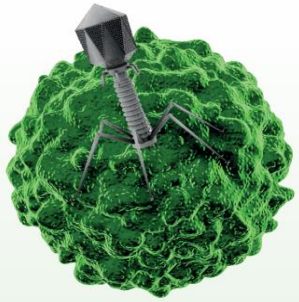
ONCOLYTIC VIROTHERAPY Summit 2017



The leading end-to-end industry forum dedicated to accelerating the clinical development of the next generation of immuno-oncolytic virotherapies for use in combinations

December 5-7 2017
MIAMI, FL

New Hope from Innovative Virotherapy & Immunotherapy for Glioblastoma Multiforme (GBM) -

Case Presentation, Rationale & Future Considerations

Benjamin Gesundheit MD PhD[1], Philip Zisman PhD[1], Ben P.H. Peeters PhD [2], Thomas Nesselhut MD[3], Jan Nesselhut MD[3], Dagmar Marx PhD[3], Gerhard Noss MD[4], Karl R. Aigner MD[5], Arno Thaller MD[6]

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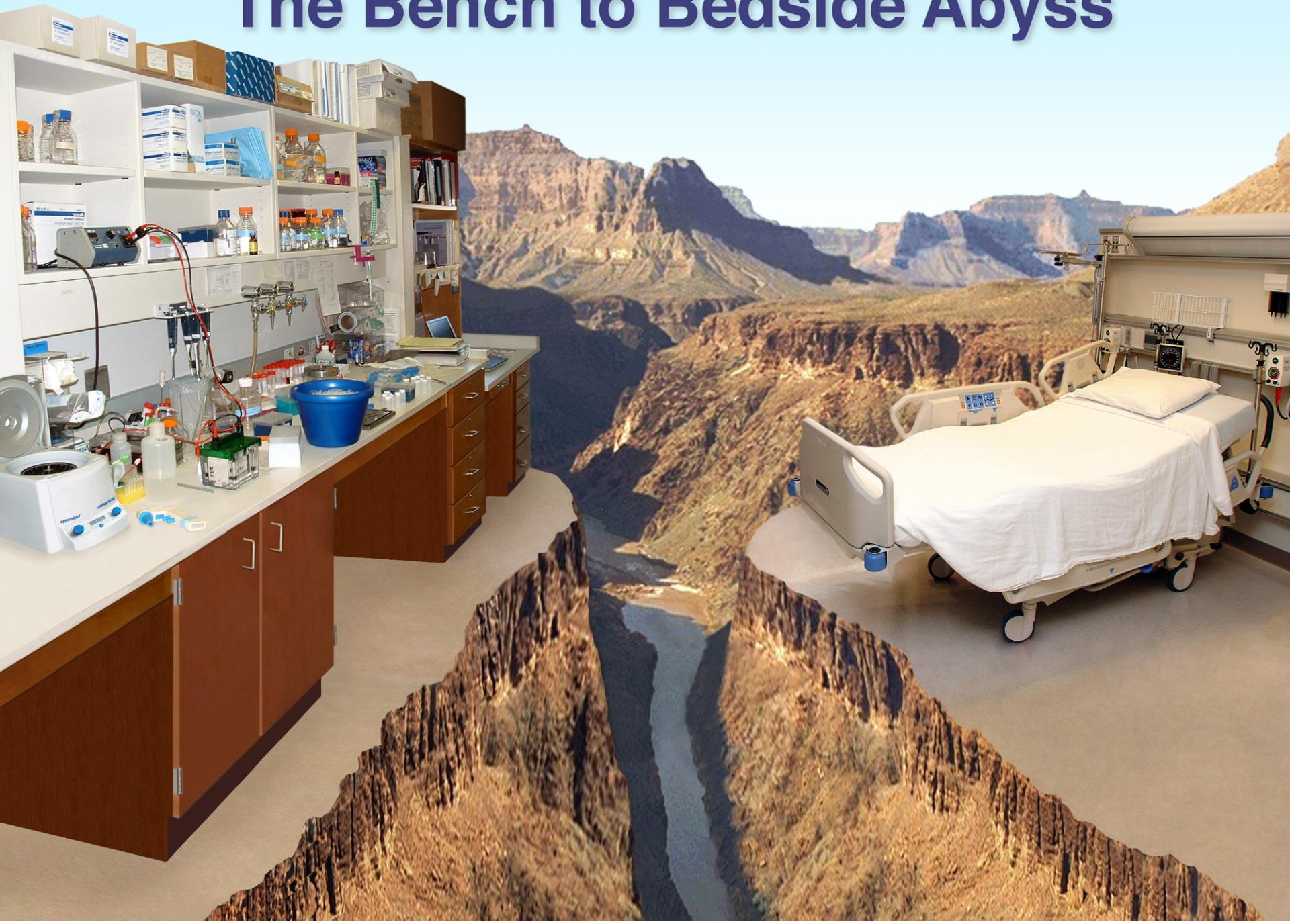
Go Viral / Rapo Yerapeh BH Ltd., Jerusalem, ISRAEL

The Bench to Bedside Abyss



GO VIRAL / RAPO YERAPEH BH Ltd. Israel

Go Viral LTD., a subsidiary of Rapo Yerapeh (founded 2016) aims to develop oncolytic immuno-therapy for Glioblastoma Multiforme (GBM) & other malignancies along with theranostic biomarkers for sensitivity and monitoring.

The Unmet Need:

- GBM represent 15% of brain tumors
- Incidence- 3.2 cases per 100,000 population
- Median Survival without Treatment-3 Months
- Median Survival with Treatment-1-2 years
- Etiology-Unknown
- Poor quality of life
- Current Standard of Care: Maximal surgical resection followed by 6 weeks of radiothera-py (dose: 60 Gy), together with concomitant chemotherapy with TMZ (75 mg/m2 daily). Once chemoradiotherapy is complete, a minimum of 6 months of adjuvant treatment with TMZ is started
- Approximate Costs to Health Care System: ~$120,000-240,000/y/patient (Raizer 2014)

GO VIRAL's Vision

- Improving treatment and outcome of GBM patients
- Testing oncolytic immunotherapeutic viruses on GBM cell lines to identify optimal virus for GBM
- Developing Theranostic Biomarkers to predict sensitivity to treatments and to monitor treatments
- Assessing clinical immunotherapy options for GBM

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Overview | 17 Articles | 82 Authors | Impact | Comments

VIEWS 27,076

ONCOLYTIC VIRUSES—GENETICALLY ENGINEERING THE FUTURE OF CANCER THERAPY

EDITED BY: Benjamin Gesundheit and Joshua P. Rosenzweig

PUBLISHED IN: Frontiers in Oncology and Frontiers in Immunology

20 Years of *Clinical* Experience with Oncolytic viruses

Benjamin Gesundheit

Gerhard Noss

Arno Thaller

haus

Resistovir™, an Efficient Method for Screening Oncolytic Viruses for Cancer Therapy

Gerhard Noss[1]

[1]Research Institute for Oncolytic Viruses, Sandgraben 4, D-88142 Wasserburg, Germany

Background and aim: Oncolytic viruses (OVs) have recently been the focus of extensive research aiming to develop their therapeutic potential for many cancer types. However not all OVs are suitable for cancer treatment because many of them have a pathogenic potential for human. In order to identify the most efficient OVs with only little side effects for human we have developed a new method called Resistovir™.

Method: Tumor tissues were collected from cancer patients and cultivated in vitro. The established cultures were genetically compared with the original biopsies regarding to their mutagenome and only cultures with a high grade of correlation were accepted for screening of our list of OVs. Numerous OVs were detected to be able to infect and lyse different cancer types. Remarkably, a novel strain of Newcastle disease virus (NDV) was found to be strongly efficient in various human cancer cells. Different researches have shown that NDV has a negligible pathogenic potential for human and is not harmful for non-transformed cells.

A B

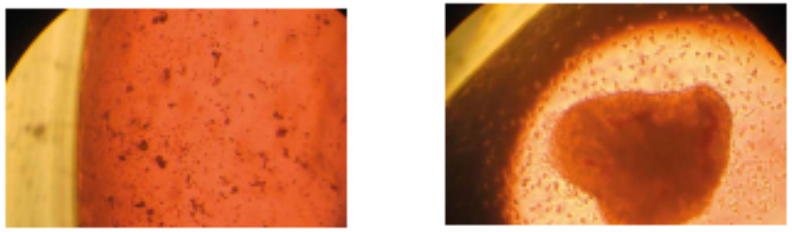


Figure 1. The effect of Resistovir™ in primary human ependymoma cells. Primary human ependymoma cells were cultivated in DMEM medium supplemented with 10% fetal calf serum and 0.5% Penicillin / Streptomycin mixture. Indicated cells were inoculated with 8 viruses of Resistovir™ at a MOI of 0.1. As control, ependymoma cells were mock-infected with DMEM without serum (Fig. 1B). Cell survival and cytopathic effects (CPE) were determined 24 hours after inoculation with NDV and Reovirus type 3. As shown in Fig. 1A ependymoma cultures were completely destroyed 24 hours after infection with Reovirus (Fig. 1A). The mock-infected cultures remained viable.

A B

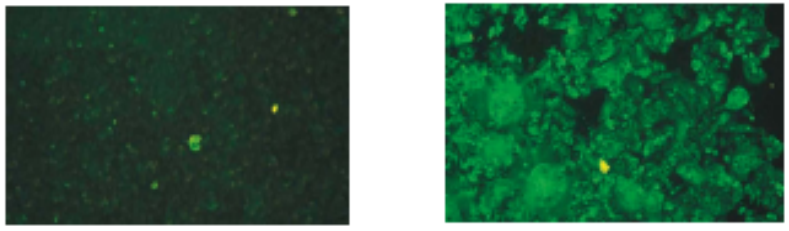


Figure 2. A novel strain of NDV adapted to HeLa cells has been found as a promising candidate for virotherapy of human cancer. HeLa cells were inoculated with NDV at a MOI of 0.025 (Fig. 2A) or MOI of 0.1 (Fig. 2B) for 1 hour. 24 hours after inoculation cells were then washed 3 times with phosphate buffered solution (PBS) and fixed in 70% acetone. Fixed cells were permeabilized and analyzed by immunofluorescence assay (IFA) using human sera which contained high - titered antibody against NDV. FITC-conjugated antiHuman-IgG from goat was used as secondary antibody.

Type of cancer	Some of oncolytic viruses tested in Re										
	Adeno5	Aujesky	EMCV	Echo7	NDV	Reo1	Reo3	P			
Pancreas					+	+	+				
Breast					+	+	+				
Stoma					+		+				
Kidney					+		+				
Ependym		+			+		+		+		
Bladder					+		+		+	+	
Bone		+						+			+
Prostate		+			+		+				+
Colon	+				+		+		+	+	
Head/Neck	+			+	+					+	
Thyreoid gl.					+		+				
Duodenum					+				+		
Mesothel					+		+	+		+	+
Thymus						+	+				
NNR					+	+	+		+	+	
Glia			+	+							

Table 1. Resistovir™ testing in primary cell lines derived from various malignomas. Different primary cancer cells cultivated in appropriate media were inoculated with various oncolytic viruses of Resistovir™ at a MOI of 0.1. Cell survival and cytopathic effects (CPE) were determined at the latest 72 hours after viral infection. (+) indicates cancer cells completely destroyed by oncolytic virus. Adeno5: Human adenovirus type 5; Aujeszky: Aujeszkyvirus; EMCV: Encephalomyocarditis virus; Echo7: Echovirus type 7; NDV: Newcastle disease virus; Reo1: Reovirus type 1; Reo3: Reovirus type 3; ParvoH1: Parvovirus H1; SIV: Sindbisvirus; Vaccinia: Vaccinia virus; VSV: Vesicular stomatitis virus; NNR: Cortex of suprarenal gland

Conclusion: Resistovir™ provides an attractive new tool to select the most efficient oncolytic viruses with low side effects for cancer treatment. Especially, our novel strain of NDV could be a promising agent for virotherapy of various tumors.

Acknowledgement: We would like to thank Prof. E. Marion Schneider and Philip Sander, Division Experimental Anesthesiology, University Hospital of Ulm, Germany for kindly providing us with primary glioblastoma cell lines.

Innovative Approaches for GBM
Oncolytic Viruses, Immunotherapy & Dendritic Cells

International Scientific Meeting / WorkShop
Markt-Berolzheim, July 3rd-4th, 2017

Consensus Report of our International Study Group

Ben P.H. Peeters

Wageningen University & Research | WUR · Central Veterinary Institute (CVI)

Praxisgemeinschaft für Zelltherapie
Duderstadt GmbH & Co. KG

PRESENTATION OUTLINE

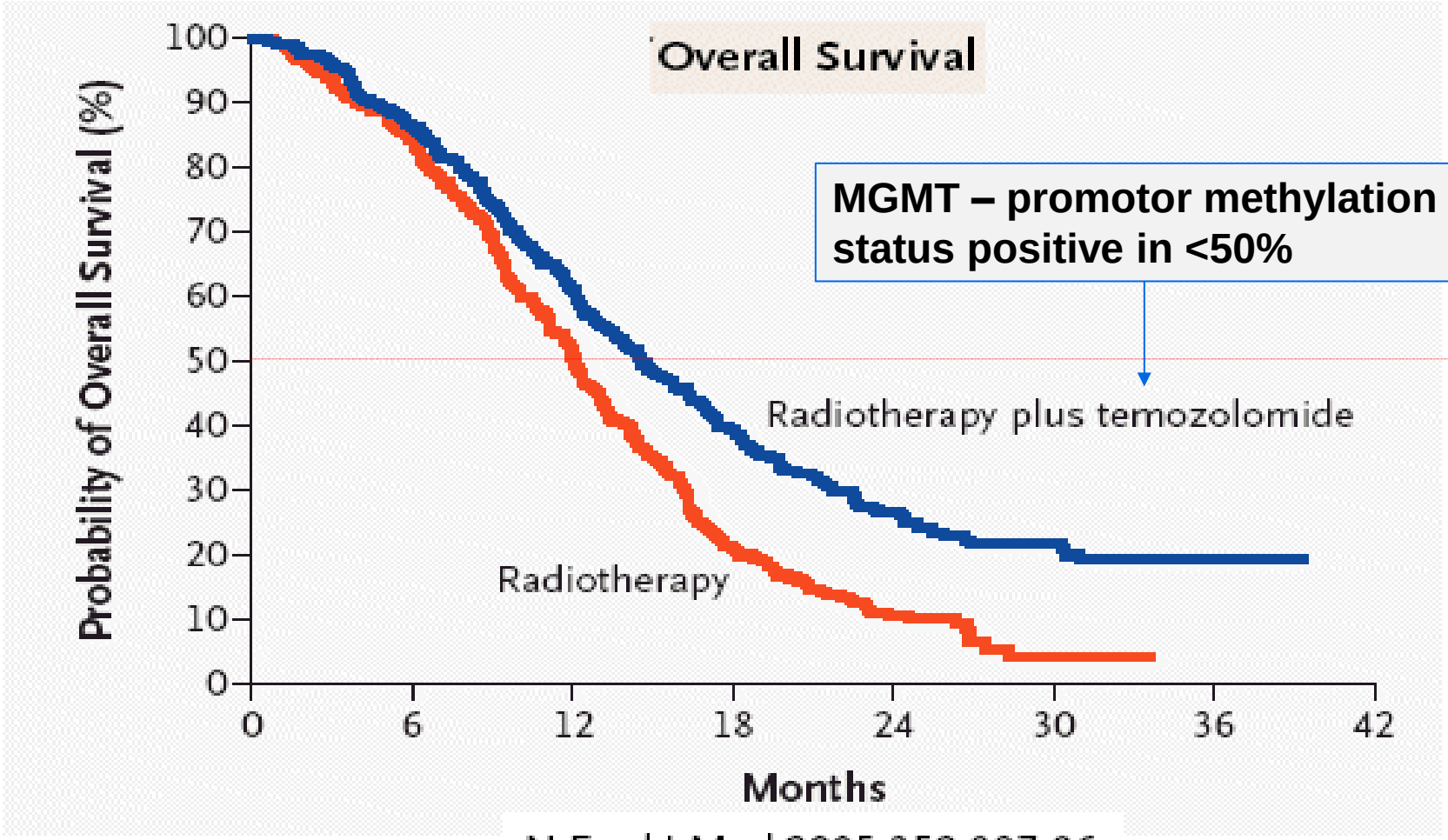
1. **GBM – classical treatment and outcome →**

   new strategies: immune & oncolytic virotherapies

2. **Oncolytic Viruses (OV)**
3. **Dendritic Cells (DC)**
4. **Checkpoint Inhibitor (CPI)**
5. **Case Reports: GBM treated with OV/DC**
6. **Summary & Future Directions**
7. **Individueller Heilversuch *(German Law)***

1. GBM: Classical Treatment & Survival

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma



N Engl J Med 2005;352:987-96.

3. Clinical Concepts: Chemotherapy & Oncolytic viruses

"His genius was essentially practical, and his military concepts evolved from **the close study of earlier commanders**… He made the **fullest use of the ideas of his predecessors and breathed life into them**."
(*Chandler - "Dictionary of the Napoleonic wars" p 18*)

“Classical” Cancer Treatments

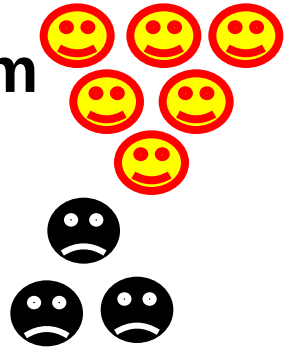
- Surgery
- Cyto-toxic = Chemotherapy
- Radiotherapy

✓ “Efficient”
✓ Fast
➢ Aggressive
➢ Toxic/Dose limiting
➢ Tolerance
➢ Immunosuppressive
➢ Morbidity/Mortality
➢ Refractory: MRD

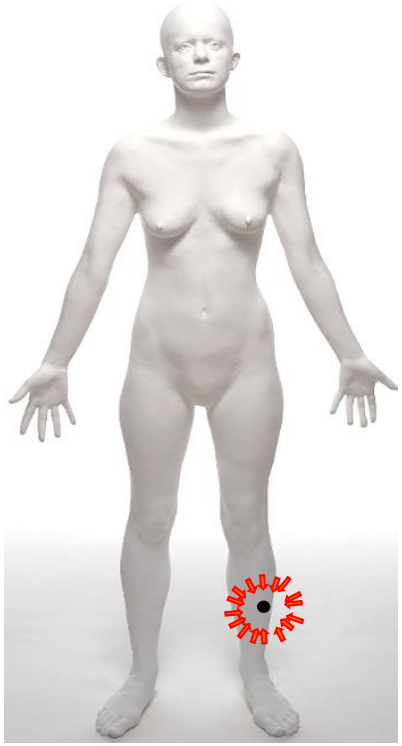
“Biological” Cancer Treatments

- Immunology
- Anti-body
- Virotherapy
- Hyperthermy
- etc.

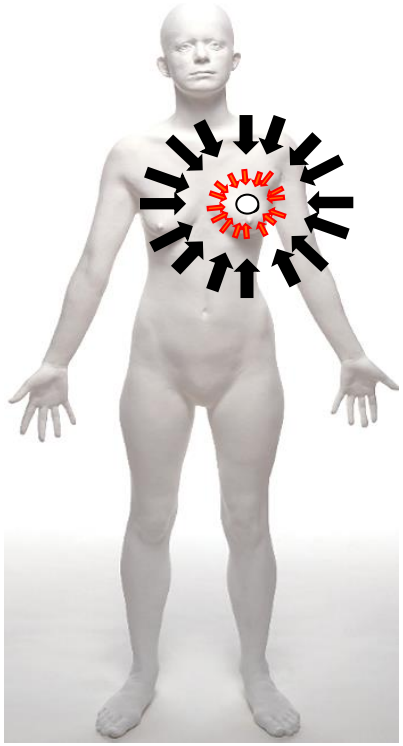
✓ Tolerance: Slow, long term
✓ Immune modulating
✓ Good for MRD
➢ “No” fast Effect



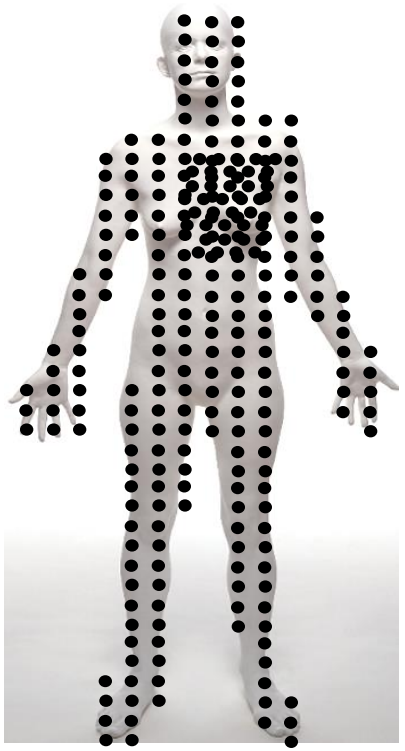
Immunotherapy for Cancer



(I) 47y F Melanoma of foot, no metastasis
⇨wide surgical Resection



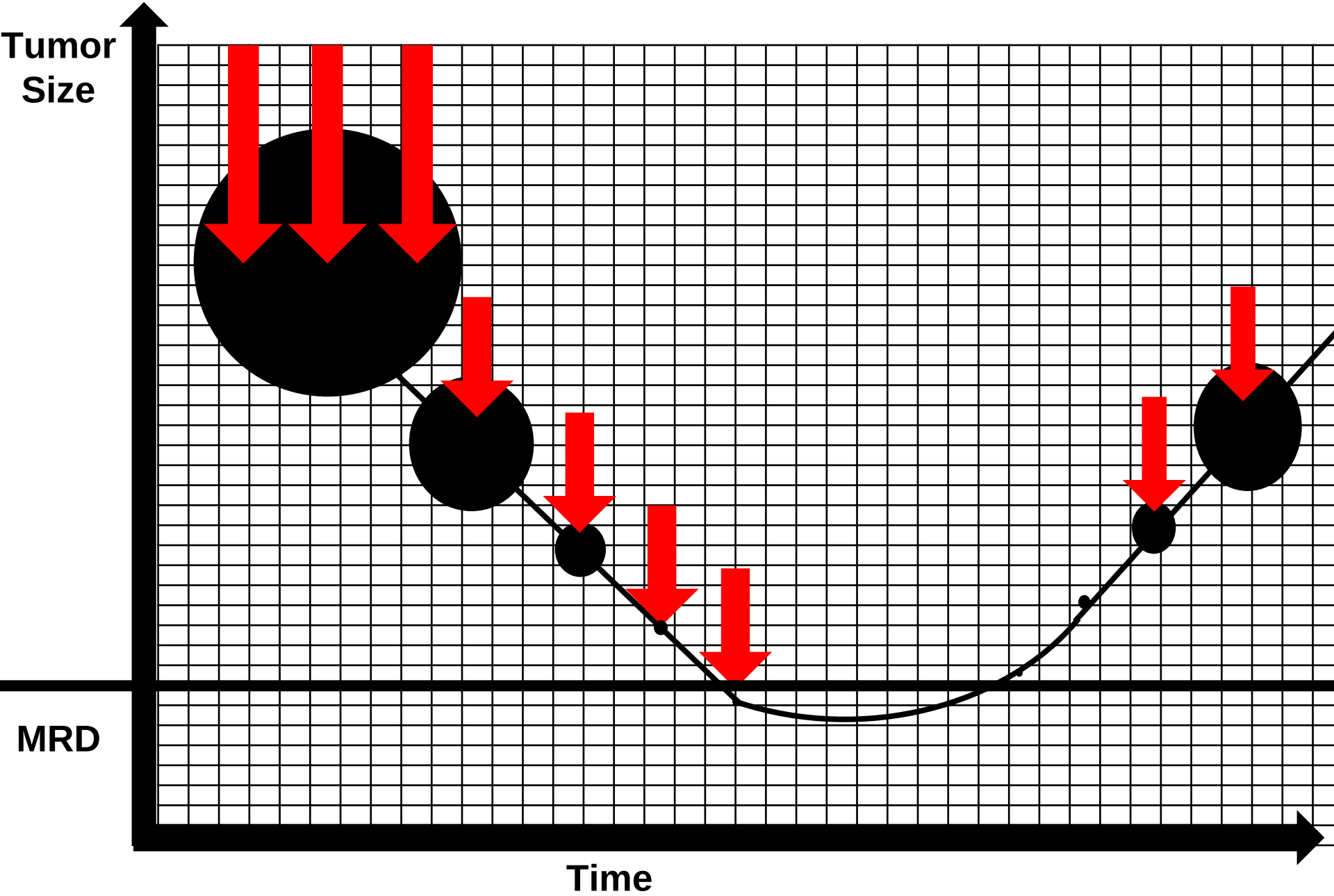
(II) 3y later: adeno-ca of breast => surgical resection and radiation to breast and axillary lN



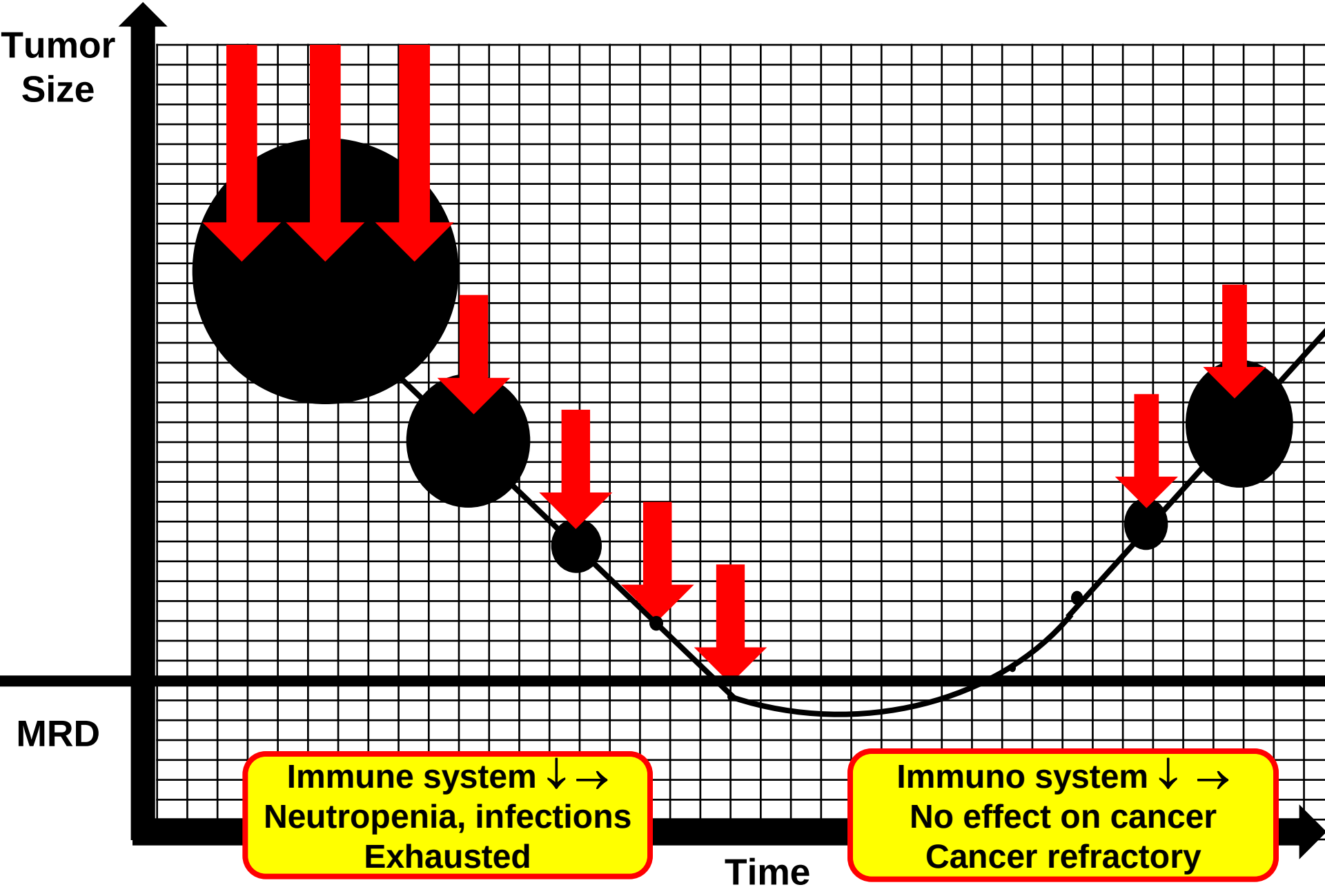
(III) 1 mo later: Multiple sc melanoma nodules in irradiated field
=> Visceral spread
=> fatal disease

Woodruff MF .Immunological Aspects of Cancer. Lancet 1964;2:265-270

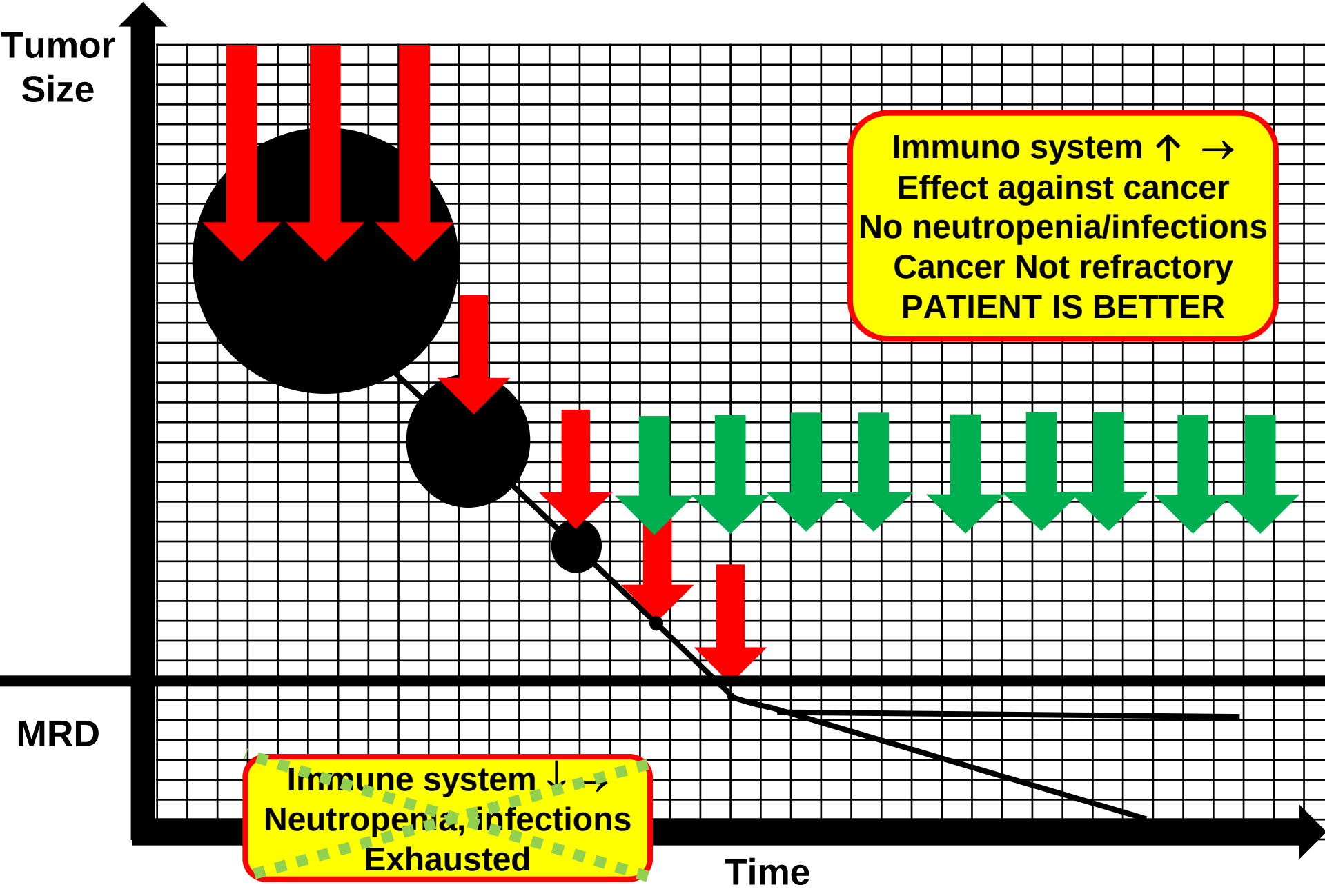
“Classical” Cancer Treatments



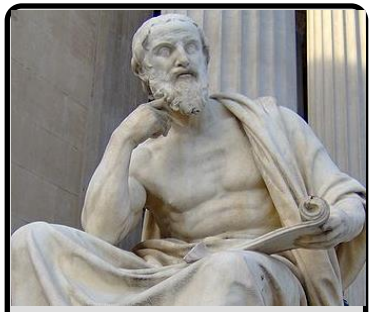
“Classical” Cancer Treatments



"Classical" & "Biological" Treatments



2. Oncolytic Viruses : History



Herodotus
(484 – 413 BCE)
"Father of History"

- 1950's-1960's: Beginning of the deliberate use of natural oncolytic viruses to treat cancer (Polio, Adenoviruses, Cocksackie, others)
- Early challenges: Some level of response, only certain types of cancers, side effects…
- Oncolytic viral therapy for cancer is mostly interrupted for many years

Why? What Changed?

- Development of genetic engineering of viruses (patents!)
  Enables changing natural viruses to **specifically target cancer cells** and **limit adverse effects**
- 2015: FDA approves first virus for treatment of cancer
  Talimogene laherparepvec (T-VEC) for Melanoma

2. Oncolytic Viruses : History

Oncolytic Immunotherapy: Conceptual Evolution, Current Strategies, and Future Perspectives

Zong Sheng Guo[1,2], Zuqiang Liu[1,2], Stacy Kowalsky[1,2], Mathilde Feist[1,2,3], Pawel Kalinski[1,2,4], Binfeng Lu[1,4], Walter J. Storkus[1,4,5] and David L. Bartlett[1,2]*

[1] University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA, [2] Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [3] Department of Surgery, CCM/CVK, Charité – Universitaetsmedizin Berlin, Berlin, Germany, [4] Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [5] Department of Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

frontiers in Immunology

REVIEW
published: 15 May 2017
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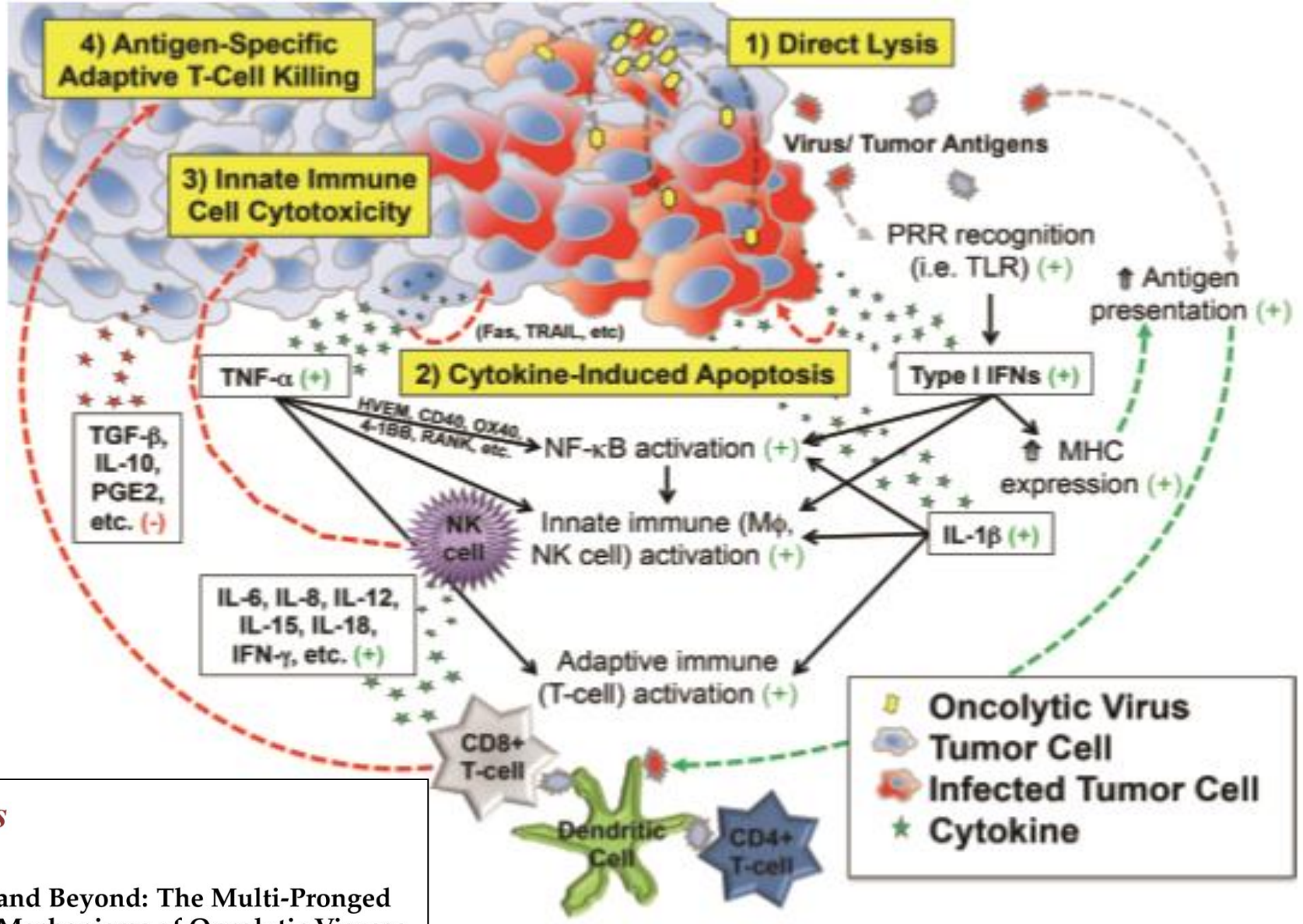
Check for updates

1) "Direct infection and oncolysis of cancer cells and endothelial cells in the tumor microenvironment (TME)"

2) "Indirect effects of necrosis/apoptosis of uninfected cancer cells and associated endothelial cells in the tumor-associated vasculature leading to reduced angiogenesis"

3) "Antitumor (and antiviral) immunity is elicited/expanded by the OV as a consequence of improved antigen cross-priming and recruitment of immune cells into the TME."

2. Virotherapy - Mechanisms of Action



viruses

Review

To Infection and Beyond: The Multi-Pronged Anti-Cancer Mechanisms of Oncolytic Viruses

Kevin A. Cassady [1,2], Kellie B. Haworth [1,3], Josh Jackson [4,5], James M. Markert [5] and Timothy P. Cripe [1,3,*]

OncoTargets and Therapy

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REVIEW

Oncolytic viruses as immunotherapy: progress and remaining challenges

This article was published in the following Dove Press journal:
OncoTargets and Therapy
4 May 2016
Number of times this article has been viewed

Laure Aurelian

Department of Pharmacology, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract: Oncolytic viruses (OVs) comprise an emerging cancer therapeutic modality whose activity involves both direct tumor cell lysis and the induction of immunogenic cell death (ICD). Cellular proteins released from the OV-lysed tumor cells, known as damage-associated molecular patterns and tumor-associated antigens, activate dendritic cells and elicit adaptive

Table 1 Mechanisms of OV-induced cell death and immunogenicity

Type of cell death	Immunogenicity
Necrosis	Releases DAMPs and TAAs; induces ICD
Apoptosis	Generally nonimmunogenic
Pyroptosis	Caspase-1-dependent cytokine release; induces ICD
Autophagic cell death	Releases DAMPs; immunogenic

Notes: OVs induce multiple tumor cell death pathways, most of which are also immunogenic. DAMPs and TAAs released from OV-infected cells induce immunogenic cell death.

Abbreviations: DAMP, damage-associated molecular pattern; ICD, immunogenic cell death; o, oncolytic; OV, oncolytic virus; TAA, tumor-associated antigen.

3. Dendritic Cells (DCs)

IDENTIFICATION OF A NOVEL CELL TYPE IN PERIPHERAL LYMPHOID ORGANS OF MICE

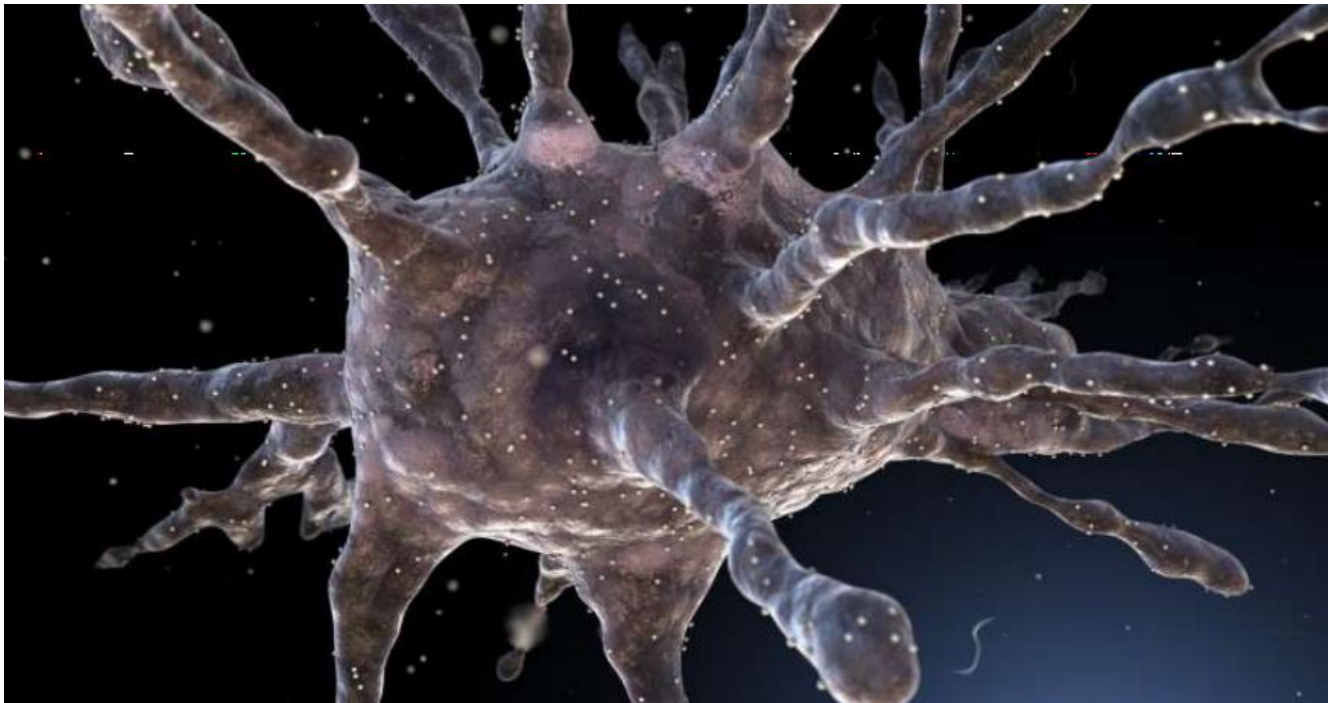
I. Morphology, Quantitation, Tissue Distribution*

By RALPH M. STEINMAN‡ and ZANVIL A. COHN

(*From The Rockefeller University, New York 10021*)

(Received for publication 19 January 1973)

Ralph M Steinman
(1943-2011)
Nobel Prize 2011



Dendritic Cells (DCs)

APC = Antigen Presenting Cells: process antigen material and present it on the cell surface to T cells = stimulation of T cell response; act as messengers between innate and adaptive immune system.

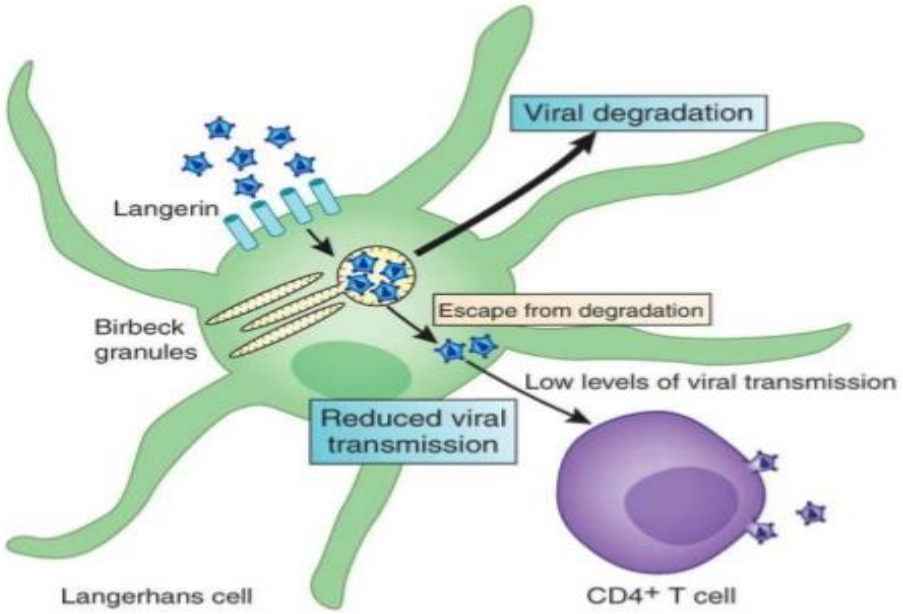
DC are present in tissues exposed to the external environment: skin (=Langerhans cells), nose, lungs, stomach, intestine.

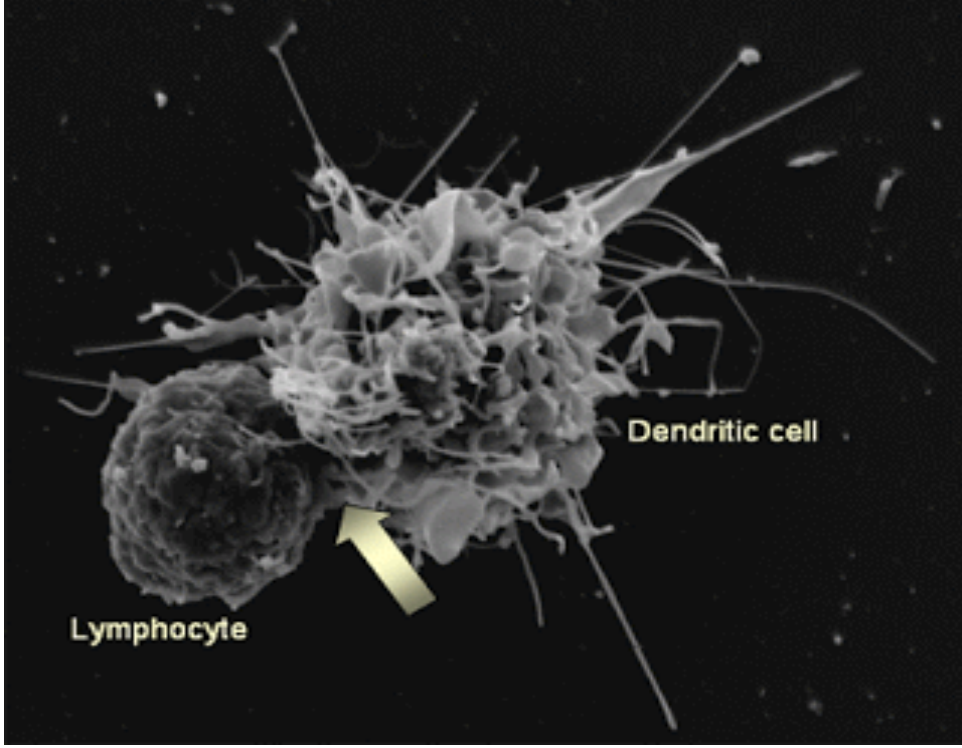
Once activated, they migrate to the LN where they interact with T cells and B cells.

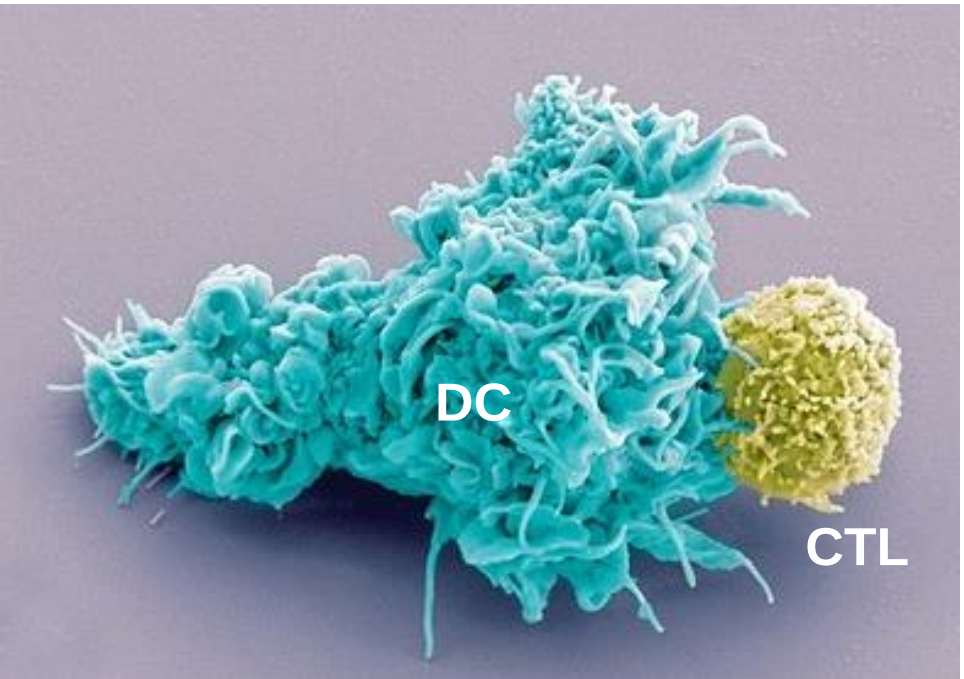
Immature DC = “veiled” cells

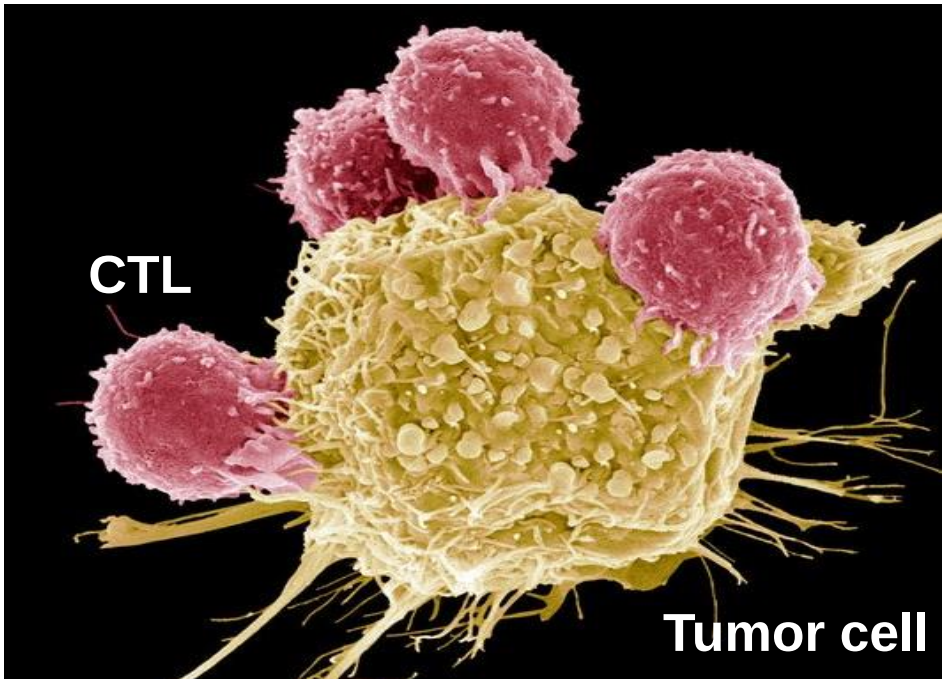
Expression of CD1a, CD1b, CD23, CD36, CD207 (Langerin)

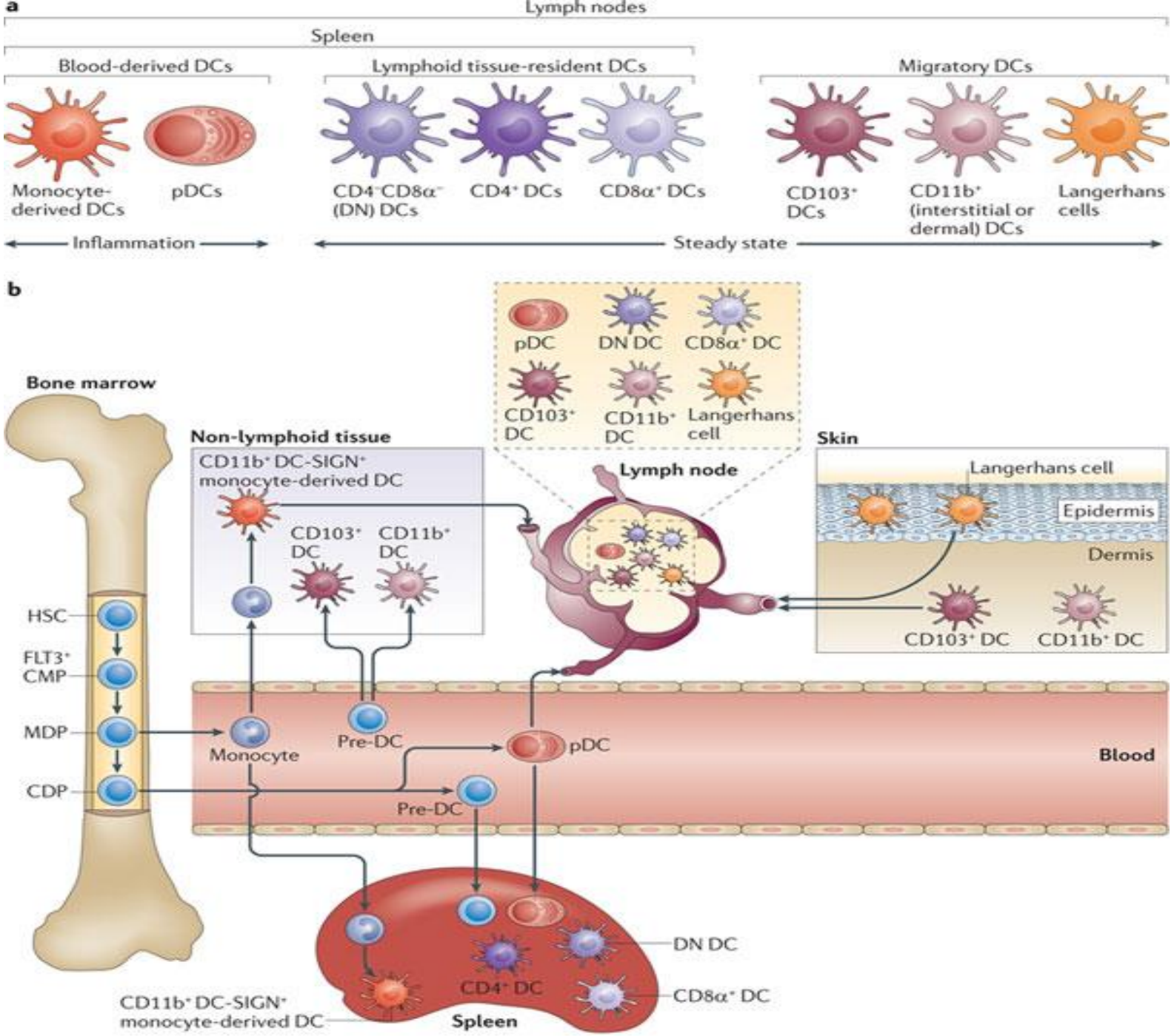
large surface-to-volume ratio



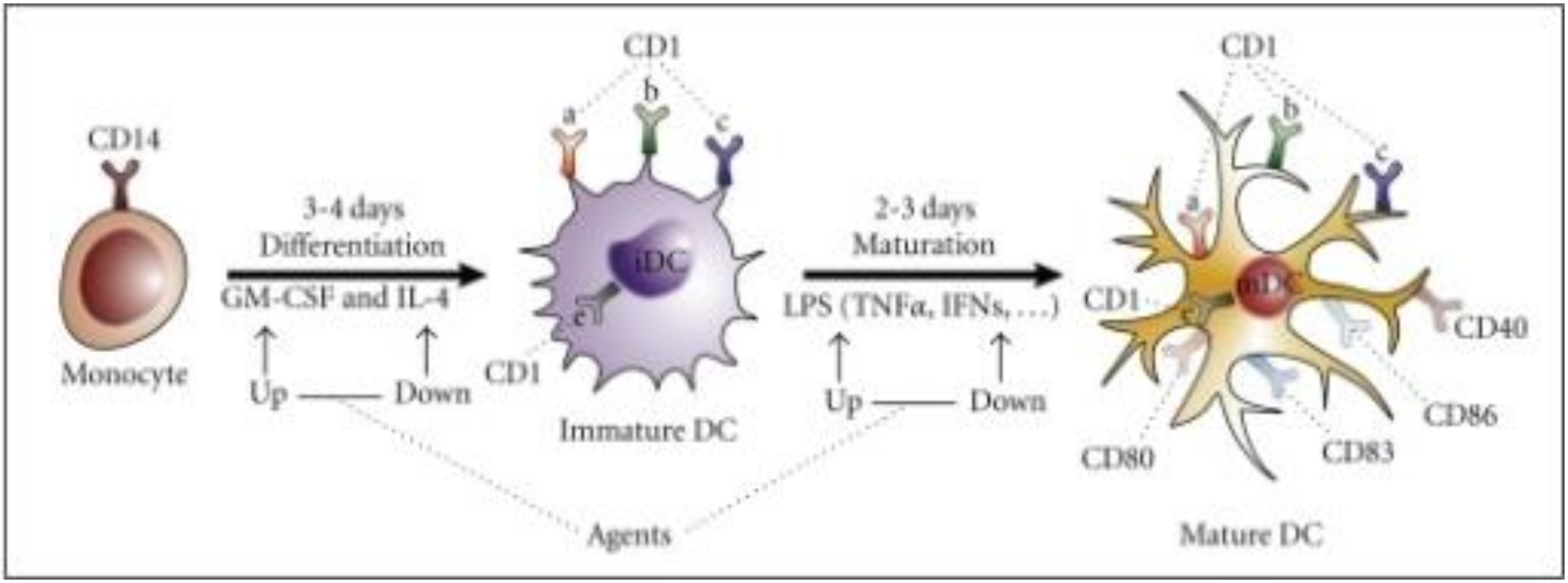







a
Lymph nodes
Spleen
Blood-derived DCs
Lymphoid tissue-resident DCs
Migratory DCs
Monocyte-derived DCs
pDCs
CD4⁻CD8α⁻ (DN) DCs
CD4⁺ DCs
CD8α⁺ DCs
CD103⁺ DCs
CD11b⁺ (interstitial or dermal) DCs
Langerhans cells
Inflammation
Steady state
b
pDC
DN DC
CD8α⁺ DC
CD103⁺ DC
CD11b⁺ DC
Langerhans cell
Bone marrow
Non-lymphoid tissue
CD11b⁺ DC-SIGN⁺ monocyte-derived DC
CD103⁺ DC
CD11b⁺ DC
Lymph node
Skin
Langerhans cell
Epidermis
Dermis
CD103⁺ DC
CD11b⁺ DC
HSC
FLT3⁺ CMP
MDP
CDP
Monocyte
Pre-DC
pDC
Blood
Pre-DC
DN DC
CD4⁺ DC
CD8α⁺ DC
CD11b⁺ DC-SIGN⁺ monocyte-derived DC
Spleen

3.1-Dendritic Cell Maturation and Activation

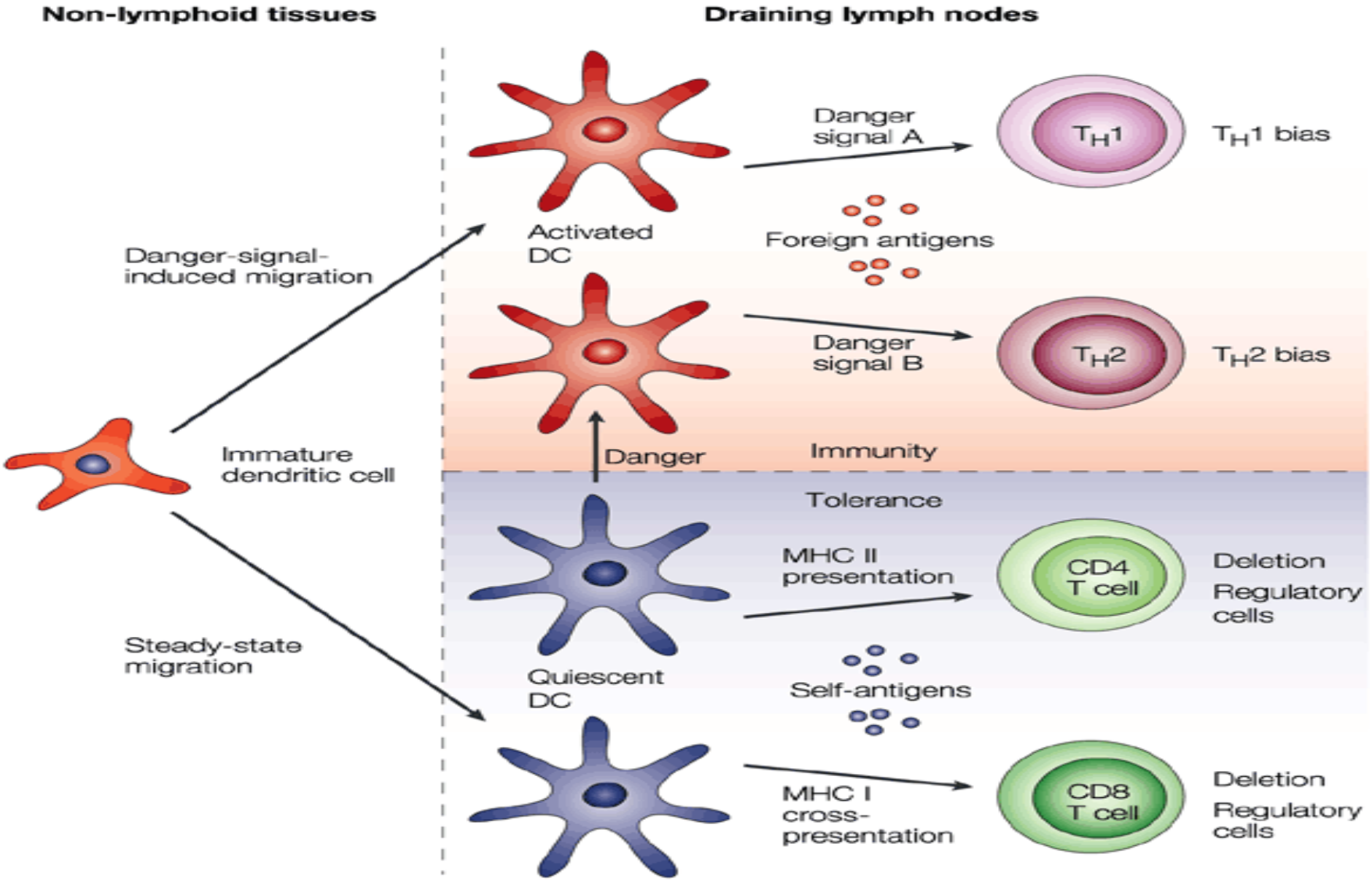


Immature Dendritic Cells

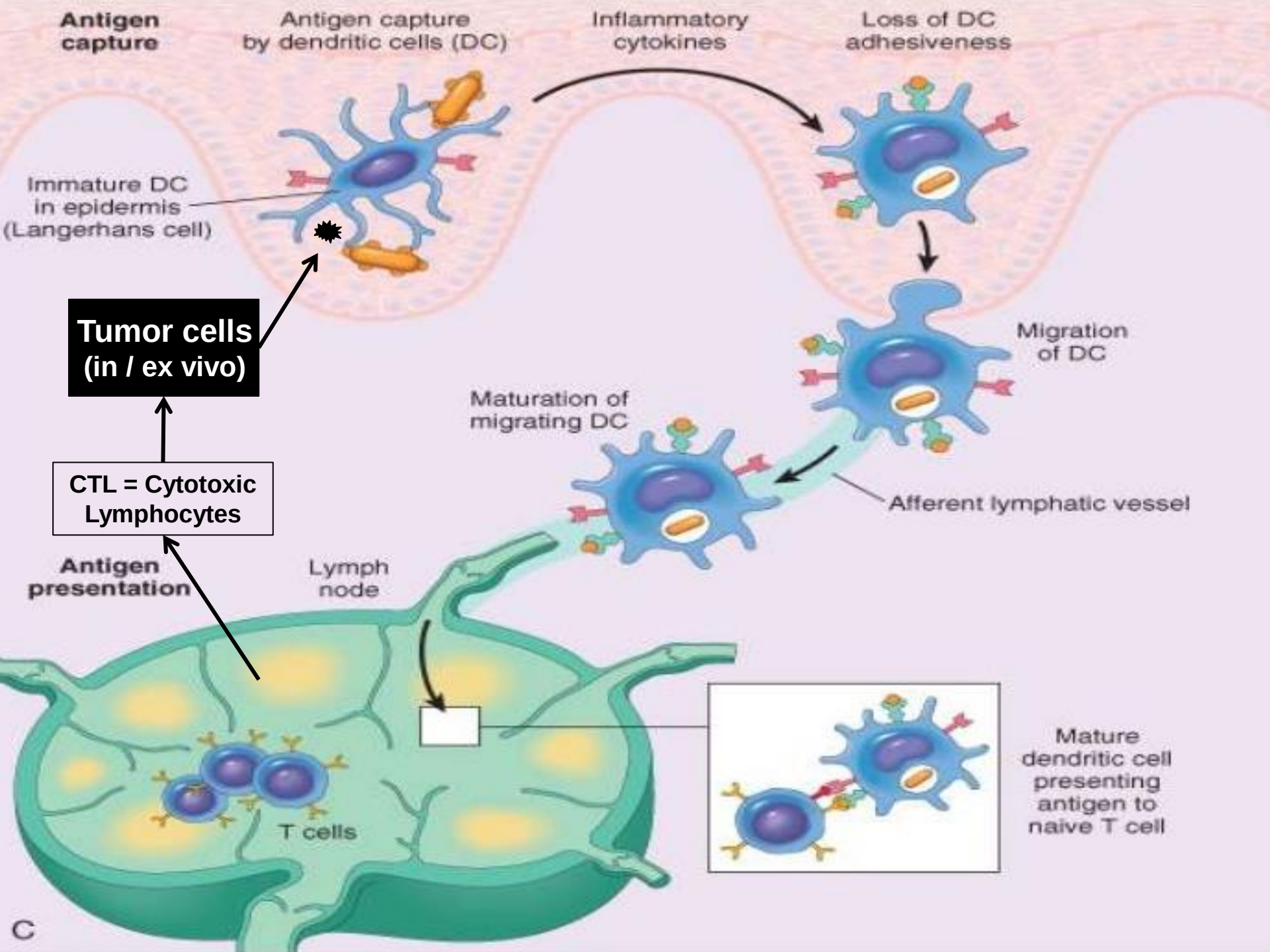
Mechanisms of Antigen Capture

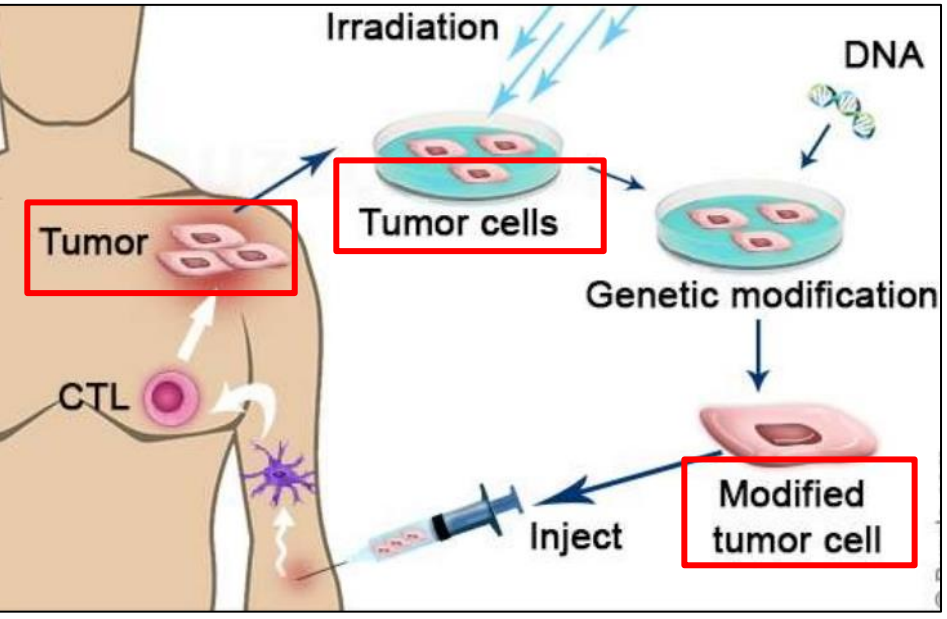
1-phagocytosis
2-micropinocytosis
3-receptor mediated endocytosis (via C-type lectin receptors or Fc receptors)
4-low levels of class I and II MHC molecules, as well as co-stimulatory molecules such as CD80 and CD86

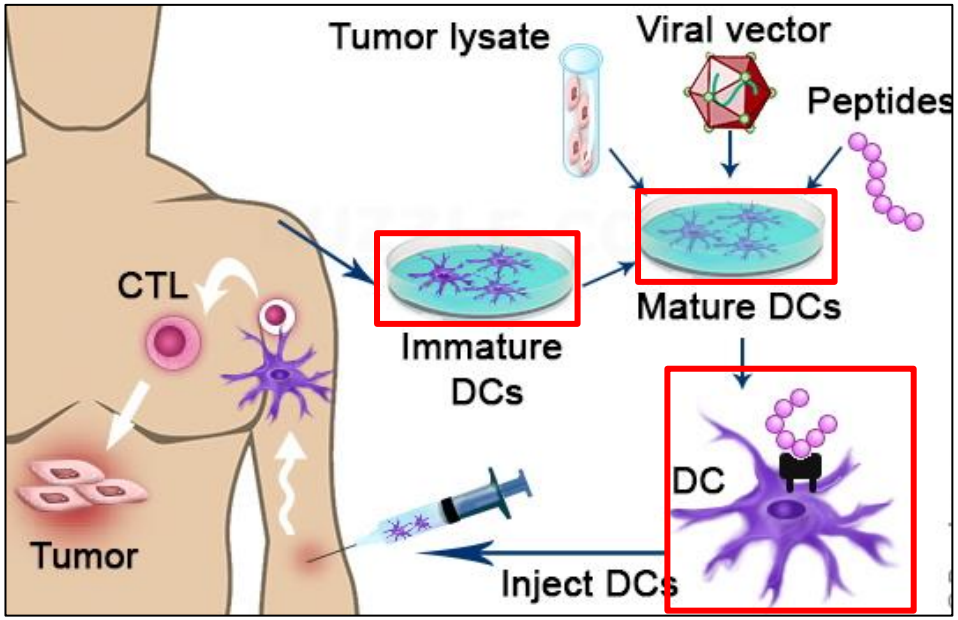
Dendritic Cell Activation



Nature Reviews | Immunology


Antigen capture
Antigen capture by dendritic cells (DC)
Inflammatory cytokines
Loss of DC adhesiveness
Immature DC in epidermis (Langerhans cell)
Tumor cells (in / ex vivo)
Migration of DC
Maturation of migrating DC
CTL = Cytotoxic Lymphocytes
Afferent lymphatic vessel
Antigen presentation
Lymph node
T cells
Mature dendritic cell presenting antigen to naive T cell
C





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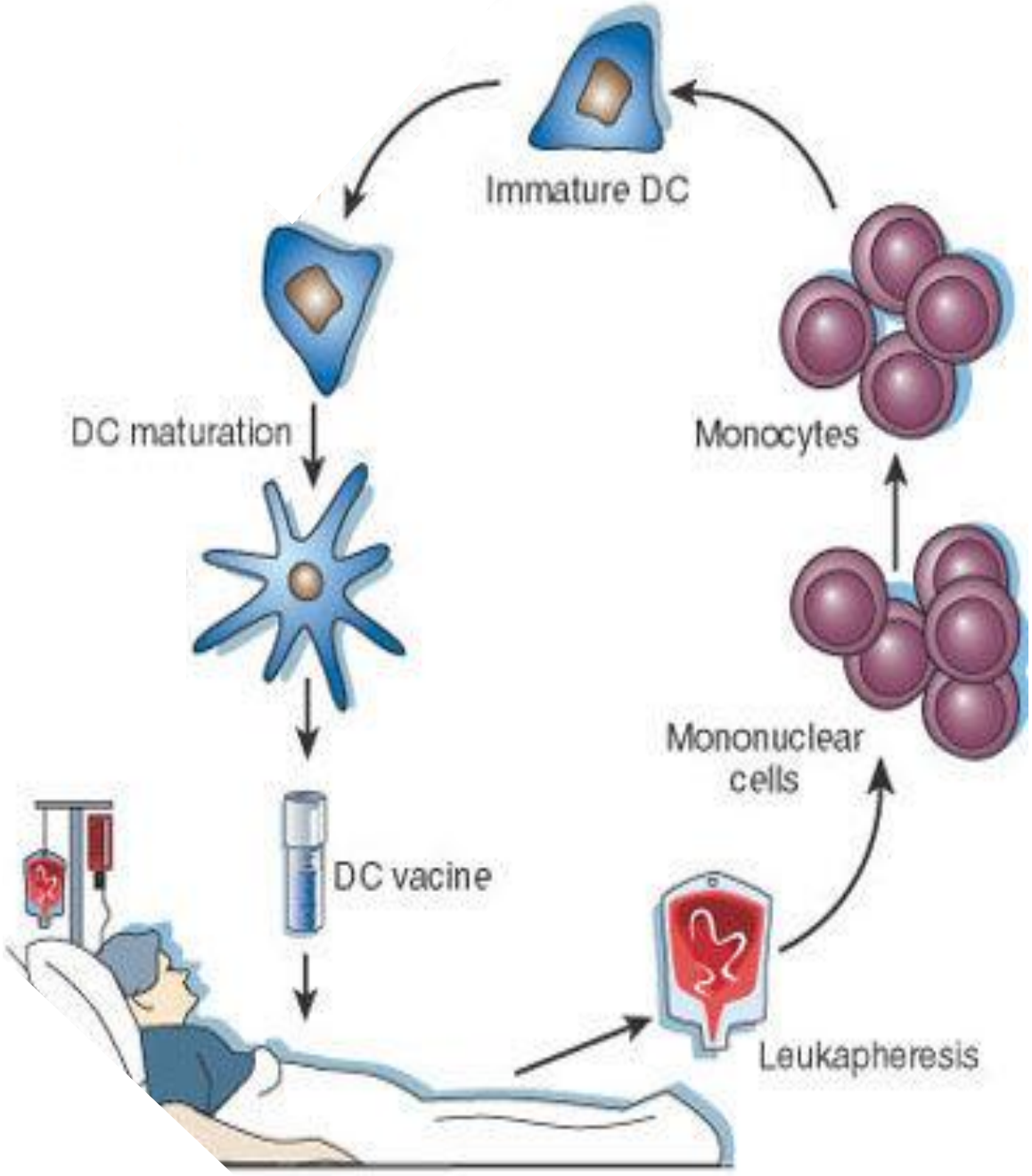
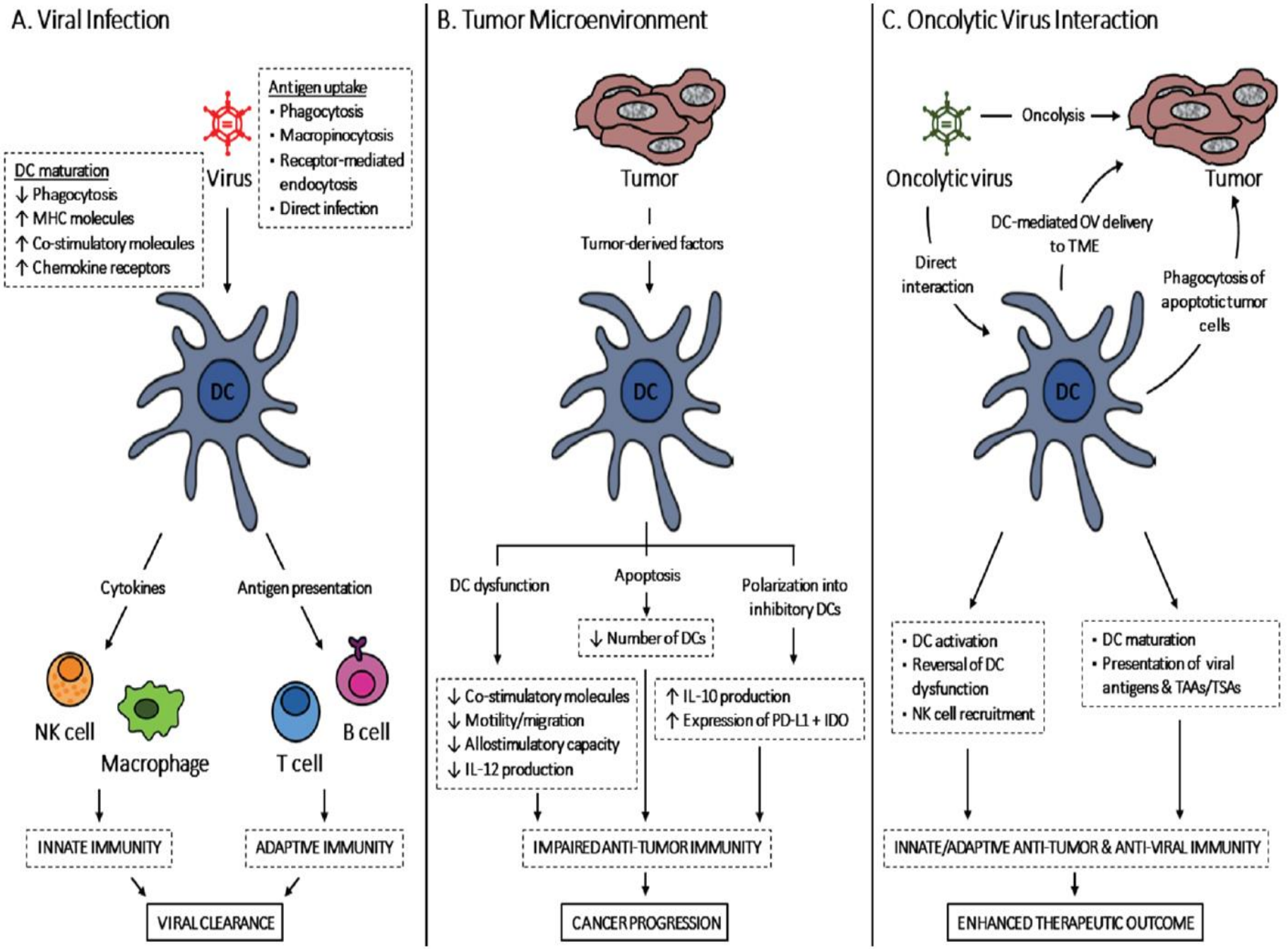
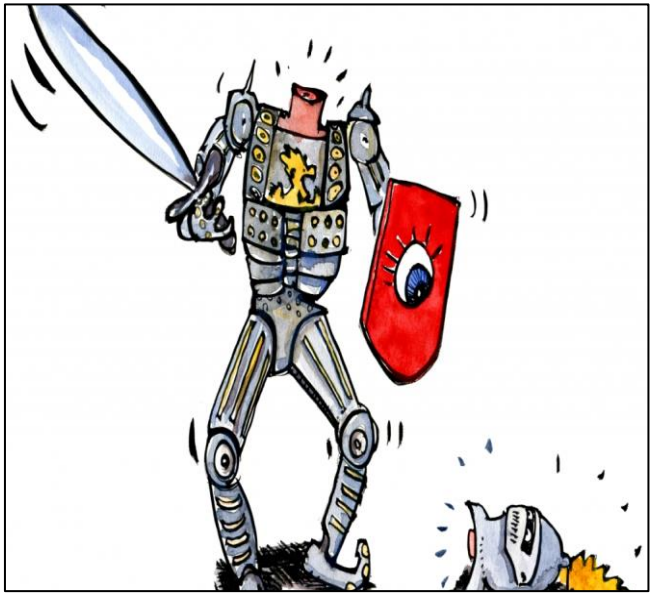
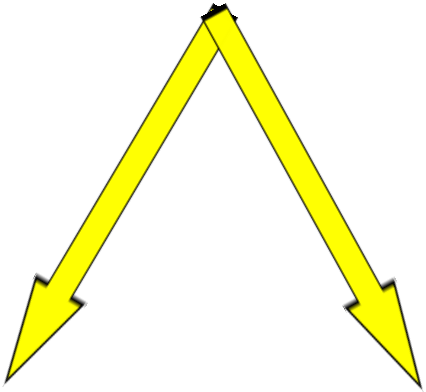

Immature DC
DC maturation
Monocytes
Mononuclear cells
DC vacine
Leukapheresis


A. Viral Infection
Antigen uptake
• Phagocytosis
• Macropinocytosis
• Receptor-mediated endocytosis
• Direct infection
Virus
DC maturation
↓ Phagocytosis
↑ MHC molecules
↑ Co-stimulatory molecules
↑ Chemokine receptors
DC
Cytokines
Antigen presentation
NK cell
Macrophage
T cell
B cell
INNATE IMMUNITY
ADAPTIVE IMMUNITY
VIRAL CLEARANCE
B. Tumor Microenvironment
Tumor
Tumor-derived factors
DC
DC dysfunction
Apoptosis
Polarization into inhibitory DCs
↓ Number of DCs
↓ Co-stimulatory molecules
↓ Motility/migration
↓ Allostimulatory capacity
↓ IL-12 production
↑ IL-10 production
↑ Expression of PD-L1 + IDO
IMPAIRED ANTI-TUMOR IMMUNITY
CANCER PROGRESSION
C. Oncolytic Virus Interaction
Oncolysis
Oncolytic virus
Tumor
DC-mediated OV delivery to TME
Direct interaction
Phagocytosis of apoptotic tumor cells
DC
• DC activation
• Reversal of DC dysfunction
• NK cell recruitment
• DC maturation
• Presentation of viral antigens & TAAs/TSAs
INNATE/ADAPTIVE ANTI-TUMOR & ANTI-VIRAL IMMUNITY
ENHANCED THERAPEUTIC OUTCOME

DC = Double Edged Sword?





Anti-Cancer

Activated DCs → Anti-tumor immunity

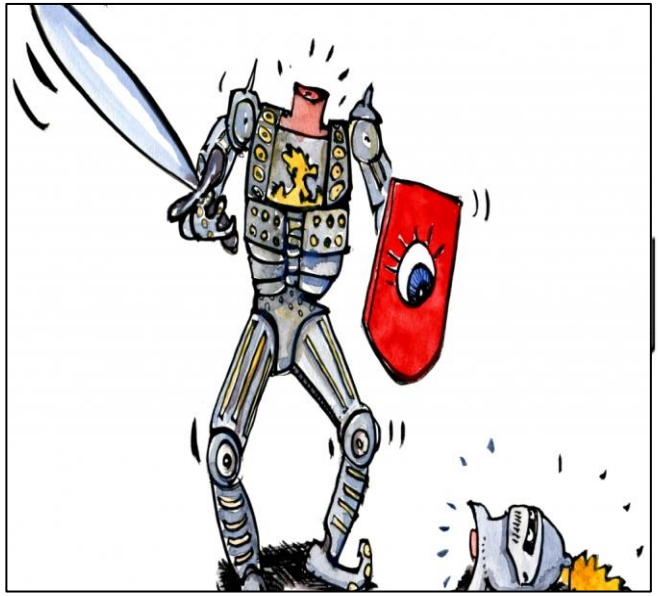
Via activation of innate immune cells and tumor-specific lymphocytes that target cancer cells

Pro-Cancer

Tumor microenvironment → Impairment of DC functions

Tumor-associated DCs fail to initiate tumor-specific immunity, and indirectly support tumor progression

4. Dendritic Cells (DC) – Rationale



viruses

Review

Dendritic Cells in Oncolytic Virus-Based Anti-Cancer Therapy

Youra Kim [1], Derek R. Clements [1], Andra M. Sterea [2], Hyun Woo Jang [3], Shashi A. Gujar [3,4,*] and Patrick W. K. Lee [1,3,*]

Conclusions

20

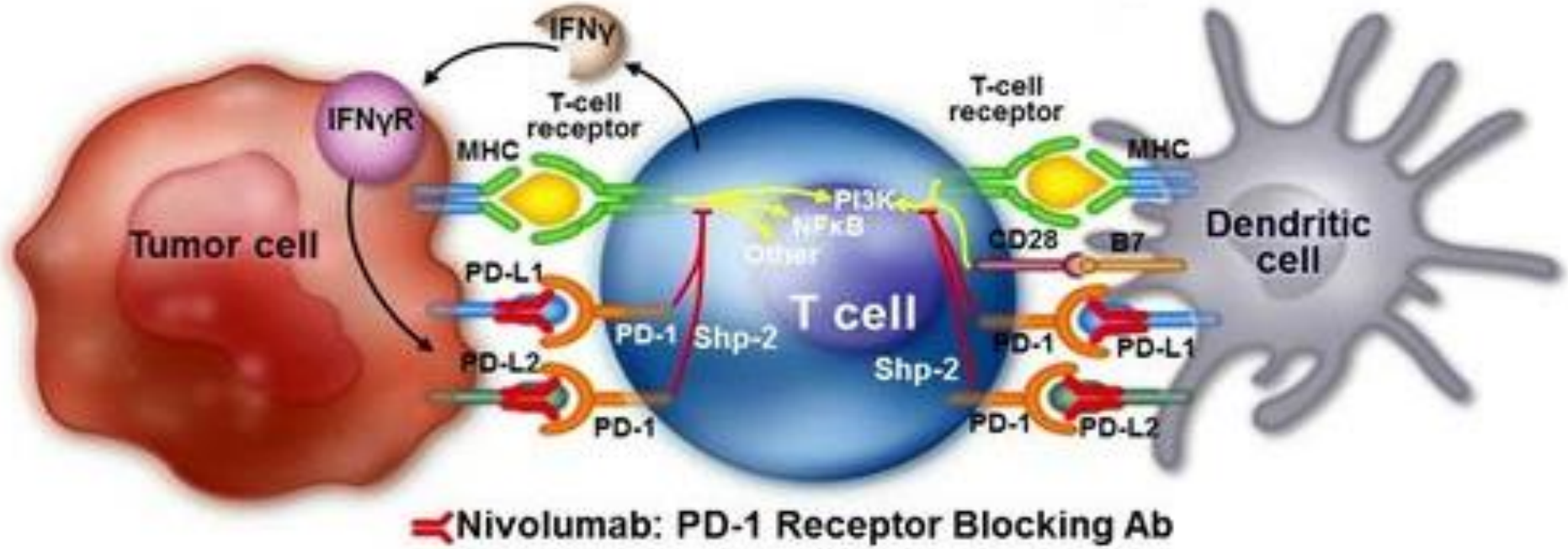
Immunotherapy with Dendritic Cells and Newcastle Disease Virus in Glioblastoma Multiforme

Thomas Neßelhut[1], Dagmar Marx[1], Jan Neßelhut[1] and Fred Fändrich[2]
[1]*Institute for Tumortherapy, Duderstadt*
[2]*Clinic for Applied Cellular Medicine, University of Kiel*
Germany

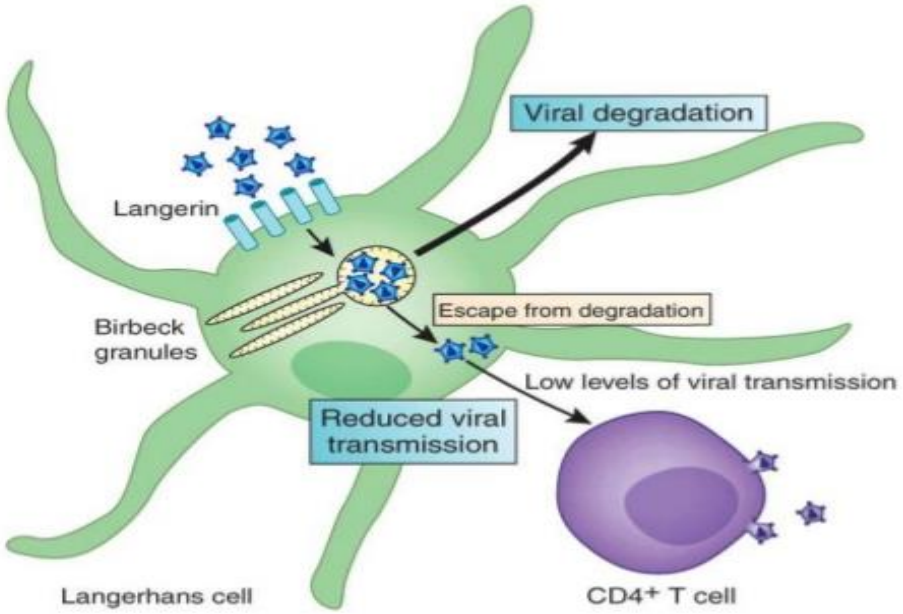
4. CheckPoint Inhibitor (CPI)

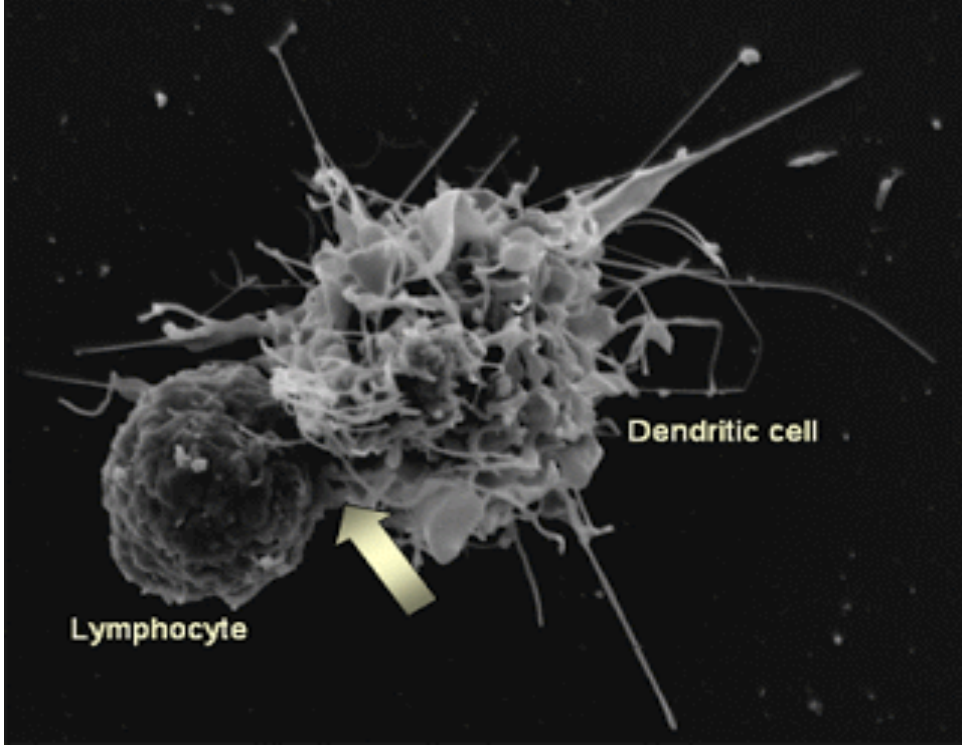
Nivolumab Mechanism of Action

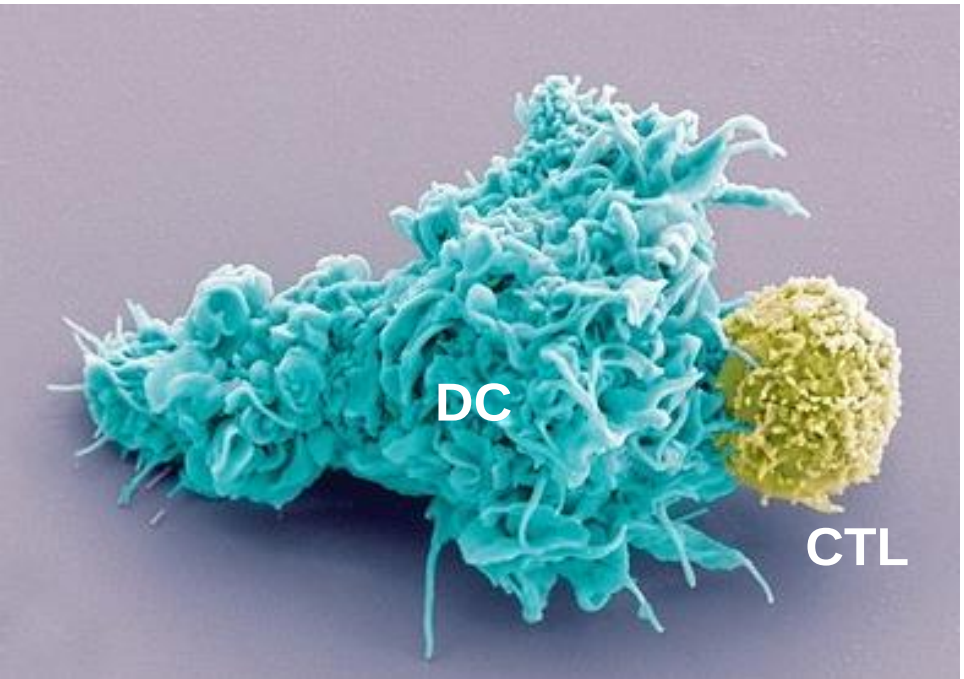
- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function[11]
- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[12–14]

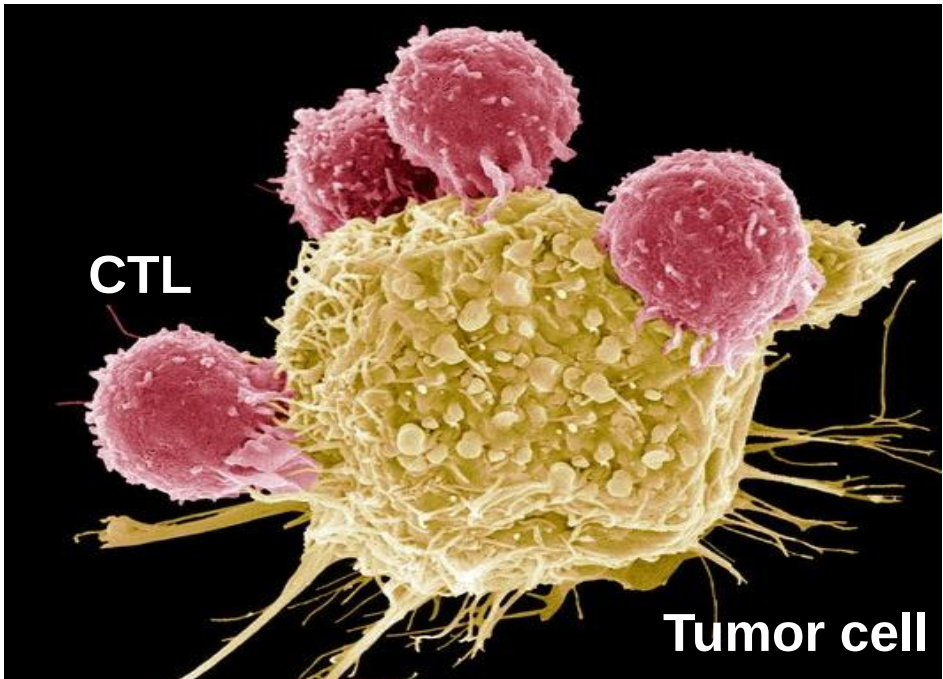


large surface-to-volume ratio









5. Case Reports: GBM treated with OV/DC (OV – DC)

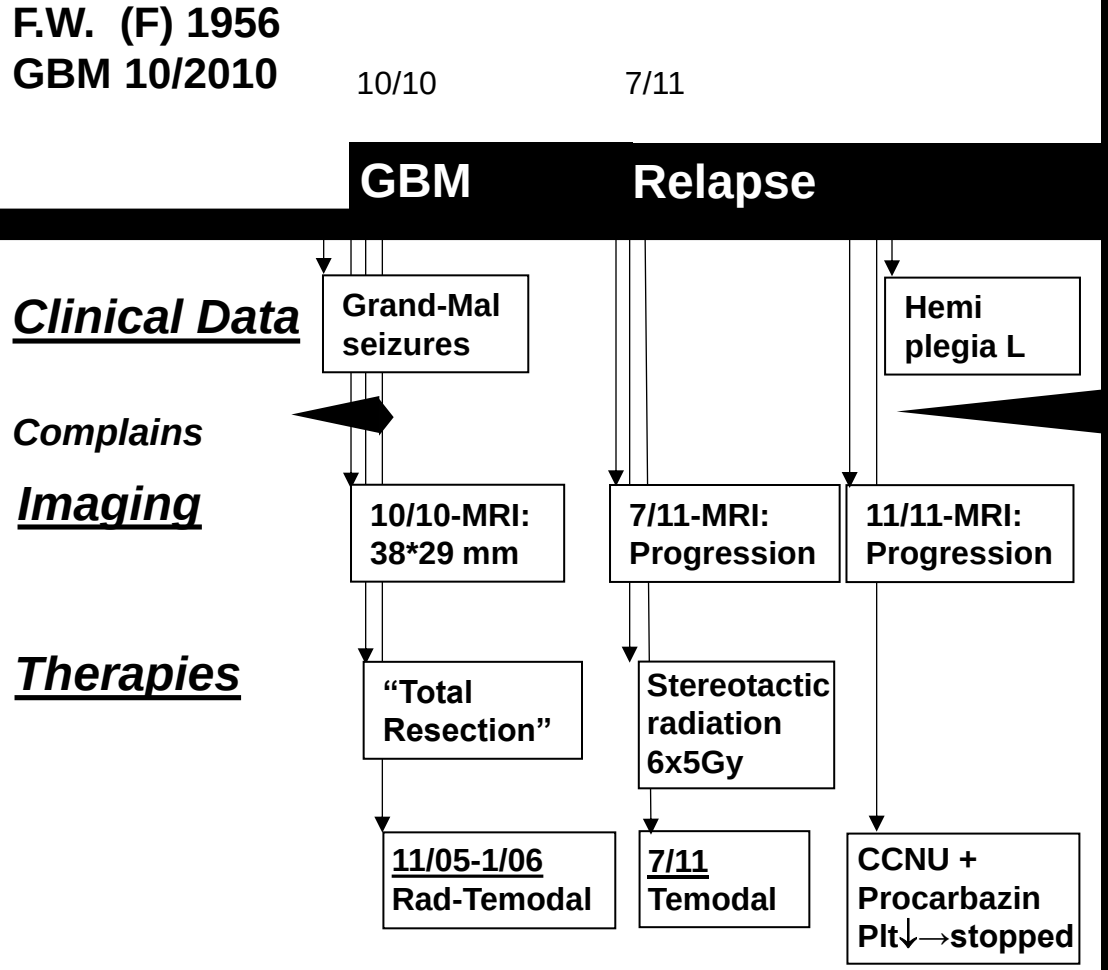
OV only	***OV & DC & CPI***
Case #1	**Case #3**
Case #2	**Case #4**

Between 1-6 months
between 6-12 months
12-30 months
30-60 months
> 60 mo = 5 years

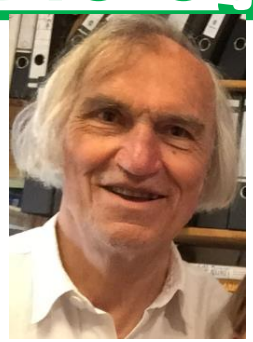
Archimedes von Syrakus

“Classical” Treatments

F.W. (F) 1956
GBM 10/2010



“Classical” & “Biological” Treatments



F.W. (F) 1956
GBM 10/10

10/10 | 7/11 | 1/12 | 2/12 | 10/12

GBM | **Relapse** | **Viro- & Immunotherapy**

Clinical Data

- Grand-Mal seizures
- Hemi plegia L
- Hemi plegia↓
- Hemi plegia↓

Complains

Imaging

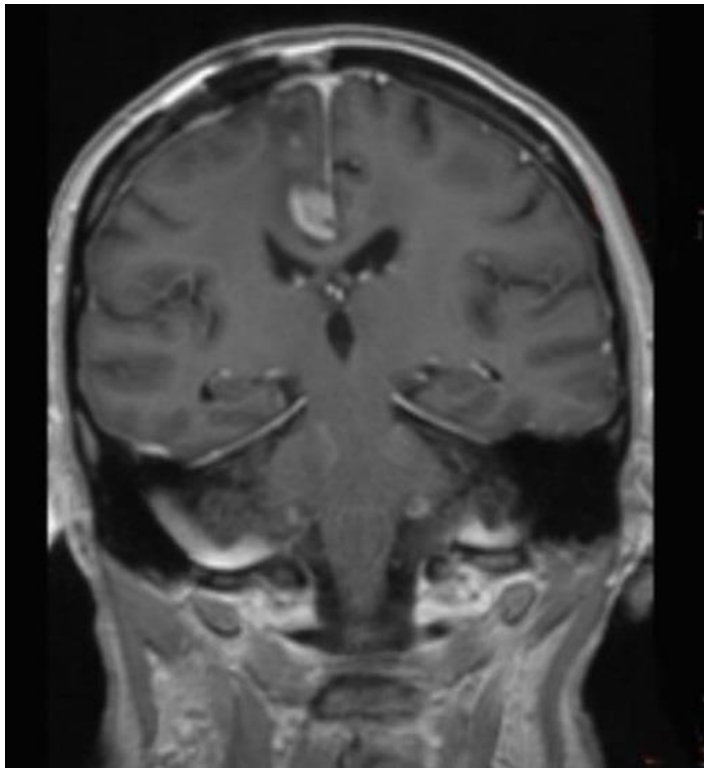
- 10/10-MRI: 38*29 mm
- 7/11-MRI: Progression
- 11/11-MRI: Progression
- 1/12-MRI: size↑ 40%
- 4/12-MRI: Stable
- 7/12-MRI: Smaller
- 10/12-MRI: Smaller

Therapies

- "Total Resection "
- Stereotactic radiation 6x5Gy
- 1-2/12: IV Virotherapy Parvo (x15VU) VSV (x8VU)
- 2-10/12: Virotherapy IA (x120 VU): Sindbis, VSV, NDV, Parvo-H1 → strength↑ L left/leg
  Fever Therapy (with Parvo followed by NDV)
  Hyperthermia (x120; 5x/w)
- 11/05-1/06 Rad-Temodal
- 7/11 Temodal
- CCNU + Procarbazin Plt↓→stopped

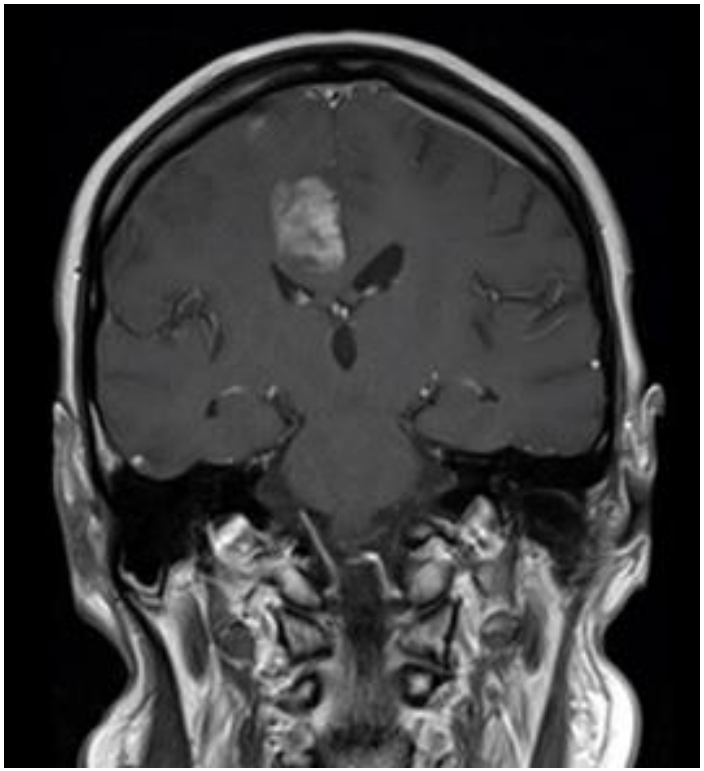
Glioblastoma multiforme Grad 4 rechts frontal (10/10) mit Rezidiv (7/11)

F.W., ♀, *01.10.56



15.11.2011

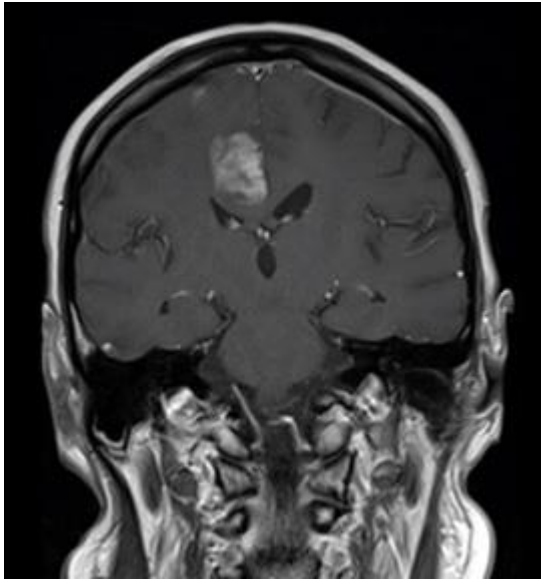
Größenzunahme des Rezidivs
trotz Operation, Radio-Chemotherapie
mit Temozolomid, Cilengitide,
stereotaktischer Bestrahlung und
Dosis-intensivierter Chemotherapie
mit Temozolomid



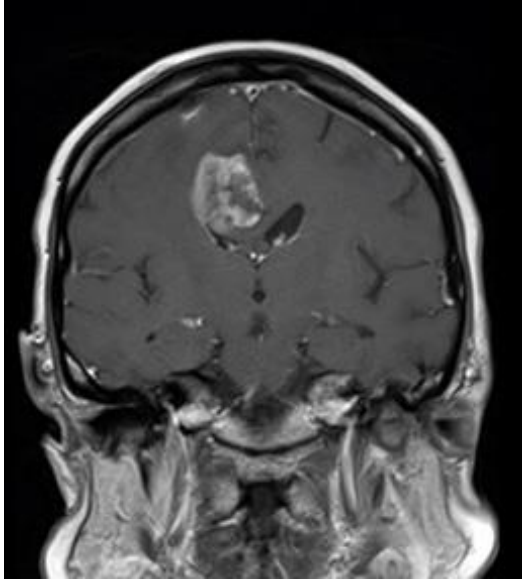
23.12.2011

Verdoppelung des Tumorvolumens
in 5 Wochen!

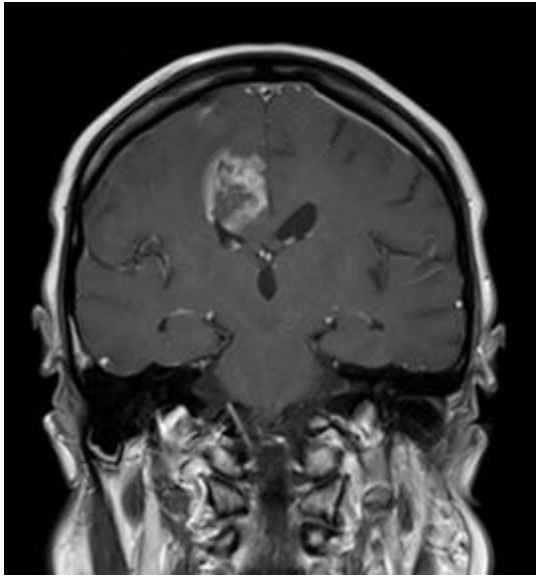
09.01.12 Beginn der Virotherapie



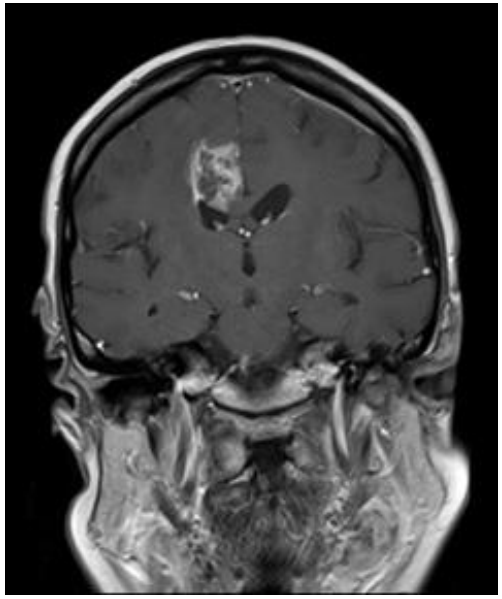
23.12.2011



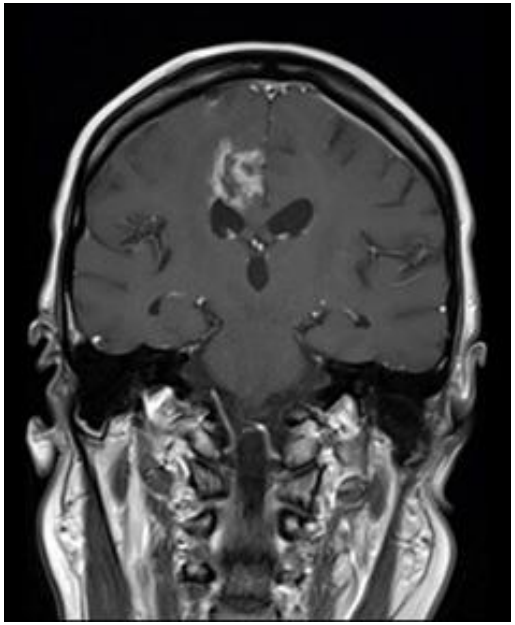
30.01.2012



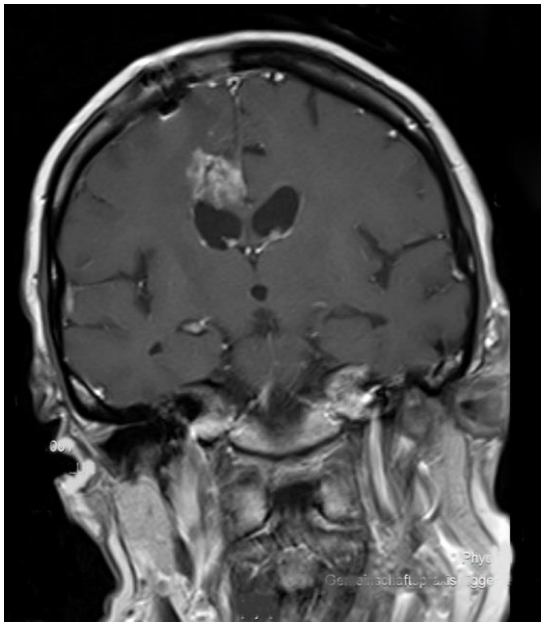
02.04.2012



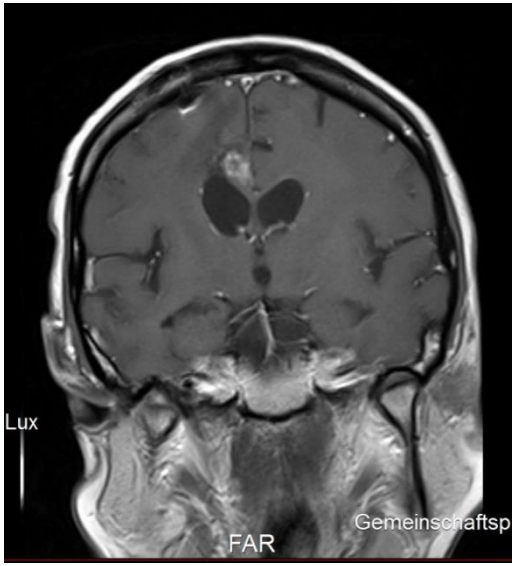
08.06.2012



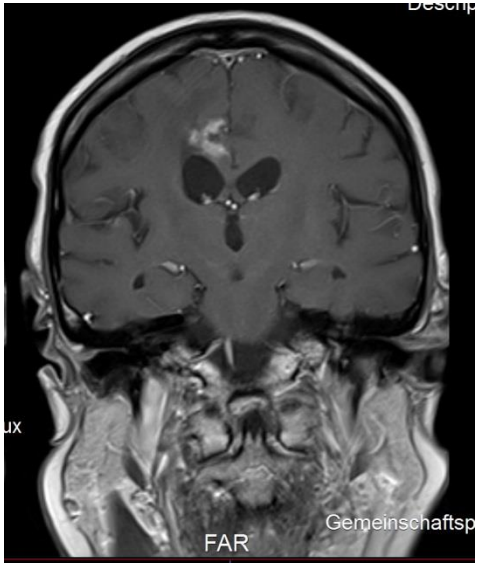
25.07.2012



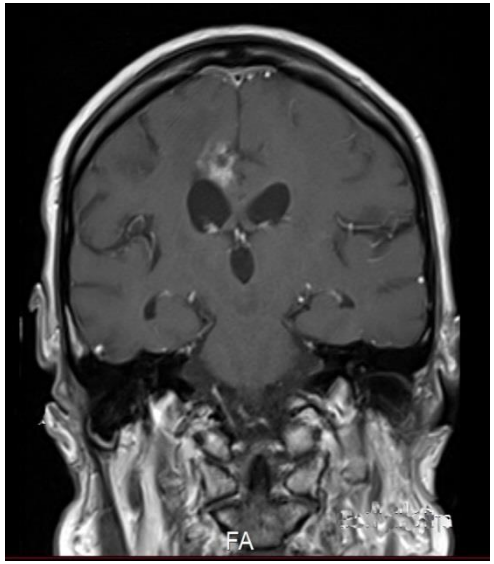
01.10.2012



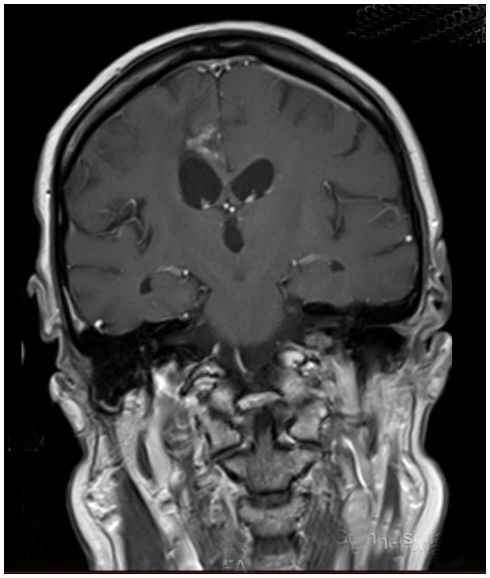
28.01.2013



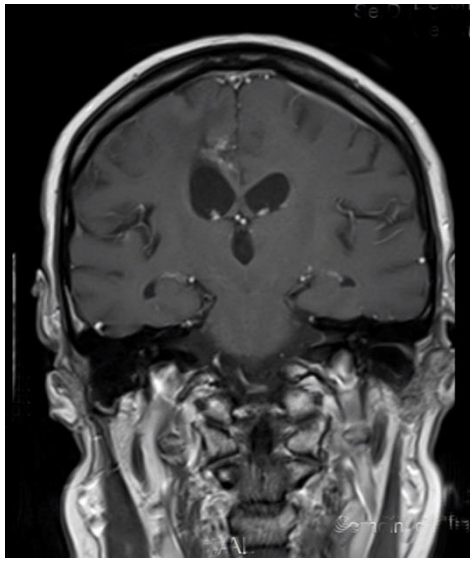
11.03.2013



22.04.2013



01.07.2013



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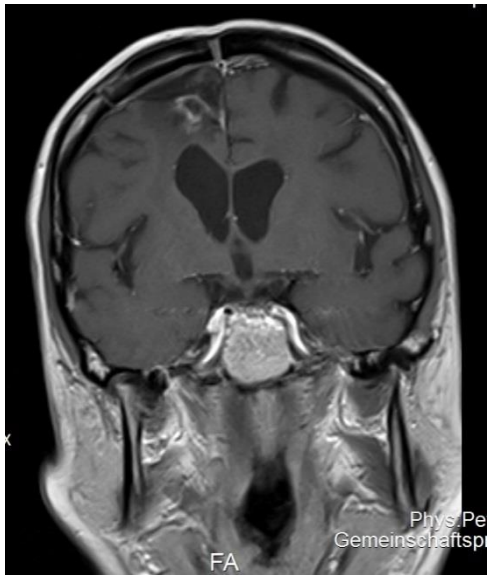

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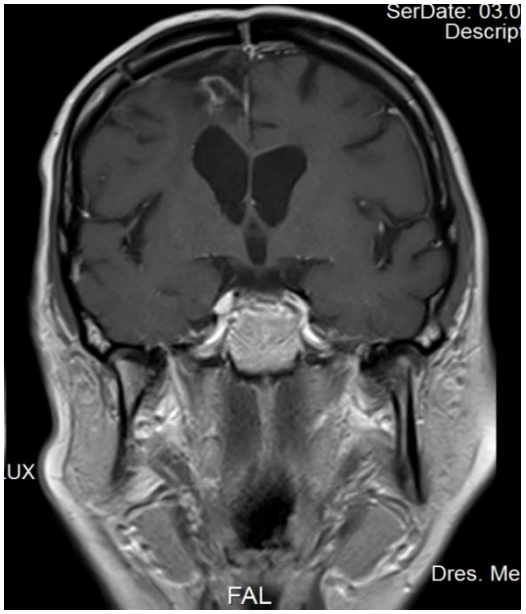
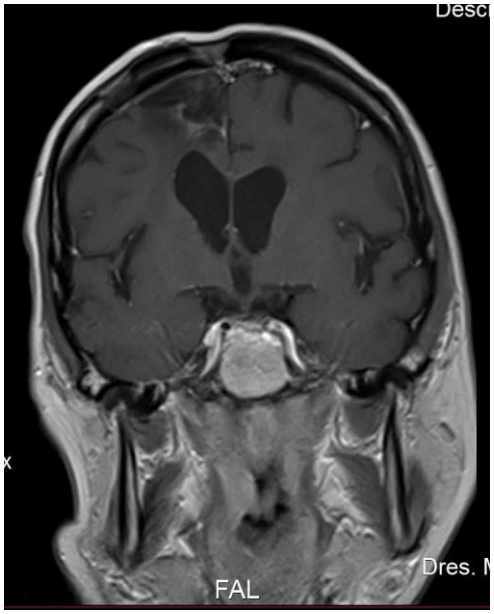
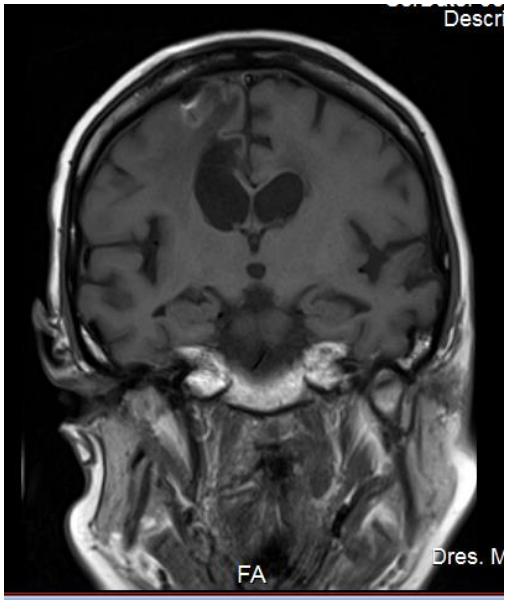


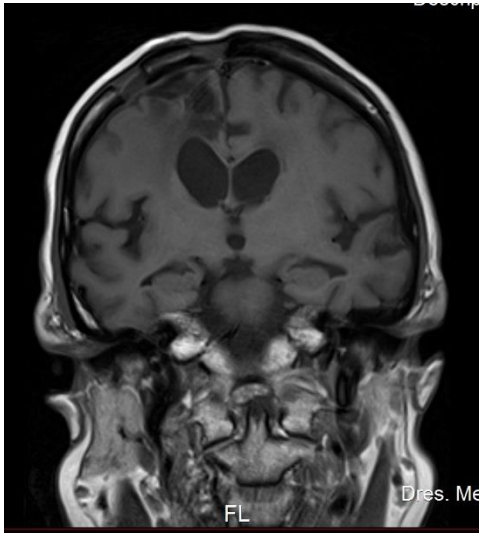
03.04.2014



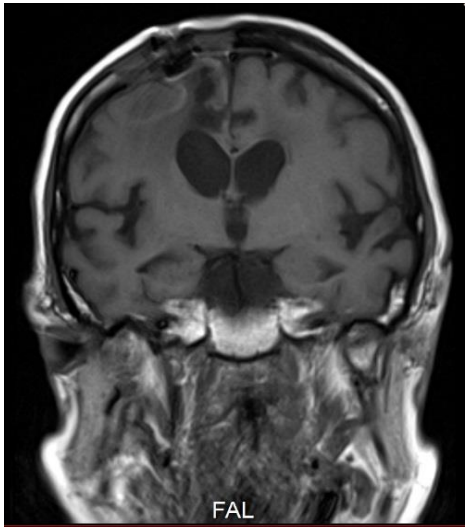
07.07.2014



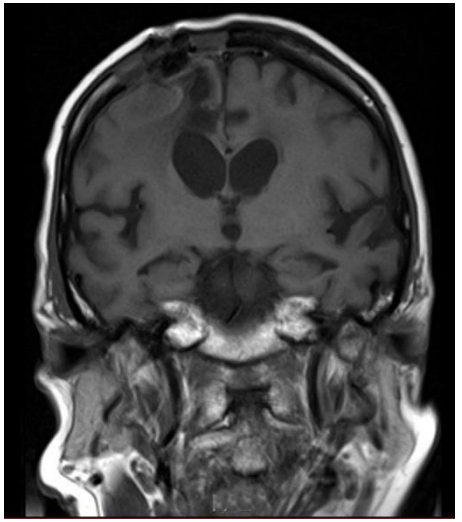
06.10.2014



07.01.2015



08.04.2015



12.10.2015

Positive & Negative Control

"Classical" & "Biological" Treatments

G.P. (F)
GBM

6/05 10/05 3/06 5/08 7/09 10/09 6/15 10/15

Diagnosis of GBM & Initial Tx

1st Tx Round Immunotherapy

Relapse & 2nd Tx

Clinical Data

Speech↓, Weak R leg, Balance↓, Headache

Pregnancy + Delivery

Speech↓, hemisphere↓, Hemianopsy, epilepsy

Complains

Imaging

MRI (date) 12*13*15

MRI shrinkage

EEG patho

EEG Normal

Therapies

"Total Resection"

11/05-1/06
Rad-Temodal
Plt↓

10/09

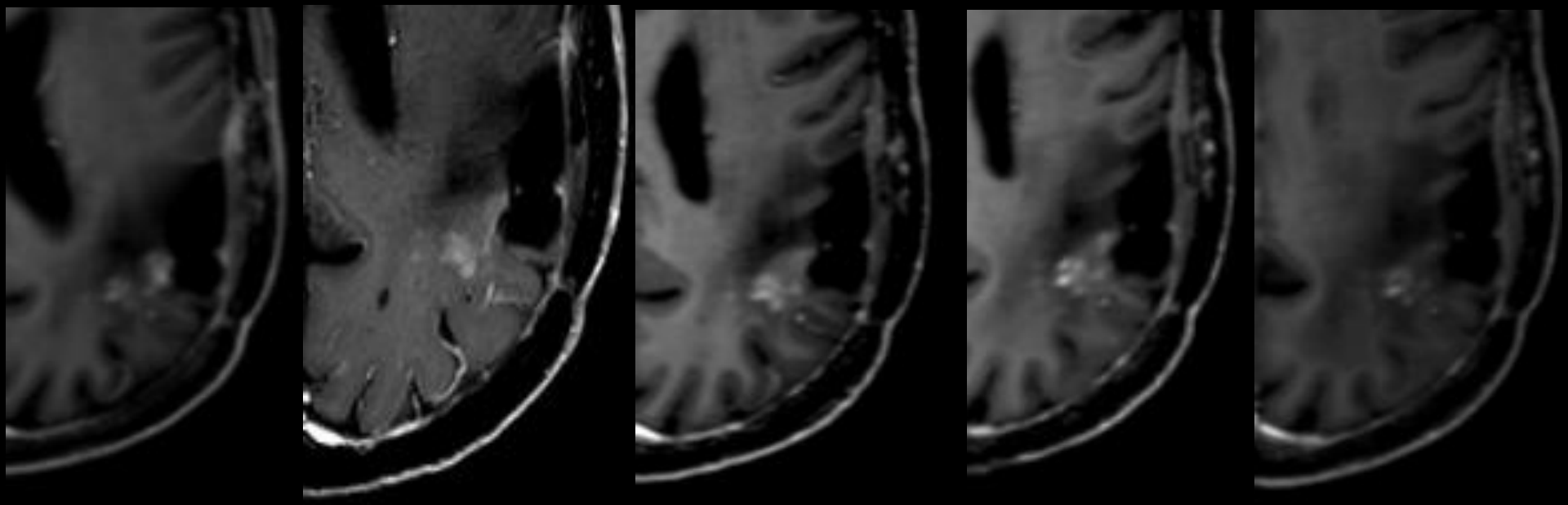
- **Virotherapy NDV (x42)**
- **NK cells + DC (x10)**
- **Fever Treatment (x54)**
- **Hyperthermia (x54)**

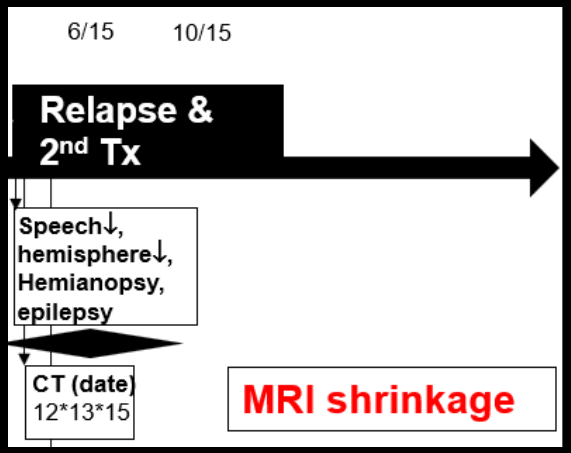
27-31/7/15
Virotherapy Parvo+NDV (4x = 80 ml) Hyperthermia (5x)

7/9/2015-4/2016

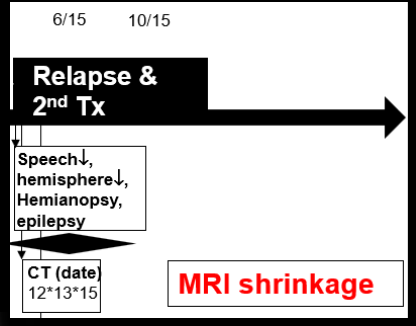
- **Virotherapy (x3) Parvo+NDV + VSV (=Fever)DC (x10)**
- **Hyerthermia**
- **Nivulomab**

6/16/2015 7/24/2015 8/21/2015 9/30/2015 11/16/2015



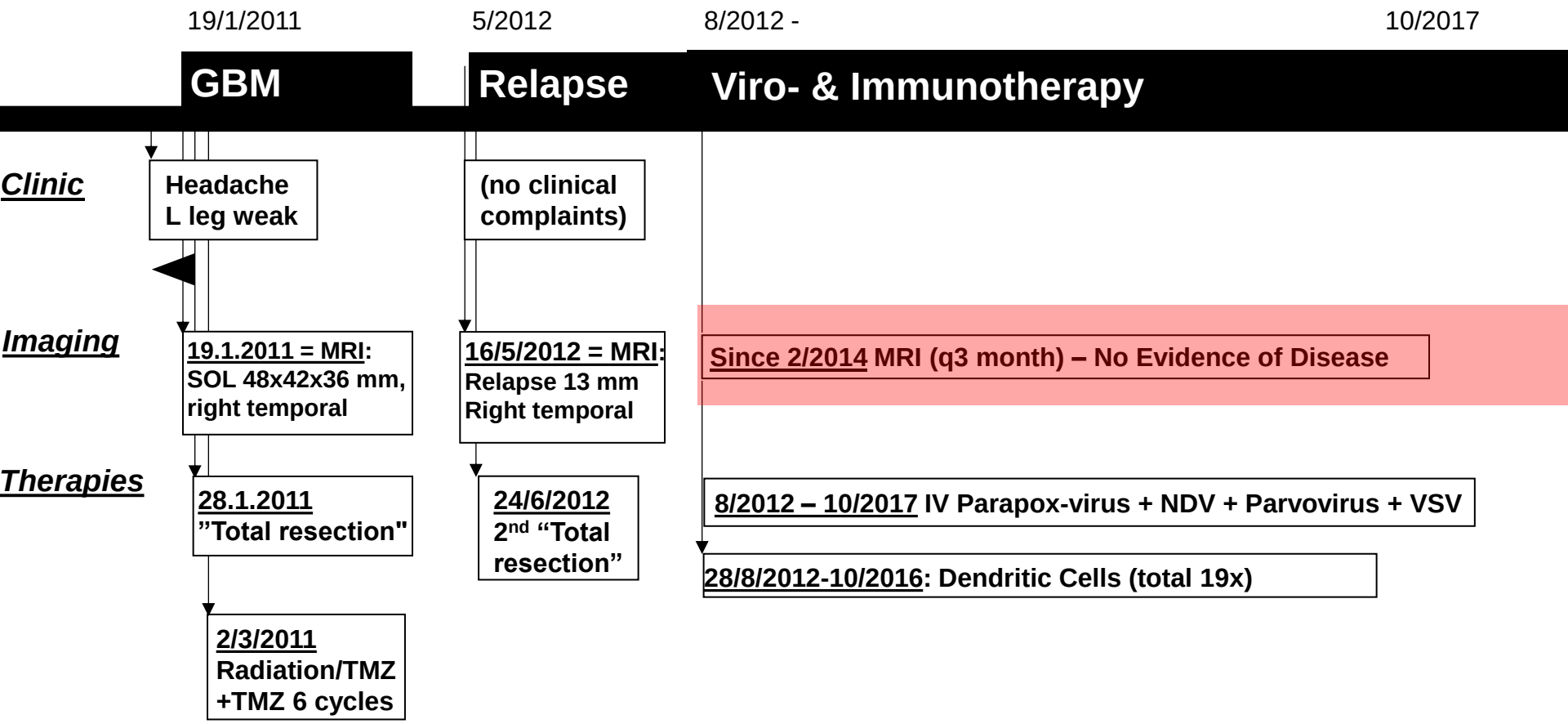


6/16/2015

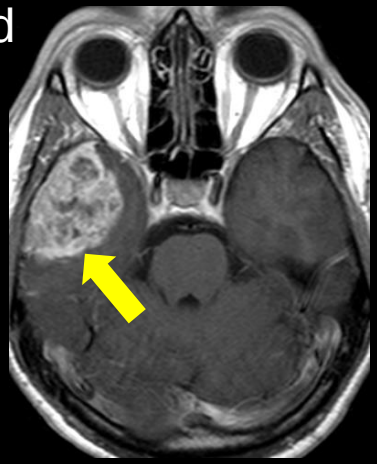


11/16/2015

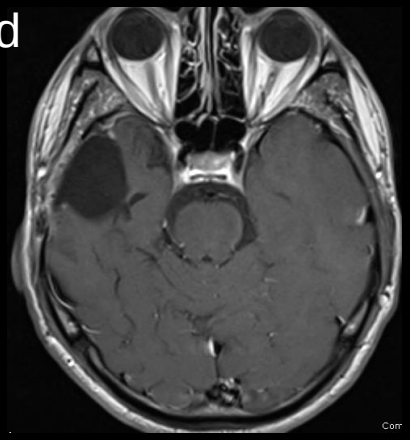
S.D. 18.7.1968
GBM (MGMT-neg)



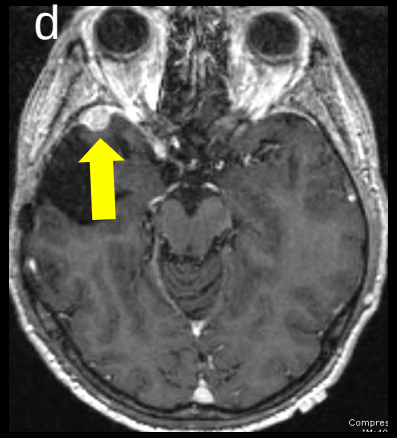
T1+Gd 20/1/2011



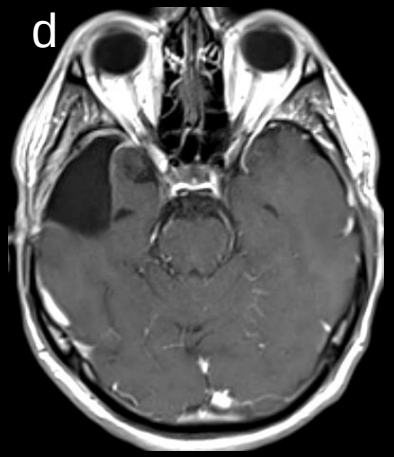
T1+Gd 1/9/2011



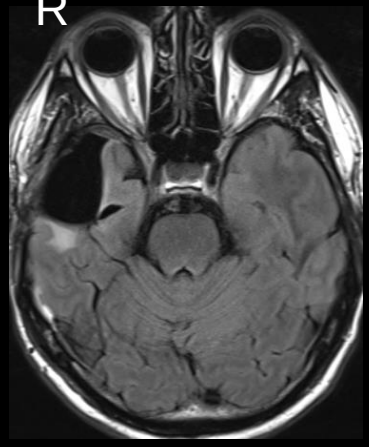
T1+Gd 25/6/2012



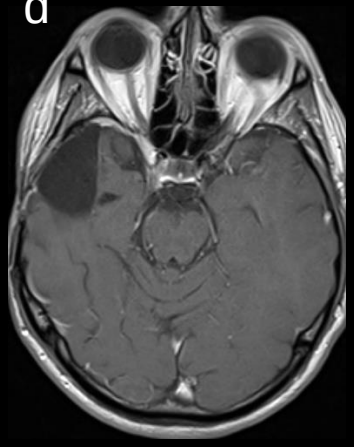
T1+Gd 20/8/2012



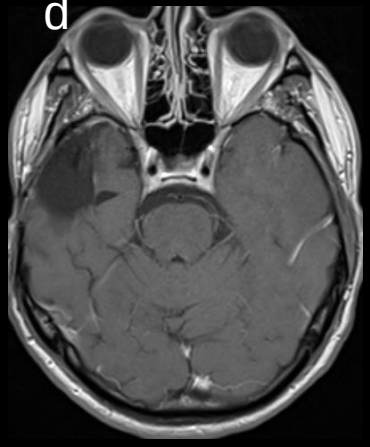
FLAIR 20/8/2012



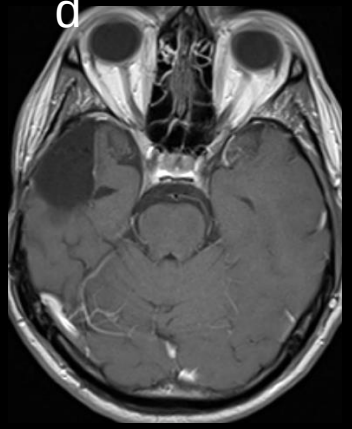
T1+Gd 23/9/2013



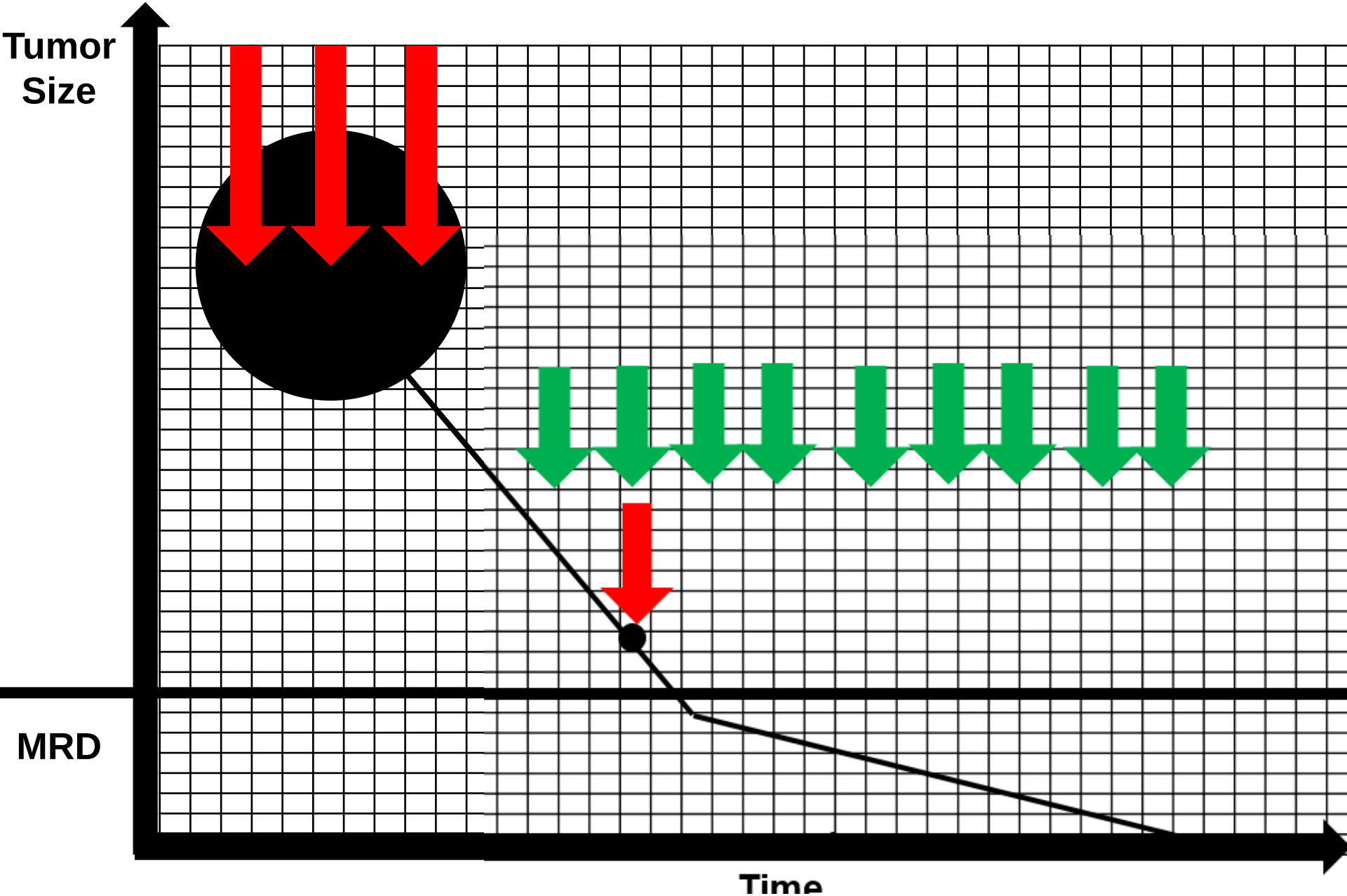
T1+Gd 20/4/2015



T1+Gd 20/7/2015



“Classical” & “Biological” Treatments for GBM



6. Summary & Future Directions

OV only	***OV & DC & CPI***	***DC only***	***Failures***
Case #1	**Case #3**	**Colleagues**	
Case #2	**Case #4**	**Literature**	

Between 1-6 months
between 6-12 months
12-30 months
30-60 months
> 60 mo = 5 years

Archimedes von Syrakus

GBM - Oncolytic Viruses & Immunotherapy (VIP) (Roadmap)

INDUCTION

Inclusion & exclusion Criteria: Karnofsky > 60% (=CCC)

Pre-Treatment Work-Up: MRI <28 days before treatment

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22

OV

Insertion of ports Arterial + Venous

Virotherapy – increasing dosages (14-21 days)

CPI

Nivolumab 40 mg

Nivolumab 40 mg

DC

Collection of DC

DC #1

DC #2

LABORATORY

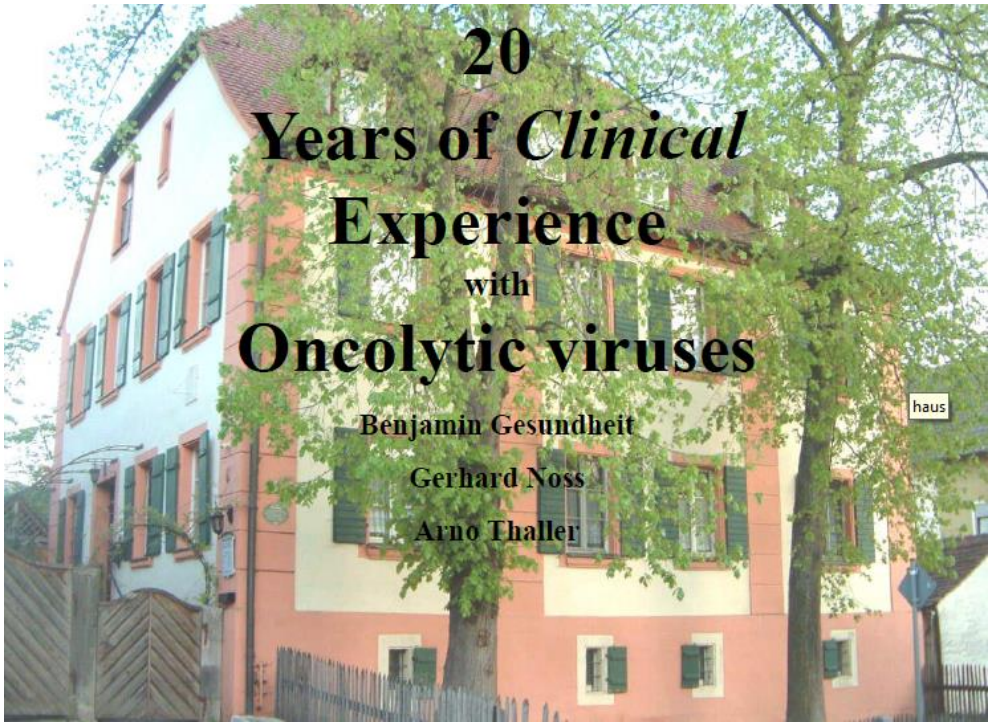
MAINTENANCE (– HOW LONG?)

6. Summary & Future Directions

- GBM is treatable & “curable”
- Early Treatment for GBM, clinical studies
- After classical GBM treatment (Sx, Rx, Temodal) => asap Viro- & Immunotherapy & CPI
- Genetic Engineering for better Viruses?
- Genetic classifications of GBM for treatments?
- Immune monitoring before, during and after Tx
- Virus specificity for various tumors “Virogram”, combination of multiple viruses (S + R)
- “Individueller Heilversuch” → Clinical Studies

Clinical Experience Dr Arno Thaller

- ✓ Breast Cancer
- ✓ Ovary Cancer
- ✓ Colon Cancer
- ✓ Pancreas Cancer
- ✓ Melanoma
- ✓ Prostate Cancer
- ✓ Lung Cancers
- ✓ Tongue Cancer
- ✓ Osteosarcoma
- ✓ Rhabdomyosarcoma



New Hope from Innovative Virotherapy & Immunotherapy for GBM & Other Tumors

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COO

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Israel

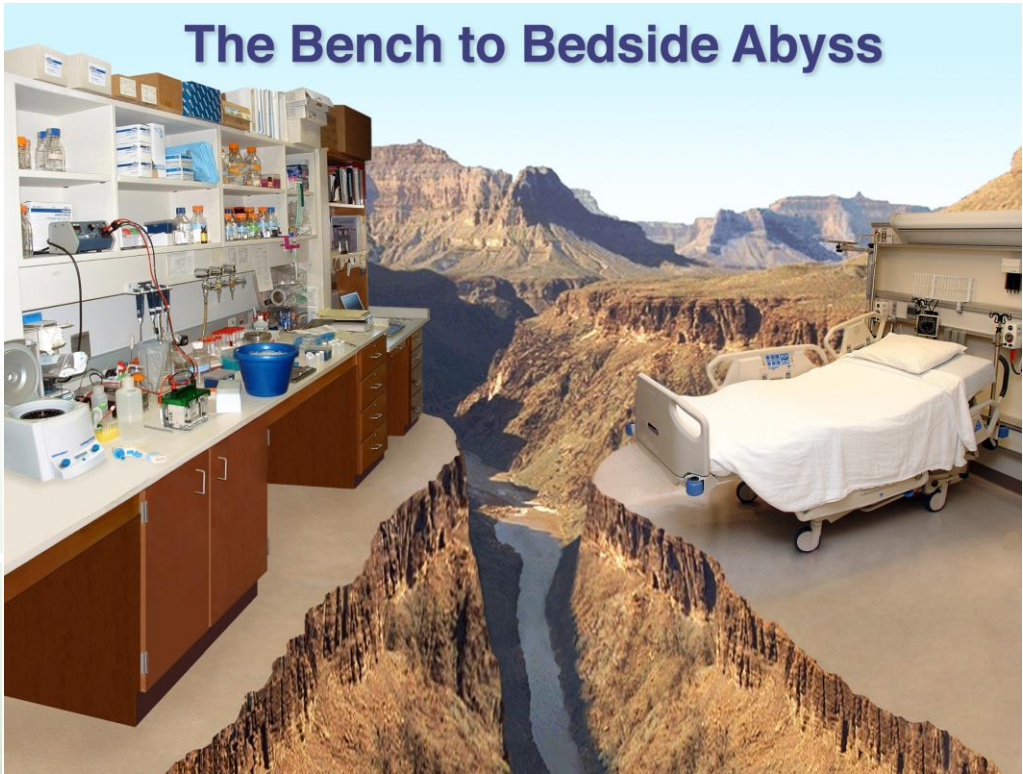
New Hope from Innovative Virotherapy and Immunotherapy for Glioblastoma

- A number of patients diagnosed with GBM were treated as a pilot group with either OV alone, DC alone, or with combination therapy of both OV and DC
- In each case their survival far exceeded the Kaplan-Meir estimator and there was a significant improvement in their clinical symptoms or their radiological evaluation
- No significant side effects from the therapy were observed
- While there are limitations of these pilot patients, the promising clinical outcome suggests that further investigations in a more controlled and well-designed clinical trials are warranted

December 5-7 2017
MIAMI, FL

ONCOLYTIC VIROTHERAPY Summit 2017

The leading end-to-end industry forum dedicated to accelerating the clinical development of the next generation of immuno-oncolytic virotherapies for use in combinations



German Law

Individueller Heilversuch - Compassionate Use

Individueller Heilversuch – Compassionate Use

Personal Accounts

Resilience: Message From a "Mengele Twin" Survivor

Benjamin Gesundheit, M.D. Ph.D.
Ephraim Reichenberg
Rael D. Strous M.D.

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