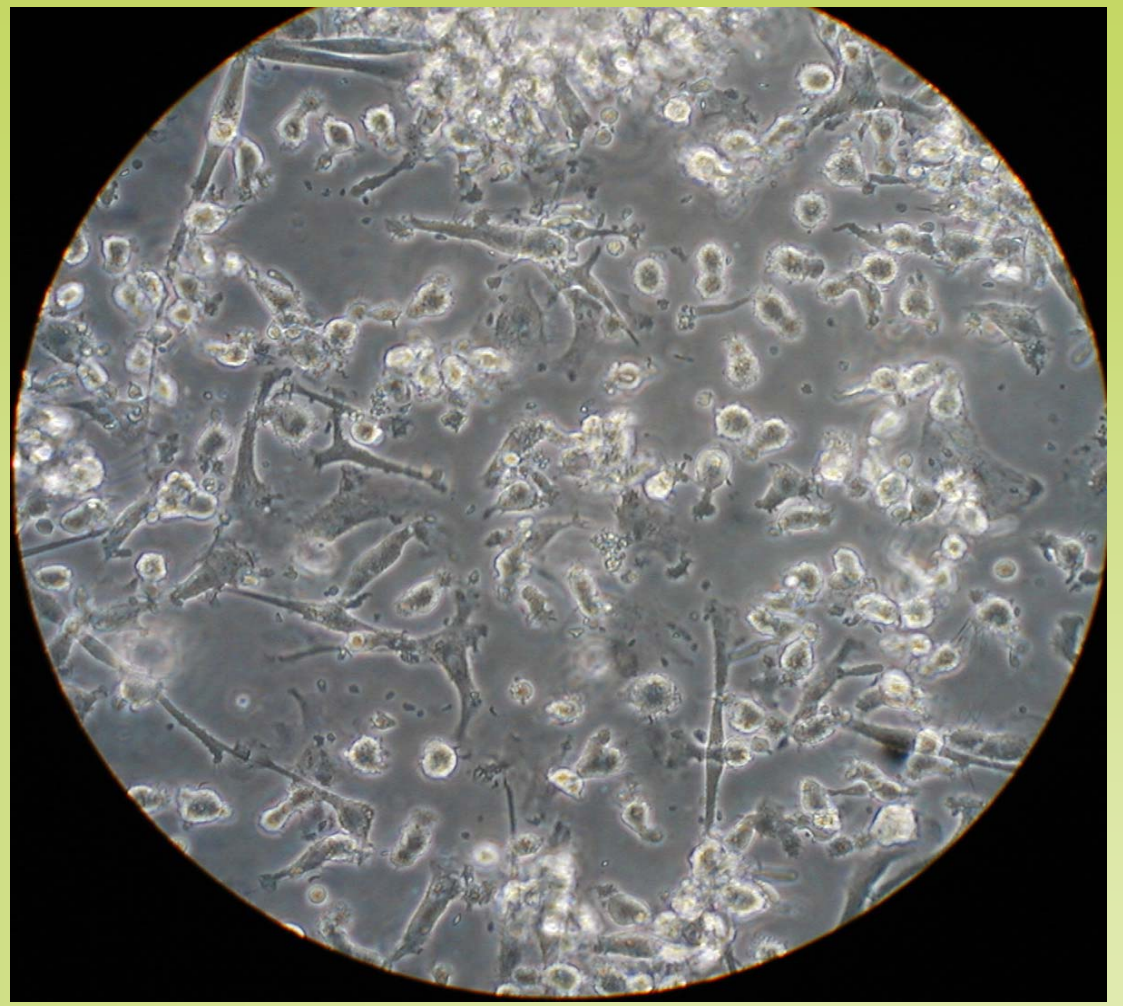
  (CD40L)

- **Mechanical stress**

  (freeze-thaw)

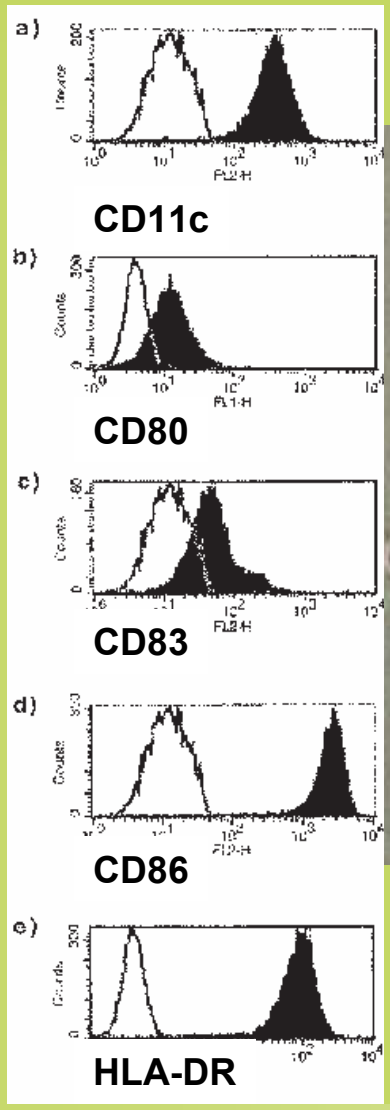
- **Pro-inflammatory stimuli**

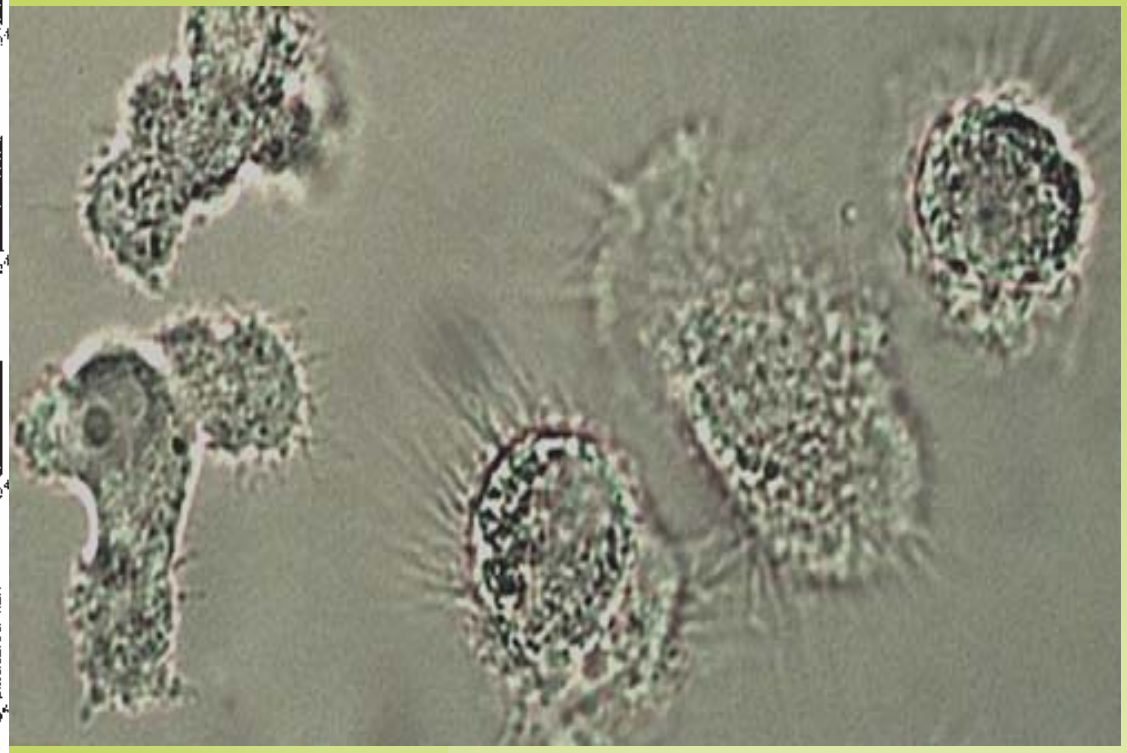
  (IL-1, TNFa, IL-6)



DC Immunotherapy

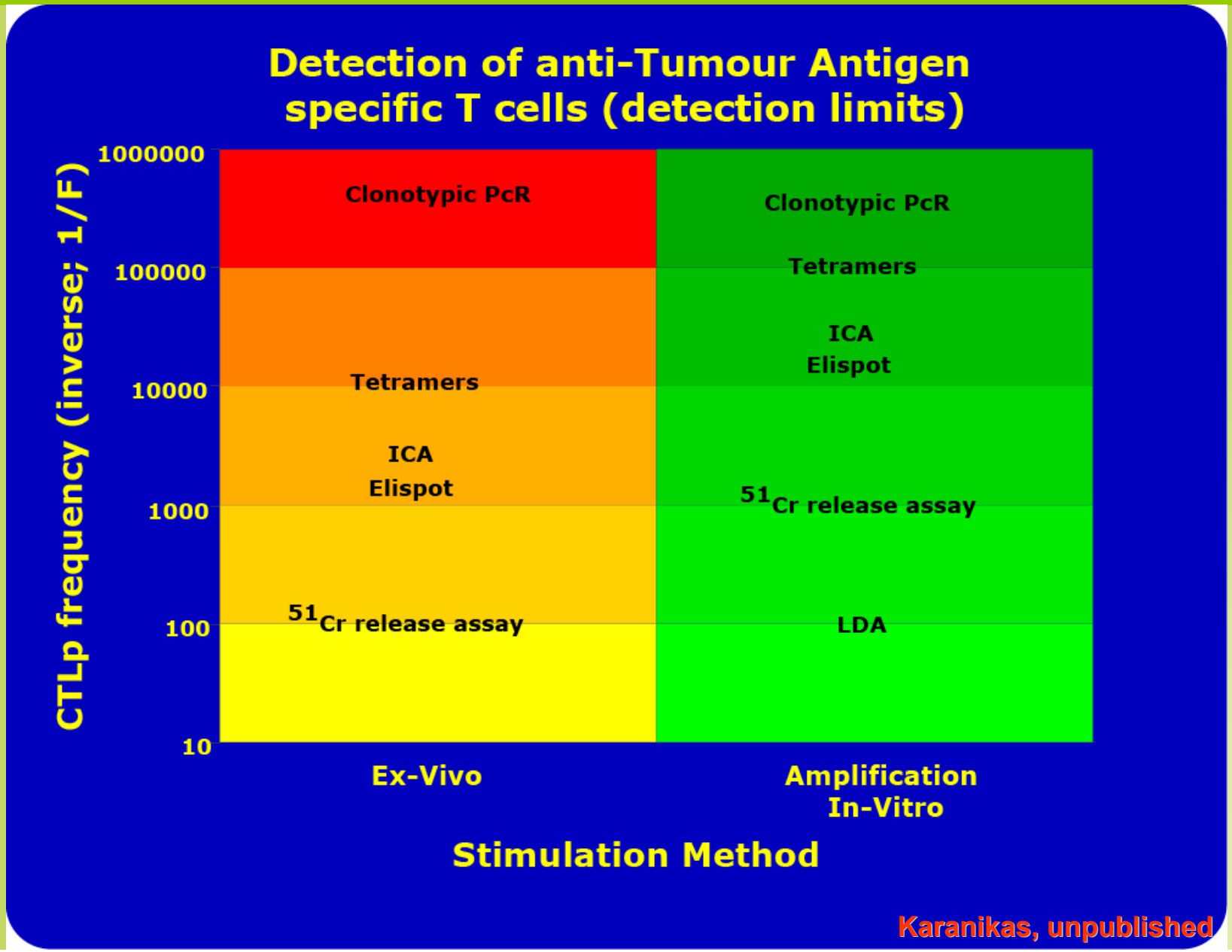
Phenotypic characterisation





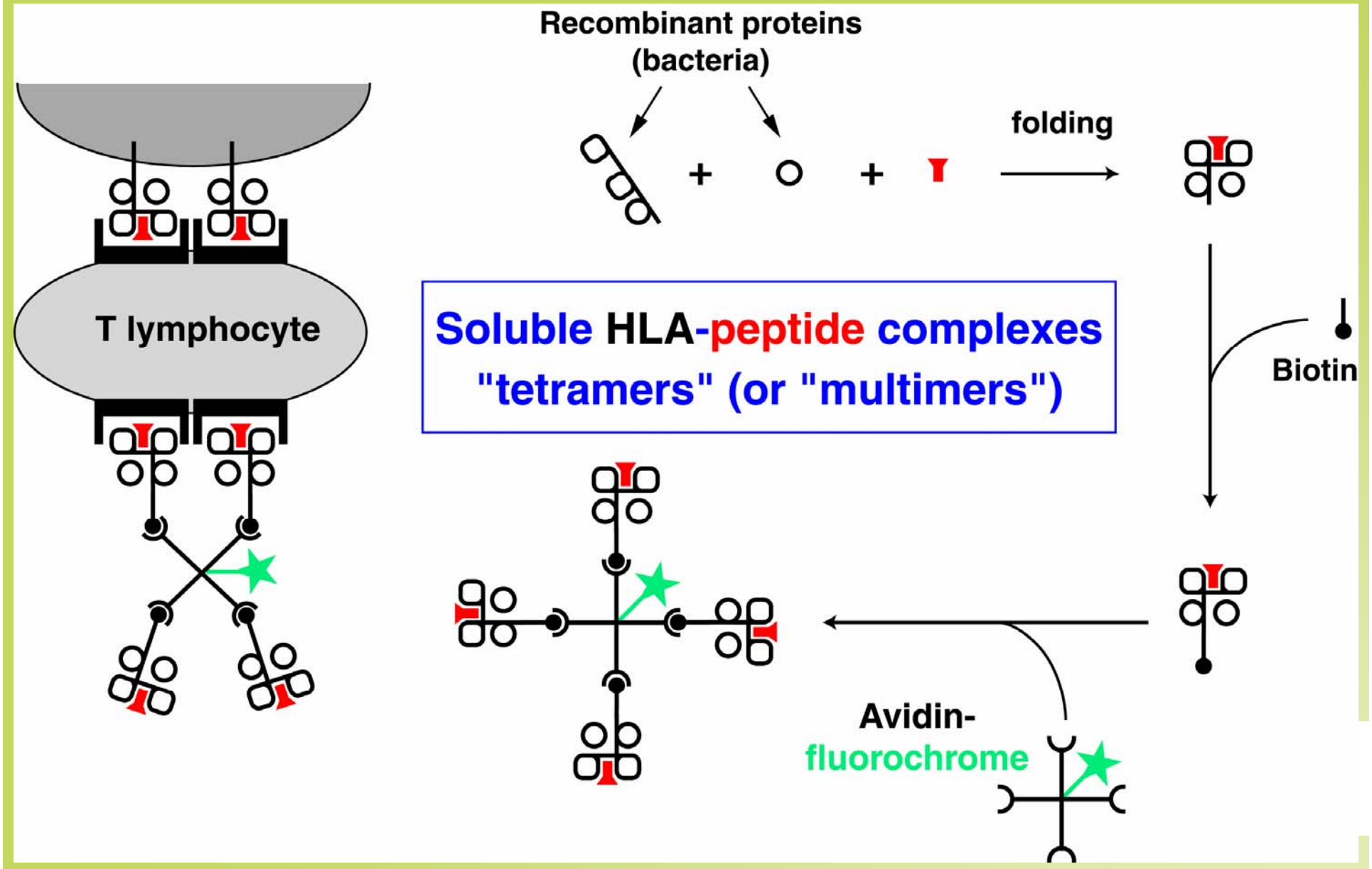
DC Immunotherapy

Immunomonitoring



DC Immunotherapy

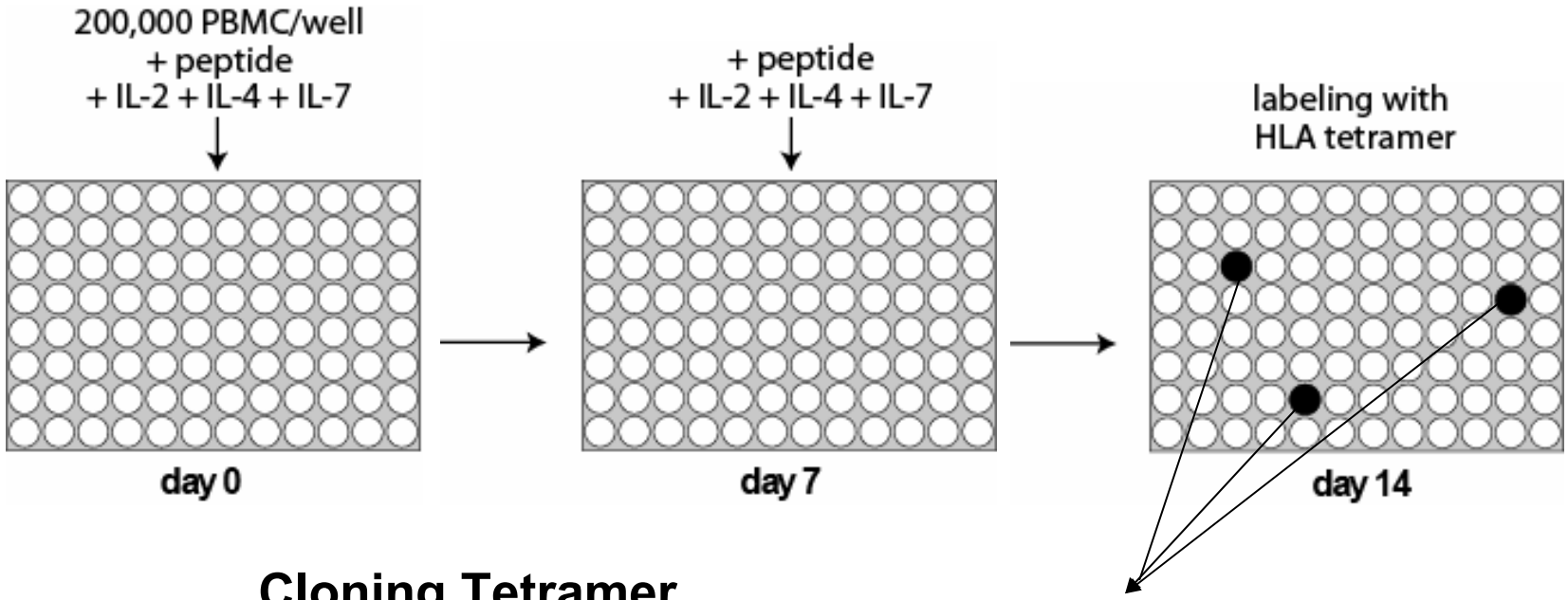
Immunomonitoring



DC Immunotherapy

Immunomonitoring

OVERVIEW OF THE MLPC/TETRAMER PROCEDURE FOR THE ANALYSIS OF PEPTIDE SPECIFIC T CELLS



Cloning Tetramer +ve CTL

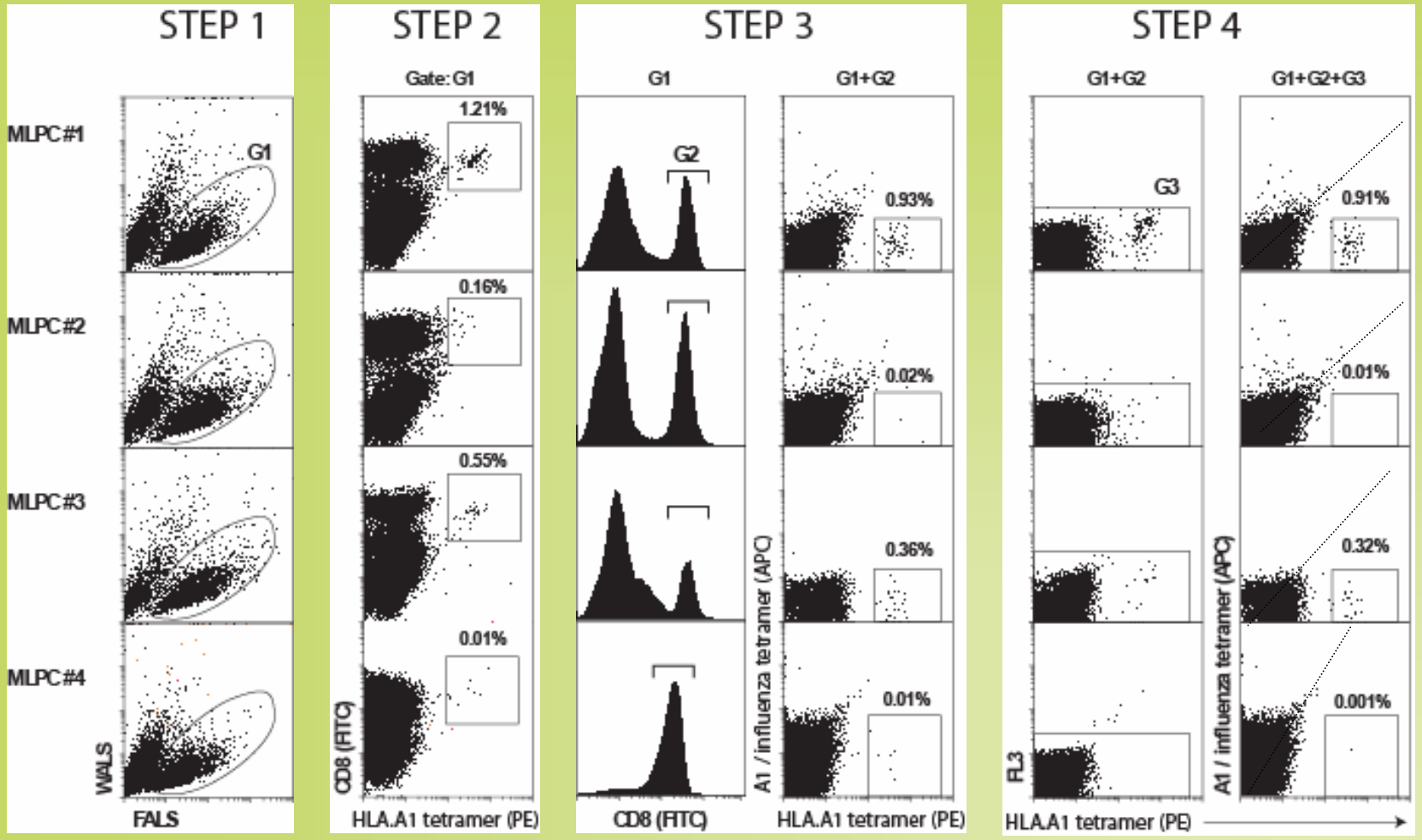
Estimation of CTL frequency

Specificity, Function, TCR seq?

DC Immunotherapy

Immunomonitoring

OPTIMIZED PROTOCOL FOR THE DETECTION OF LOW NUMBER TETRAMER POSITIVE CELLS



First trial using DC

Hsu FJ, Benike C, Fagnoni F, Liles TM, Czerwinski D, Taidi B, Engleman EG, Levy R

'Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells'

Nat Med 1996, 2:52-58

DC + tumour specific idiotype protein

Immune responses 4/4
2/4 CR, 1/4 PR

DC Immunotherapy

The most elegant DC Clinical Trials

C Schmidt, Australia

DC loaded with tumour lysates

Anti-tumour specific T cell responses in 100%

3/12 Complete responses (>3ys)
S100-B levels (Ca binding protein) correlating with disease

3/12 PR, 6/12 PD

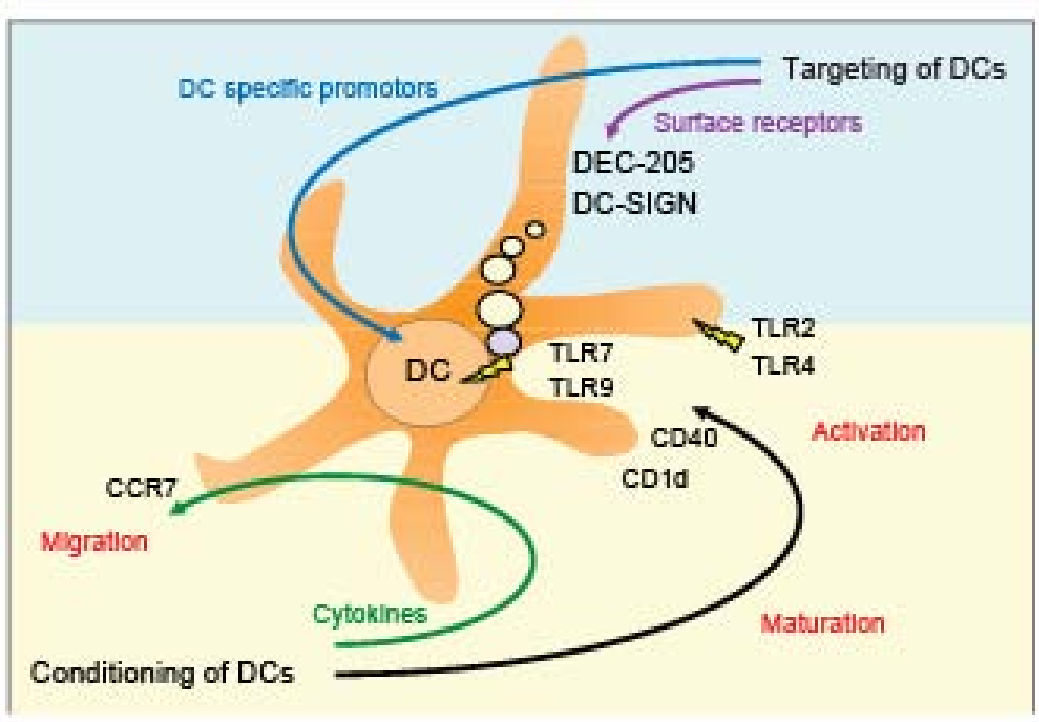
DC Immunotherapy

The most elegant DC Clinical Trials

CJM Melief, The Netherlands

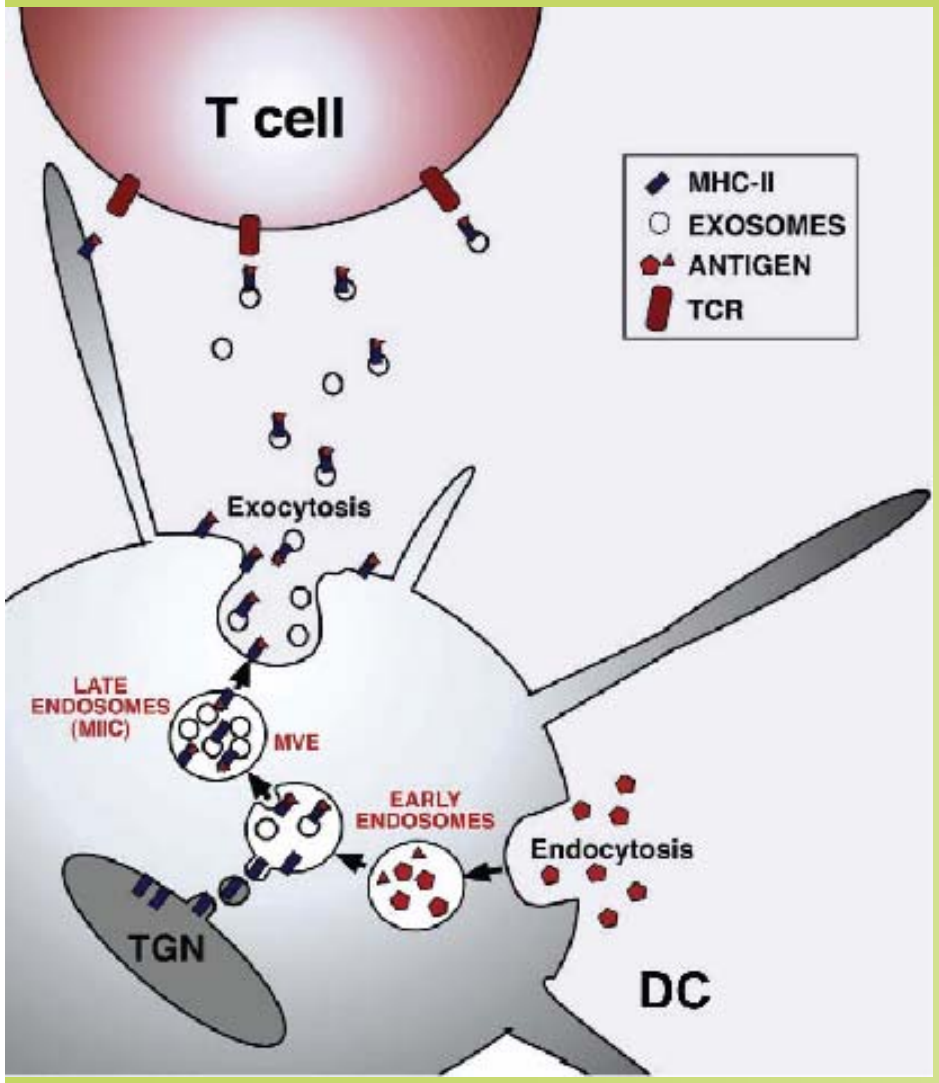
Mature DC loaded with long E7 peptides of HPV and CpG or IFA

<5% Clin Responses



DC Immunotherapy

The most elegant DC Clinical Trials



L. Zitvogel, France

First phase I clinical trial using dendritic cell derived-exosomes

DEX loaded with MAGE3

Some T cell responses (upregulation of markers)

0/15 CR, 1/15 MR, 2/15 SD

DC Immunotherapy

The most elegant DC Clinical Trials

G. Schuler, Germany

Vaccination with monocyte-derived dendritic cells

"learning by doing"

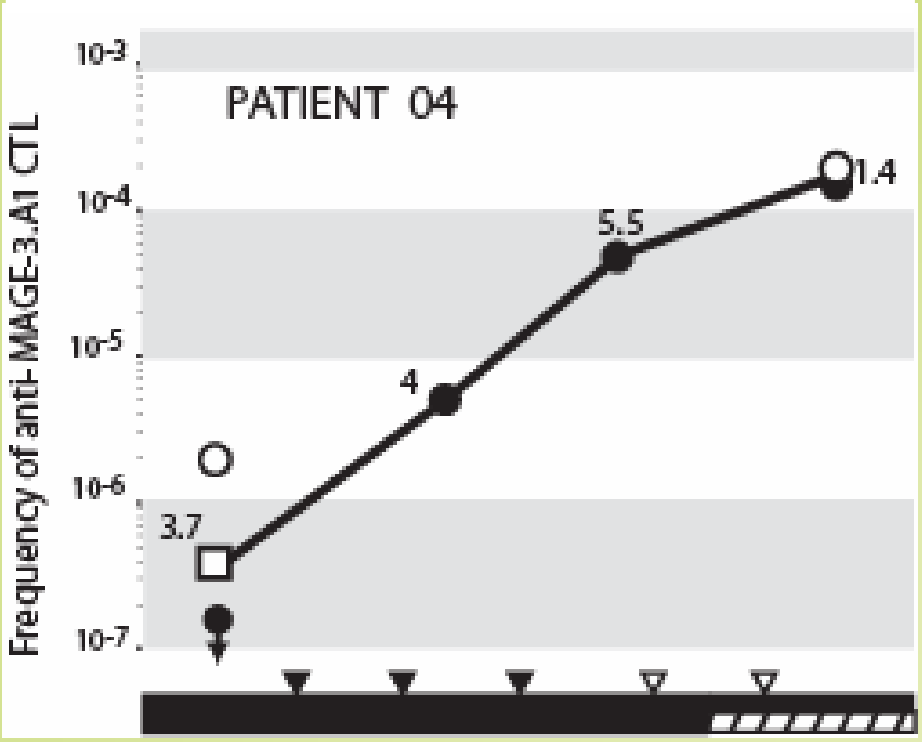
(DC with GM/IL4 for 7d, matured with IL1b, IL6, TNFa, PGE2)

19 patients: **M3A1 DC (fresh)**

16 patients: **DC frozen and then pulsed with multiple peptides (4million DC per peptide). Low CR**

40 patients: **DC pulsed with multiple peptides and frozen. Inject with DMSO, 10million DC per peptide**

Frequency of anti-MAGE3.A1 CTL after DC vaccination



DC vaccine trial Outcomes

Wide variation of immunogens

peptides, proteins, tumour lysates, mRNA etc

Wide variation in immune response

DTH, CD4 proliferation, CTL in periphery, TIL etc

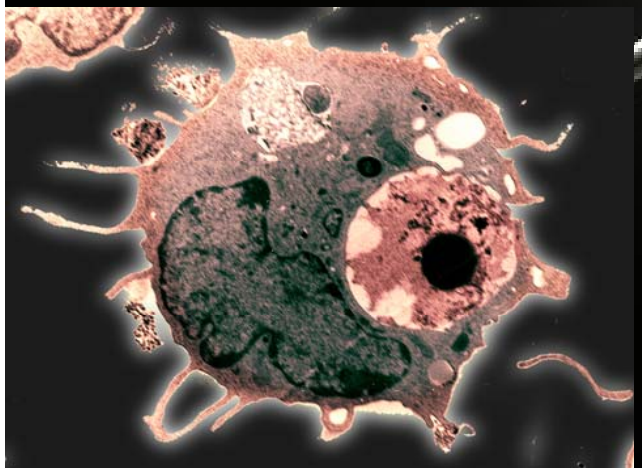
Clinical responses are short lived and of low frequency

Type of DC	No.	T cell response	Complete Regression
iDC	161	55/86 (64%)	3/161 (2%)
mDC	214	91/139 (65%)	11/214 (5%)

Improved quality of life

ΔΕΝΤΡΙΤΙΚΑ ΚΥΤΤΑΡΑ
ΚΑΙ
ΕΜΒΟΛΙΑ ΓΙΑ ΤΟΝ ΚΑΡΚΙΝΟ

DENDRITIC CELLS
AND
CANCER VACCINES



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-Laboratory of Anatomical Pathology, UTH: Prof Koukoulis G, Dr Nakou M
-Genetic and Cellular Unit, Ludwig Institute for Cancer Research, Belgium: Prof Coulie
-Cancer Trials Laboratory, Austin Research Institute, Melbourne, Australia: Prof. Loveland
-2nd Department of Surgery, University of Kitakyushu, Japan: Dr M. Takenoyama

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EU, GSRT, GSK, Pfizer,

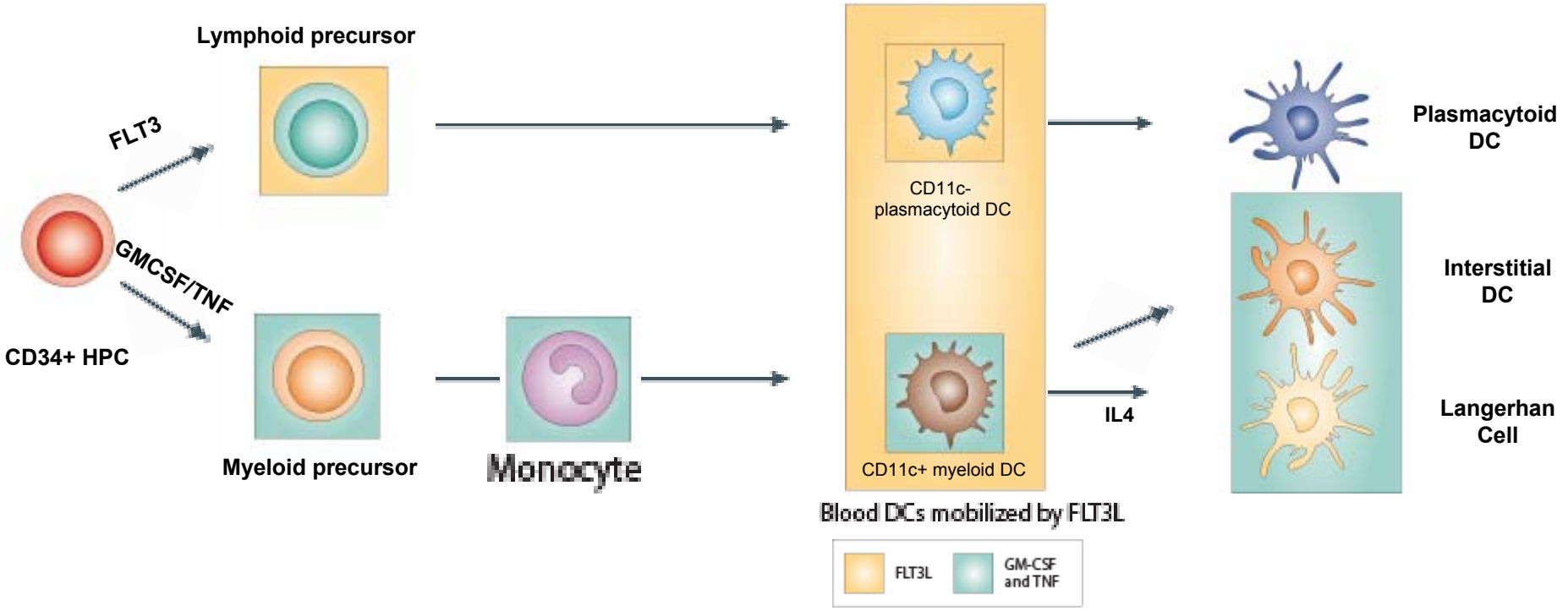
Tumour Immunology

Tumour Ags recognised by T cells

- tumor-specific, shared antigens (cancer-germline genes)
- encoded by mutated genes
- differentiation antigens
- overexpressed, or ubiquitously expressed

Dendritic Cells

Types of human DC



Nature Reviews Immunology 2005