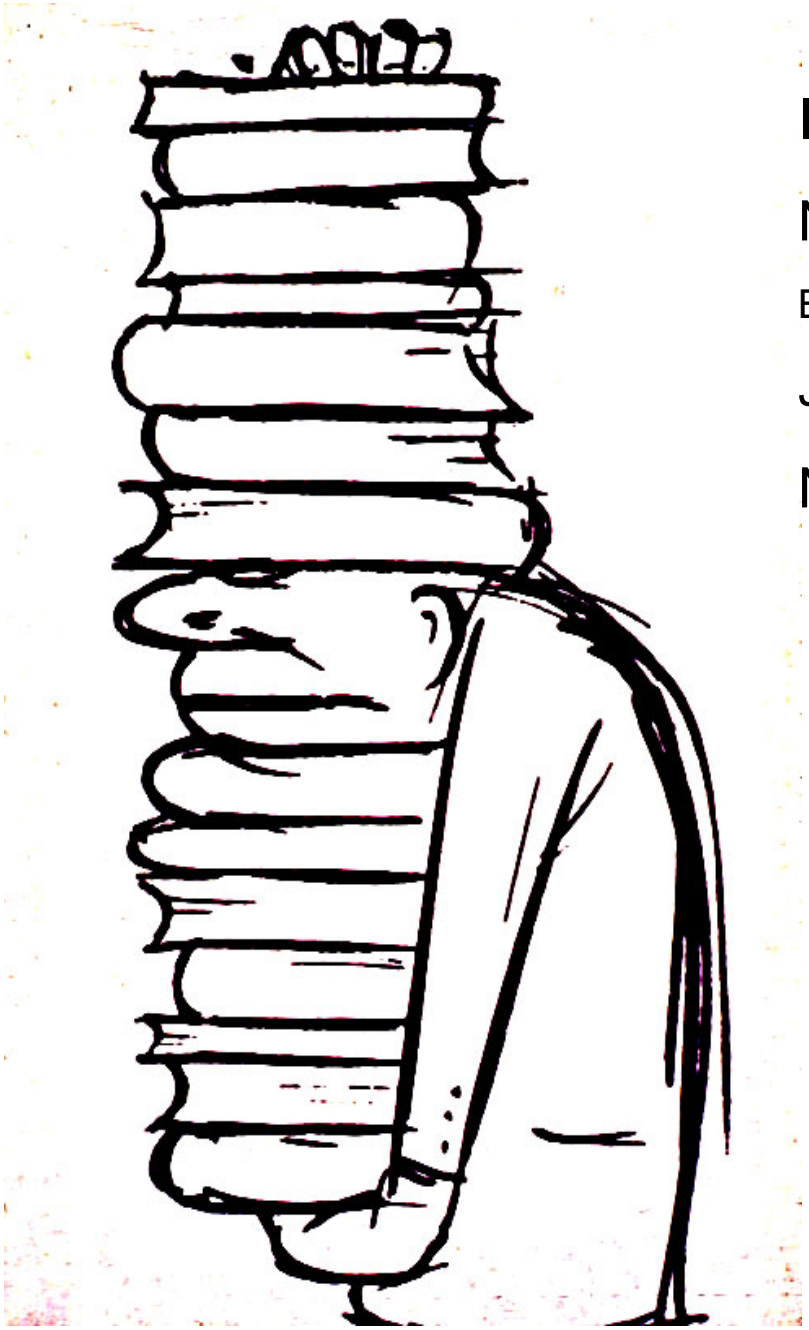
Immunterapi og samhandling; utvikling og bruk av cellebasert terapier- erfaring fra tverrfaglig samarbeide ved OUS

Seksjon for Celleterapi-historikk

- **1987: HMAS med renset benmarg. Prosessering av BM ved Tumorbiologisk avdeling (1 forskningsbioing + 1 lege)**
- **1993: Stamcellelabben etablert ved hematologisk seksjon , s-lab (3 bioing + 1 lege)**
- **1994: HMAS med perifere blod progenitor stamceller**
- **1995: Stamcellelabben(3 bioing+1 lege) + Mikromet.programmet (5 bioing + 1 lege) Hematologisk seksjon flyttet til nye lokaler,s-lab**
- **1996: Stamcellelabben flyttet til nye lokaler i U1**
- **1998: Stamcellelabben (6 bioing + 1 lege) Mikromet. Progammet flyttet til pat. avd.**
- **2001: DC prosjektet**
- **2005: Stamcelleaktivitet fra IMMI flyttet til Avd. for Celleterapi (10 bioing. + 1 lege + 2 post.dok +1 stipendiat,)**
- **2009: Stamcelleaktivitet fra Blodbanken, Ullevål, flyttes til Avd. for Celleterapi(14 bioing + 3 leger + 1stipendiat + 1 postdok)**
- **<u>2009: Flytter inn I nye lokaler på instituttet (24 ansatte)</u>**
- **2013: Immunmonitoreringsgruppen flytter fra Immunologisk Seksjon på Instituttet til celleterapi(6 ansatte)**
- **2015: Pga plassmangel flytter Immunmonitoreringsgruppen fra celleterapi til OCC inkubatoreren**
- **2018: 42 ansatte hvor bare 19,9 ansatte er budsjetterte faste stillinger selv om de fleste øvrige har rettigheter**

Department of Cellular Therapy - for GMP production of cell products - in size one of the largest in Europe

THERAPEUTIC BIOBANK



INSPECTED AND ACCREDITATED BY:

Norwegian Health and Social Department

EU cell directive (2004/23/EC)

JACIE(FAHCT)

National Marrow Donor Program(NMDP)

The Norwegian Medicines Agency (SLV)

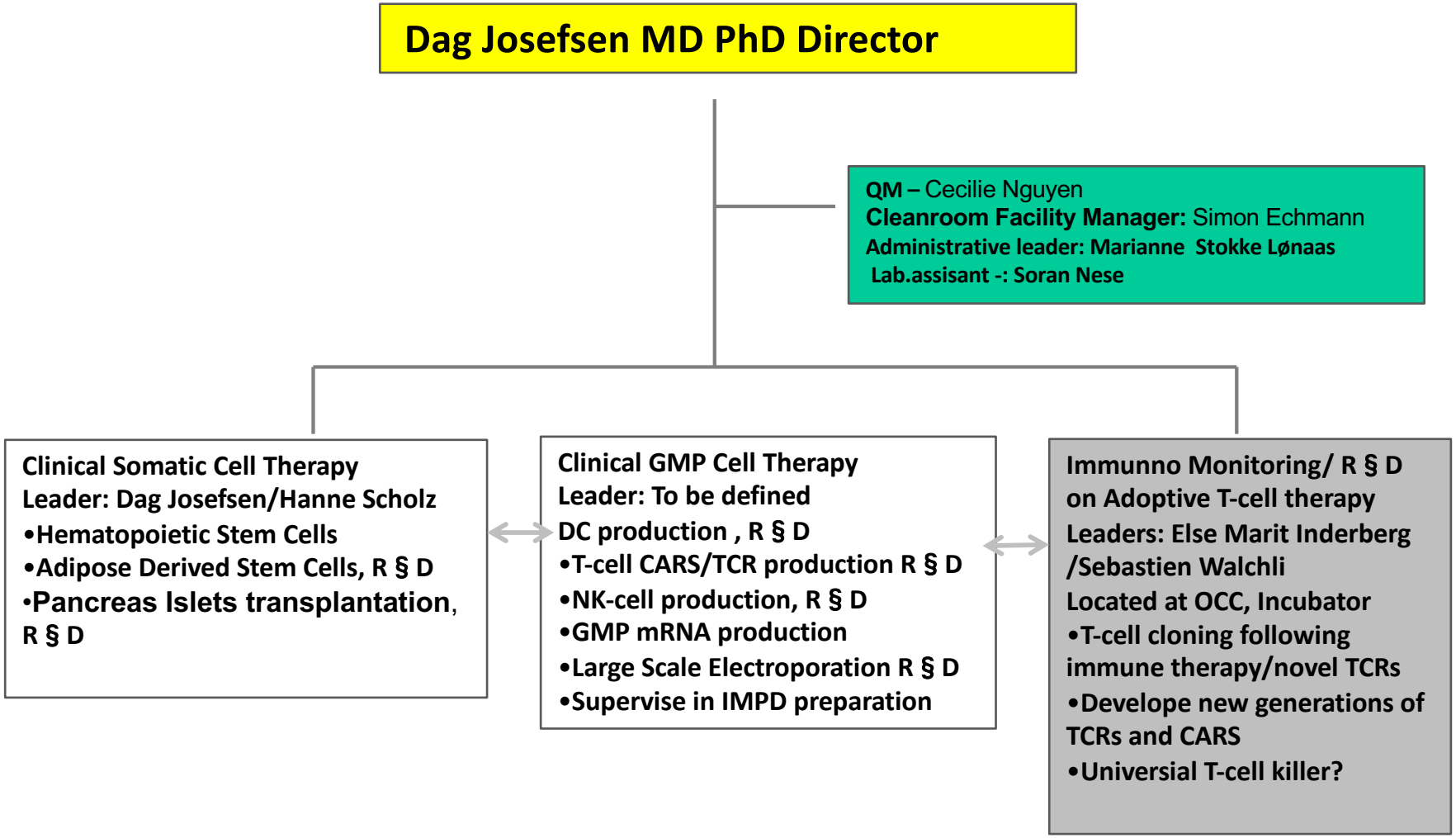
GMP production of cell products

(EU directive 2003/94EC/91/412/EC)

Paul Ehrlich Institute, Germany

GMP production of DCs for German AML patients

Department of Cellular Therapy, OUS, RAD



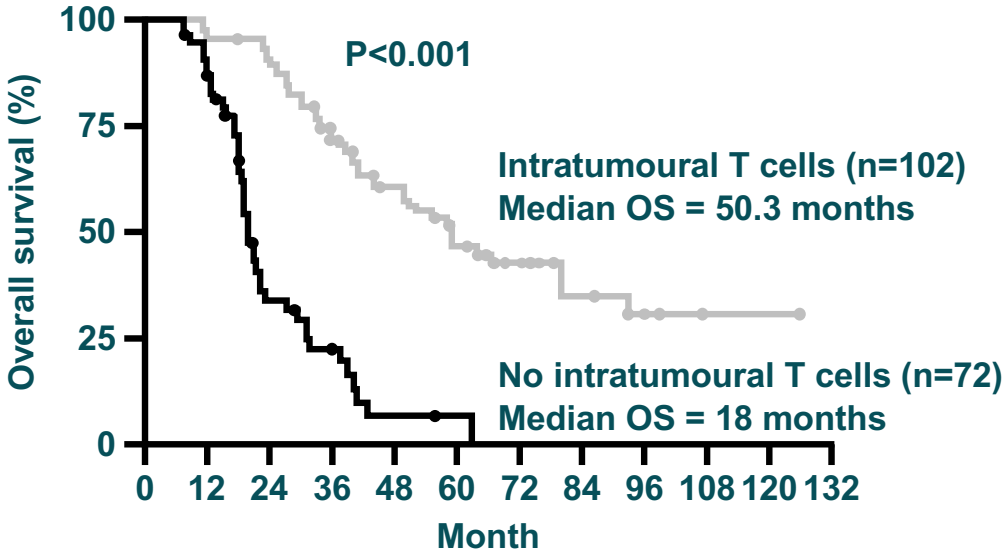
Translational research and clinical activites on somatic stem cells at Department of Cellular Therapy

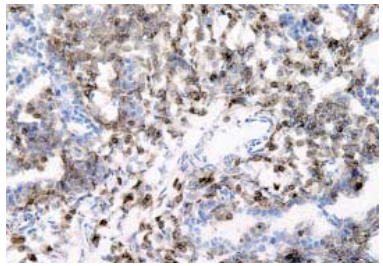
Translational research and clinical use of Somatic Stem Cells:

- Hematopoietic stem cells – auto/allo stem cell program
- Pancreatic Islets treatment in diabetes – preclinical …clinical 2013
- Adipose Derived Stem Cells :
- Vascular Stromal Fraction(SVF) and or Mesenchymal Cells (MSC)cells …. clinical program on non-healing chronic wounds following curative radiotherapy and in breast reconstruction after radiotherapy
- Adipose derived MSCs: Translational research program on MSCs and hypoxia and future use in treatment of diabetes
- MSCs delivery of therapies for brain disorders?

Prognostic[a] tumour infiltrating lymphocytes are identified in many tumour types

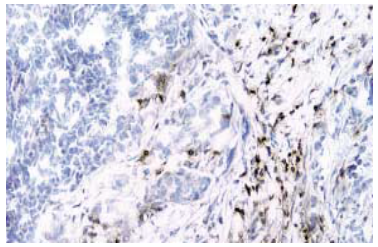
- Example: presence of intratumoural T cells correlates with improved clinical outcome in advanced ovarian carcinoma[1]
- Also seen in NSCLC,[2] CRC,[3] breast,[4,5] melanoma,[6,7] renal,[8,9] prostate,[10] head and neck,[11] cervical[12]





"Hot tumour"

T cells infiltrating tumour cells



"Cold tumour"

No intratumoural T cells: T cells restricted to tissue surrounding tumour

[a]Correlation with improved overall or progression-free survival, disease stage, or therapy outcome; type of lymphocyte dictates where there is a correlation with improved or worsened outcome

Figures adapted from Zhang L, et al. N Engl J Med 2003;348(3):203–213, Copyright ©2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

1. Zhang L, et al. N Engl J Med 2003;348(3):203–213; 2. Hiraoka K, et al. Br J Cancer 2006;94(2):275–280; 3. Galon J, et al. Science 2006;313(5795):1960–1964; 4. Mahmoud SM, et al. J Clin Oncol 2011;29(15):1949–1955; 5. Loi S, et al. J Clin Oncol 2013;31(7):860–867; 6. Piras F, et al. Cancer 2005;104(6):1246–1254; 7. Azimi F, et al. J Clin Oncol 2012;30(21):2678–2683 8. Siddiqui SA, et al. Clin Cancer Res 2007;13(7):2075–2081; 9. Donskov F, et al. Br J Cancer 2002;87(2):194–201; 10. Flammiger A, et al. APMIS 2012;120(11):901–908 11. Badoual C, et al. Clin Cancer Res 2006;12(2):465–472; 12. Piersma SJ, et al. Cancer Res 2007;67(1):354–361

How do we interprete these results?

- In a subgroup of patients, a spontaneous immune reaction results in T cells finding their way to the tumour before surgery
- The number and type of lymphocytes inside the tumour has an influence on survival
- The effect of the surgical treatment is consolidated by the immune system – and:
- Surgery has much less effect on survival if the immune system is not involved!
- But: no clue as to which antigens are recognized
- Challenge: how to make a “cold” tumor to become “hot”

Induced Tumor Immunity in man:

- Immunogenic cell death as a new paradigm in cancer immunology
- ”Cryptic” vaccination induced by chemotherapy, irradiation, cryotherapy and targeted therapies
- Combination of local (in situ) treatment with systemic treatment (checkpoint blockade, cancer vaccines, adoptive T-cell therapy)

Cancer treatments

Classical mainstays

Surgery

Radiation *

Chemotherapy*

*** Induces immunogenic cell death –low dose?**

Other treatments

Hormone therapy*

Small molecule targeted therapy

* ADT induces immune-responses in prostate cancer

Immunotherapy

Bone marrow transplantation

Antibody therapy

Immune checkpoint blocking antibodies

BITE

Cancer vaccines

Peptides

Dendritic Cells

Adotive T-cell Therapy

Immunotherapy programs at Department of Cellular Therapy

Academic protocols:

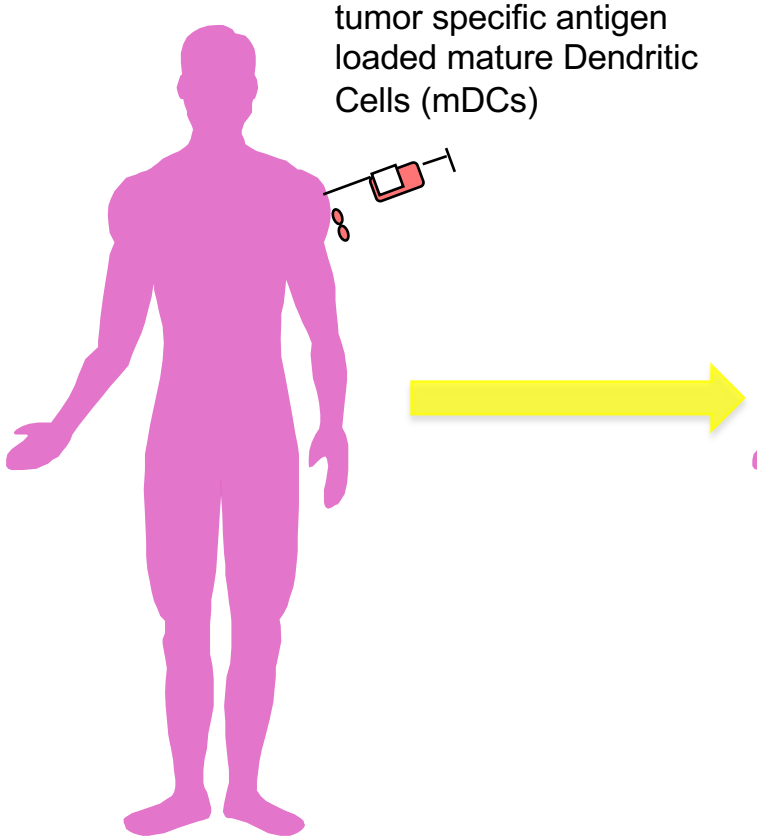
- Adjuvant DC vaccines in operable high risk prostate cancer – closed. Pi: Svein Dueland
- Randomized DC vaccines in operable Glioblastoma under development PI: Einar Vik-Mo
- DCs in NHL. PI: A. Kolstad
- NK cell therapy under development PI: Kalle Malmberg
- LMU DC AML (DCs produced in Oslo for patients treated in Munich) PI: Marion Subklwe
- TCR-CRC-001: MSI+ colon ca (REC approved) PI Svein Dueland

Comercial protocols:

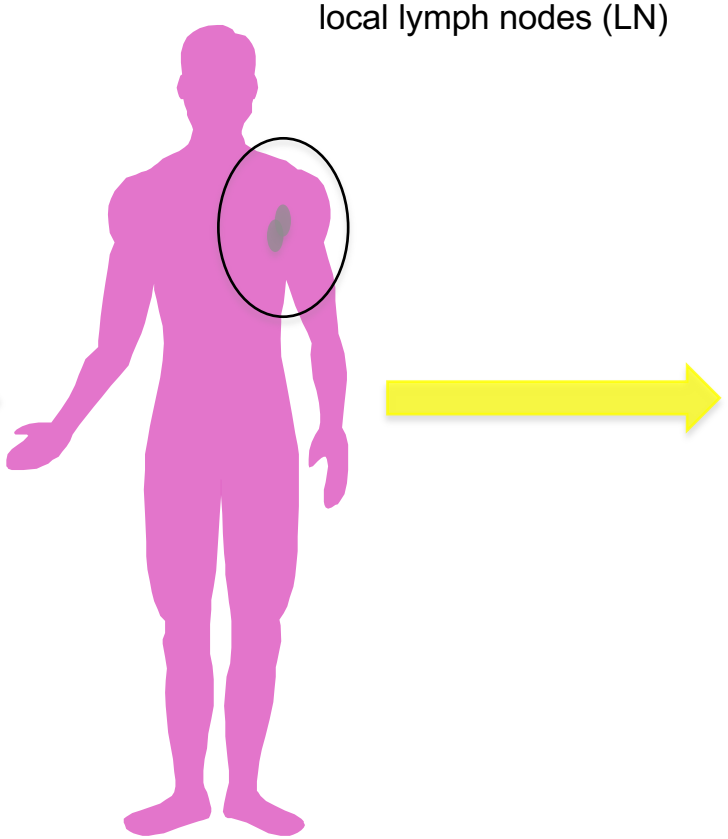
- Medigene DC AML – phase I/II only Norwegian patients. Pi Yngvar Fløisand
- Alden DCs in metastatic prostate cancer (DCs produced in Oslo for patients in Bergen)
- Norvartis CAR CD 19: Relapsed and refractory peadiatric ALL and adult NHL. PI ALL Jochen Buchner, PI NHL Harald Holte

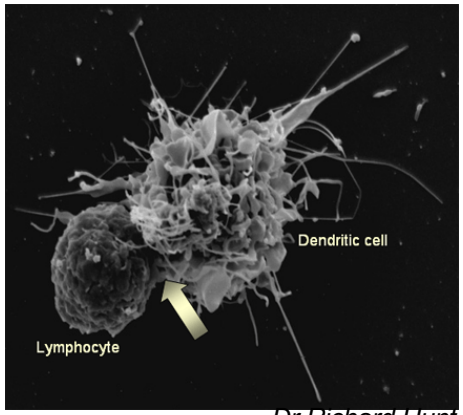
DC based vaccines for treatment of cancer since 2000

Intradermal injection of tumor specific antigen loaded mature Dendritic Cells (mDCs)



Migration of mDCs to local lymph nodes (LN)





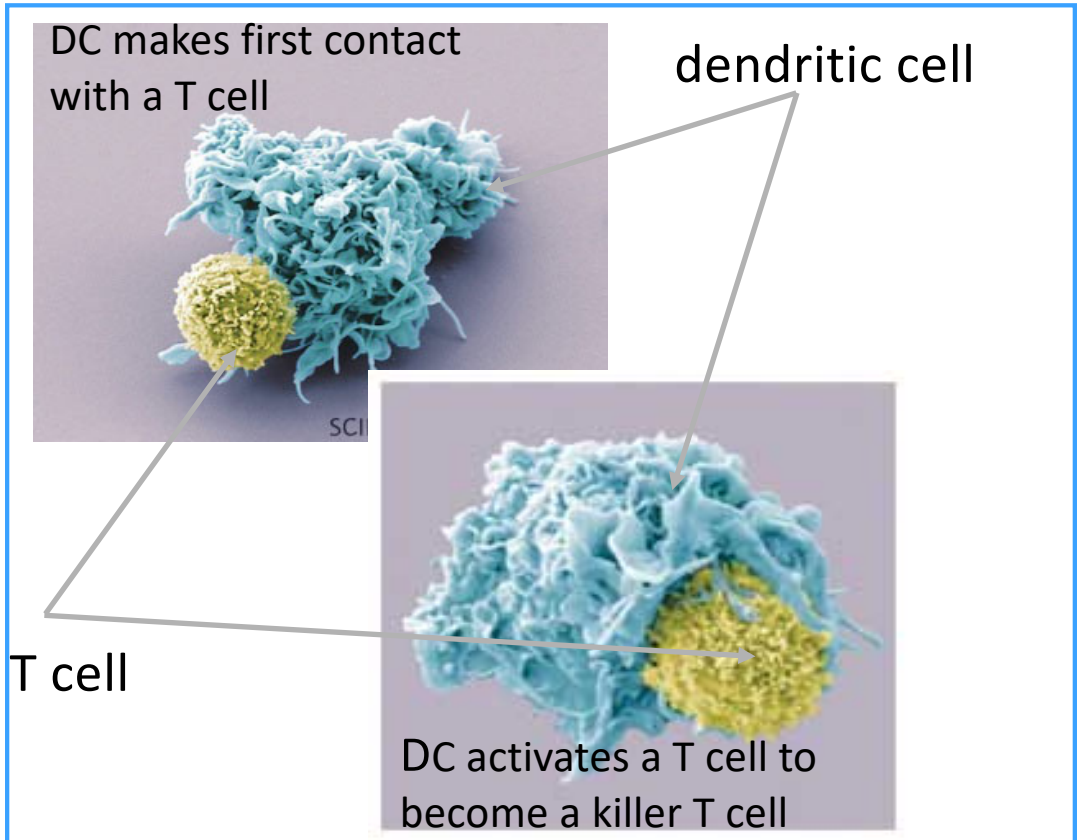
Dr Richard Hunt

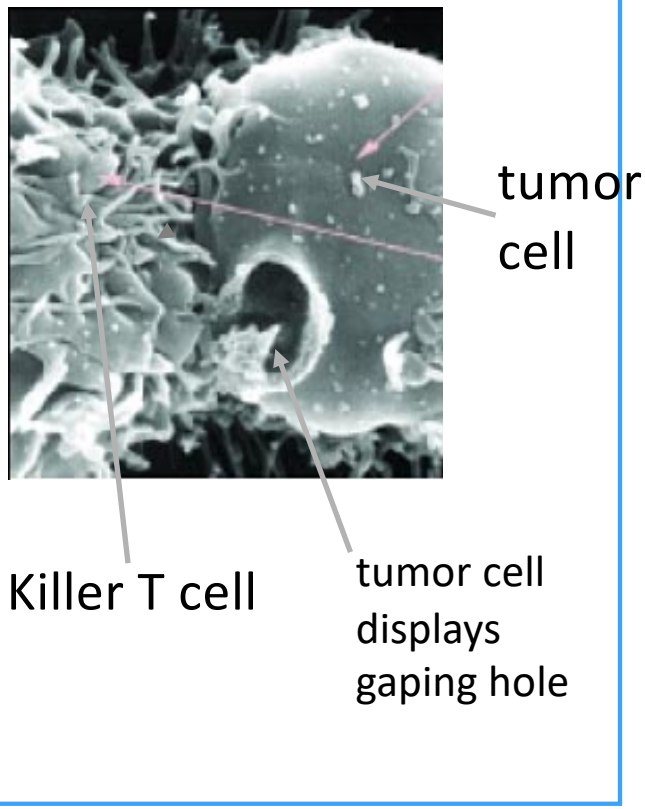
Activation of tumor specific lymphocytes in LN

Dendritic cells (DCs) are the cells that stimulate immune responses

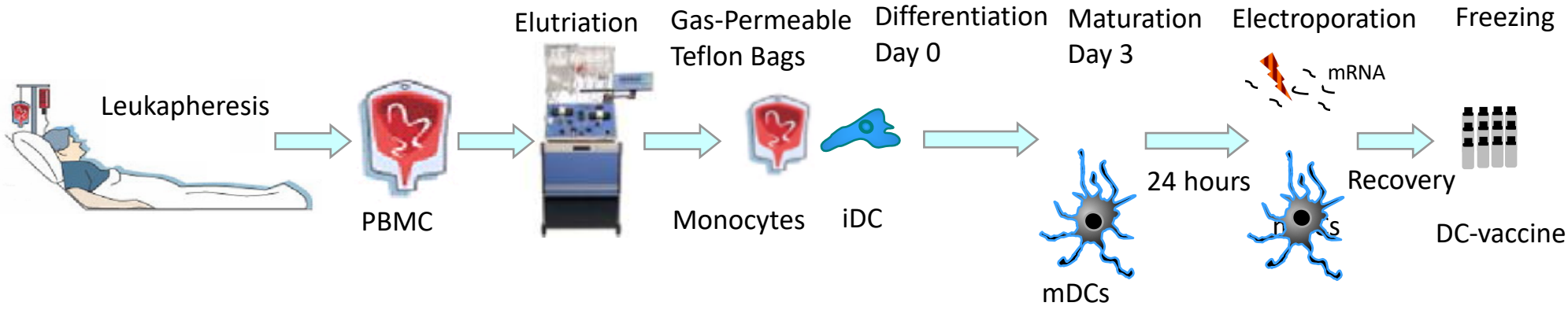
Dendritic cells (DCs) make contact with T cells and instruct them to become active killer cells

Killer T cells activated by DCs search out tumor cells in the body and kill them by creating holes in their surface





Robust GMP-production platform for Dendritic Cell vaccines is established



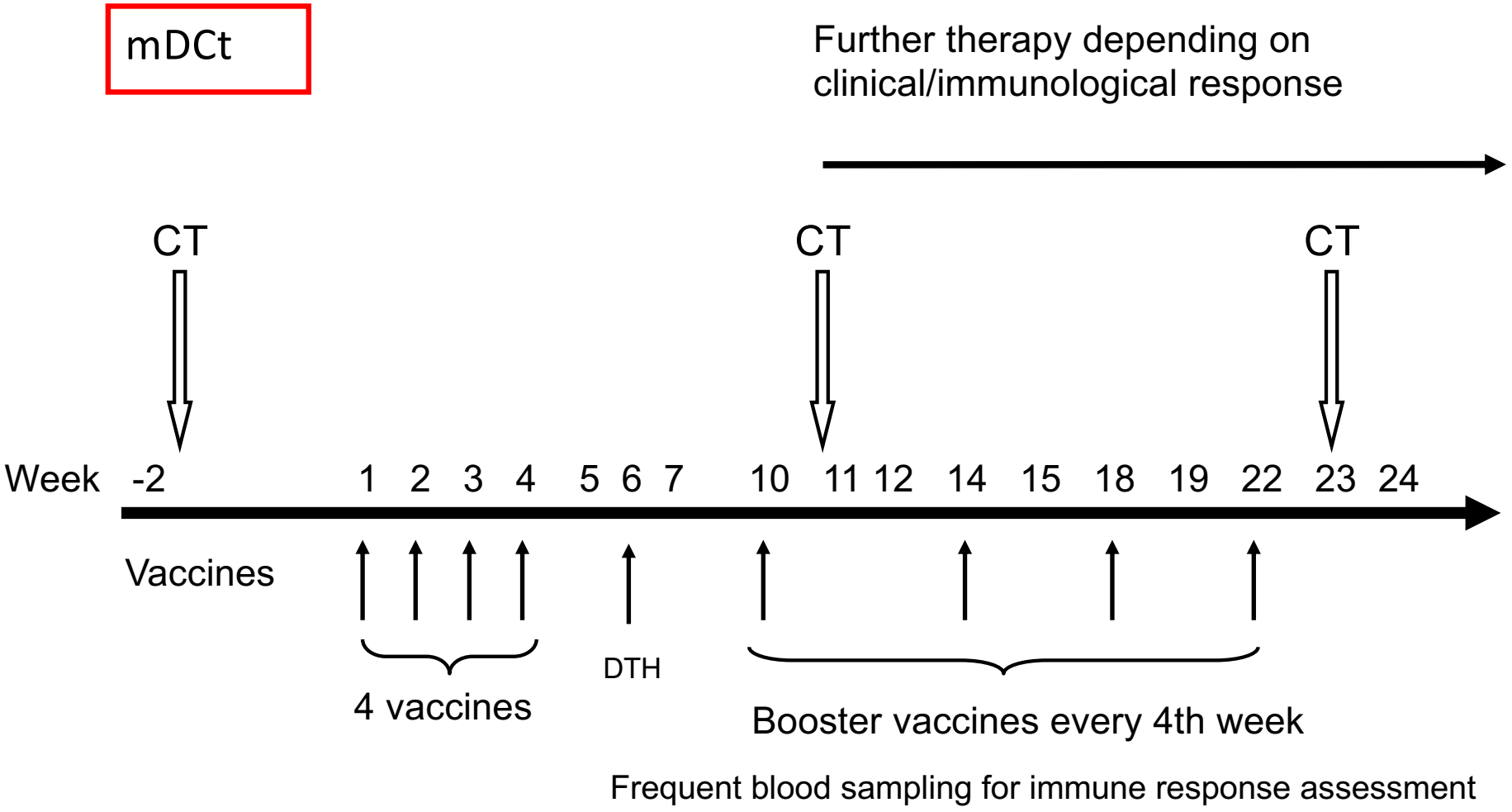
GMP production and analysis in the cleanroom facility of the
Department of Cellular Therapy at the Oslo University Hospital

Oslo University Hospital

Norwegian Regulatory Authority approval: 08/2013; 12/2014

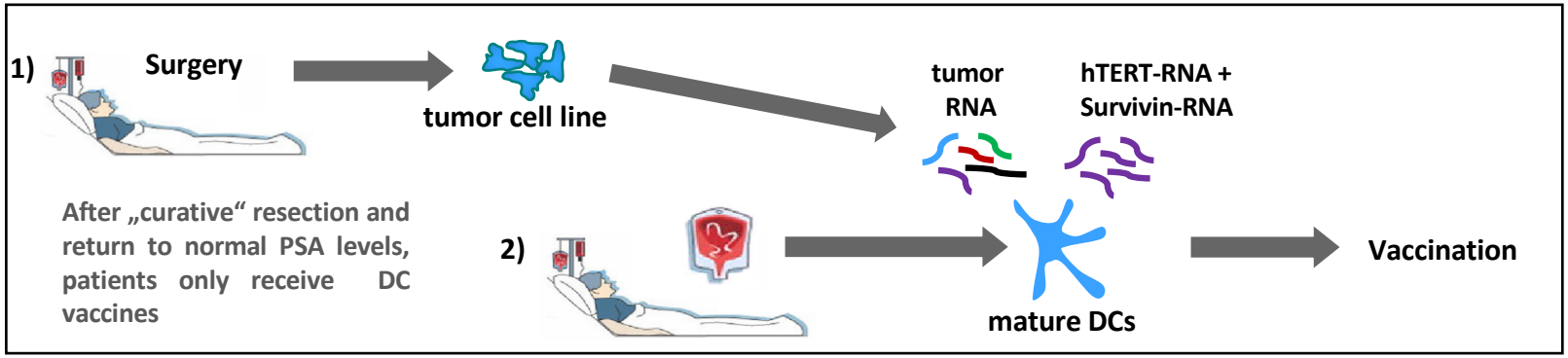
German Regulatory Authority approval: 10/2013

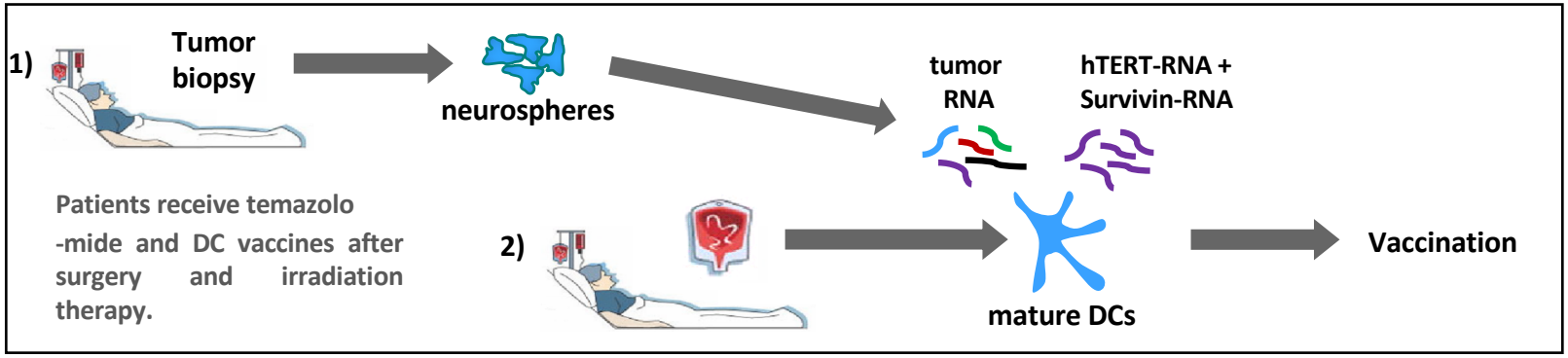
Study flow chart



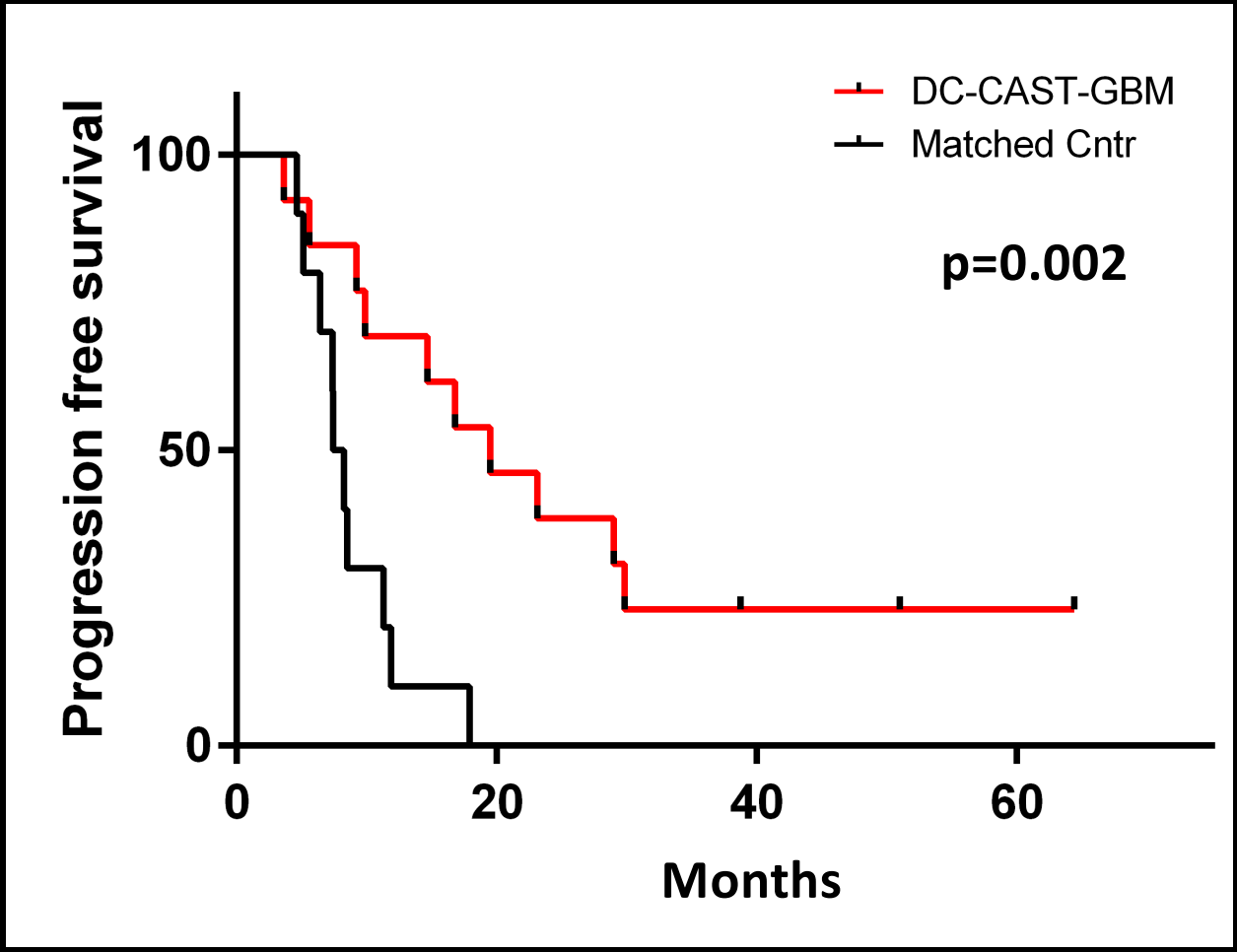
2-step approach of OUH in two different clinical indications

	Patient-derived tumour material	Patient-individualized vaccine preparation
Prostate Cancer: adjuvant high-risk Phase II OUS	1) Prostatectomy Establishment of tumor cell line Isolation of tumor RNA	2) Leukapheresis and generation of 3d DCs Loading of DCs with tumor RNA + hTERT + survivin ivt-RNA
GBM Adjuvant CU* OUS	1) Radical surgery. Establishment of neurospheres Isolation of tumor RNA	2) Leukapheresis and generation of 3d DCs Loading of DCs with tumor RNA + hTERT + survivin ivt-RNA





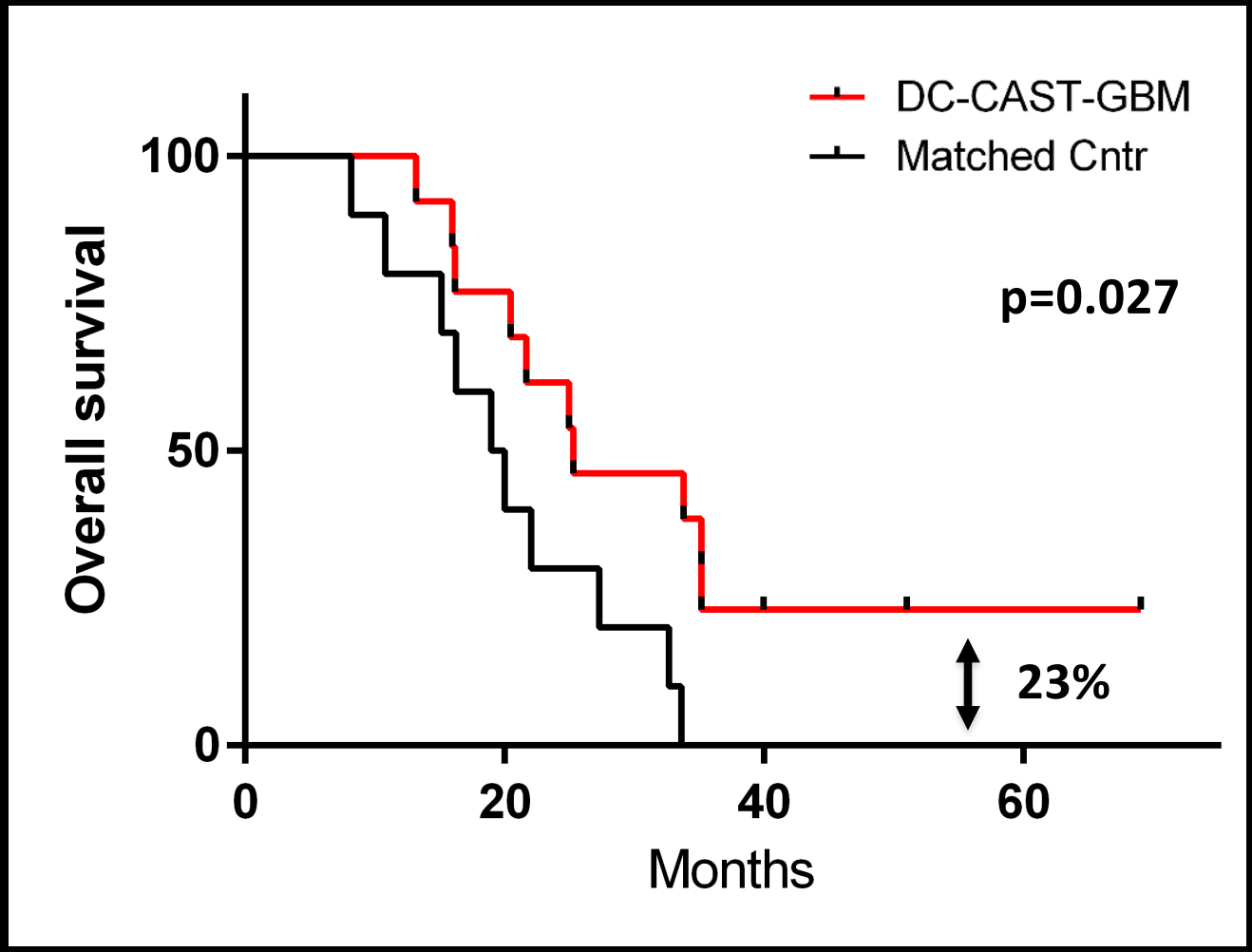
Progression Free Survial



Historical controls matched by:
- Age
- ECOG
- Pre- and postoperative tumor volume
- Oncology treatment
-No progression before 3 months

Median PFS 7.9 vs 19.9 months

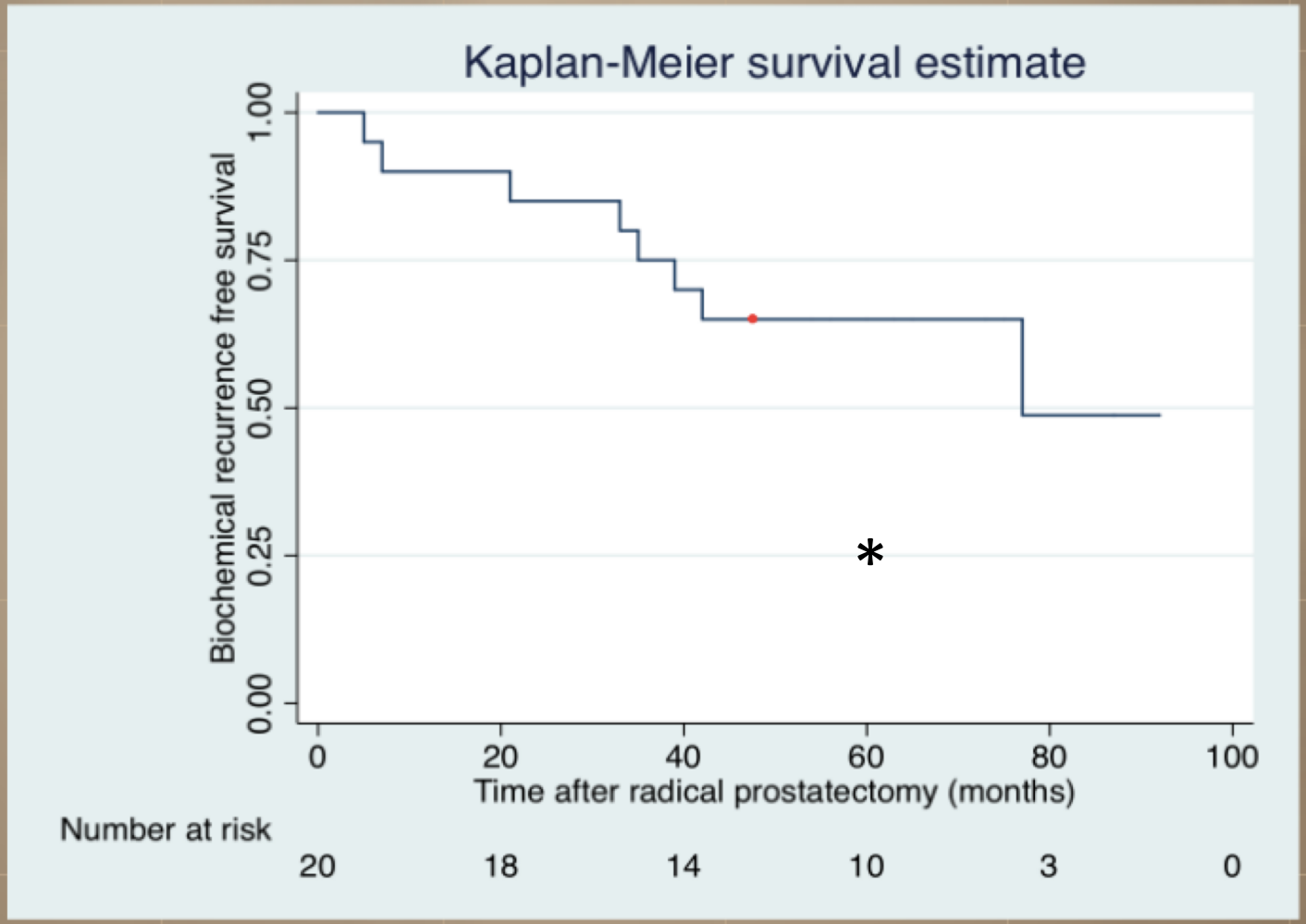
Overall Survival



Historical controls matched by:
- Age
- ECOG
- Pre- and postoperative tumor volume
- Oncology treatment
-No progression before 3 months

Median OS 19.5 vs 25.3 months

* Minimum follow up time: 48 months

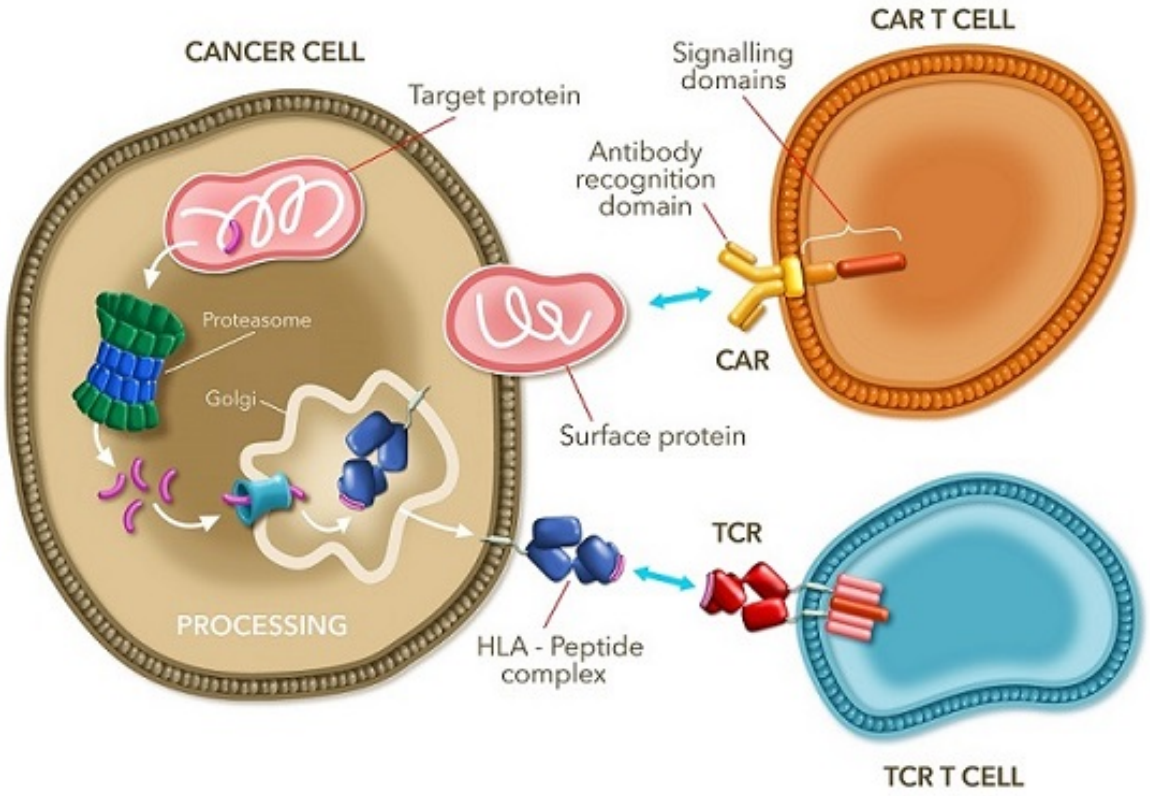


* Epstein JI et al. Eur Urol (2015)

Will DC cancer vaccines have a place in future immunotherapy programs and which patients can benefit of this?

- Treatment of patients with MRD following primary therapy
- Adjuvant treatment in high risk patients following radical surgery
- DC vaccine combined with check point inhibitors
- DC vaccines as boost following adoptive T-cell therapy in solid tumors

CAR and TCR therapy



From http://www.adaptimmune.com/technology/

CAR:

- Clinical responses
- Not dependent on HLA
- Limited target antigens
- On-target toxicity

TCR:

-Clinical responses

-Many targets

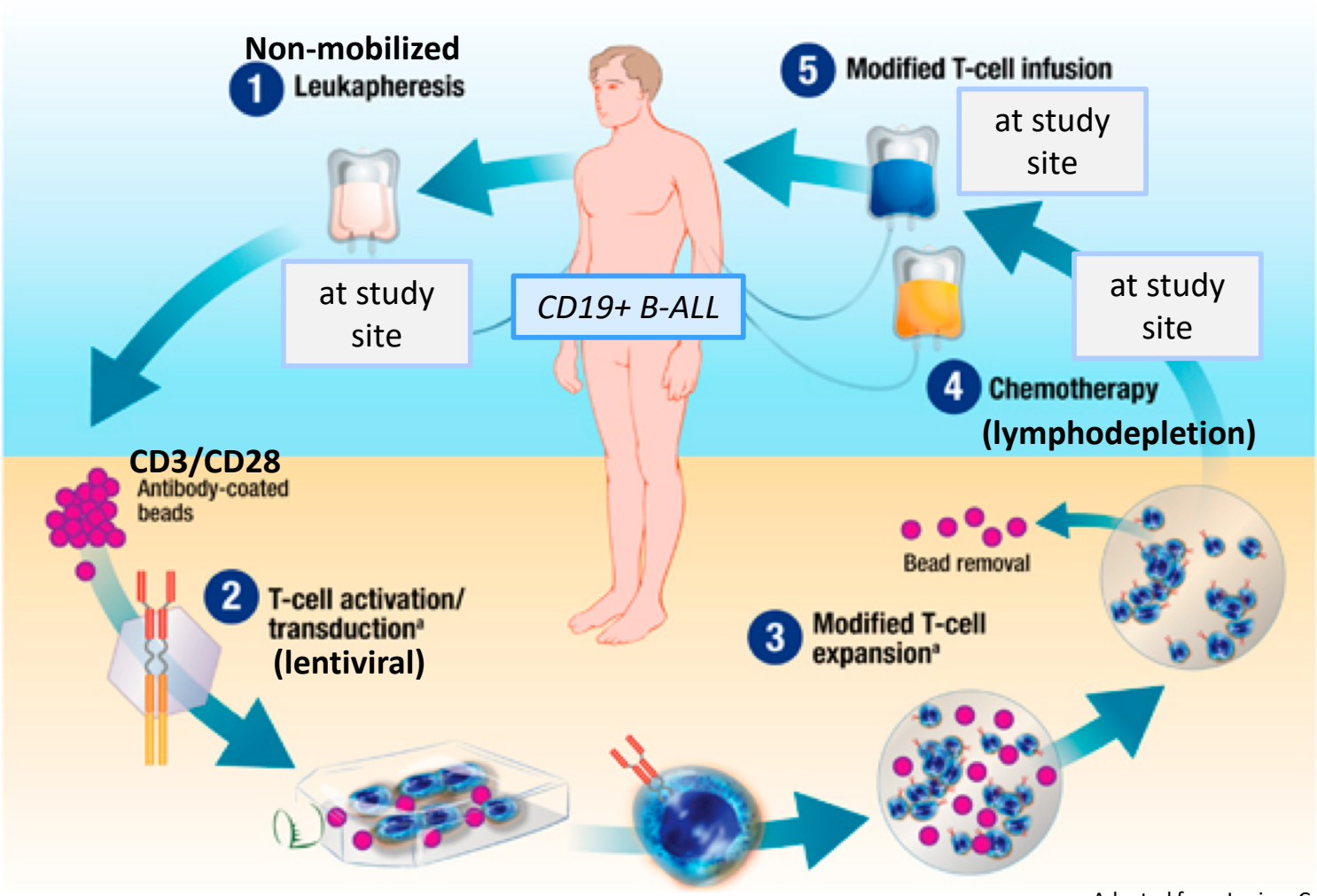
- Toxicity
- HLA downregulation (tumour escape)

Novartis study

- Evaluate efficacy and safety of CTL019 CAR-cells
- Pediatric protocol: CCTL019B2202

Pediatric ALL	
Country	Site
US	14 sites (running in 13 sites per Oct 2015)
Spain	**Barcelona**
France	**Paris**
Germany	**Frankfurt**
Italy	**Monza**
Austria	**Vienna**
Norway	**Oslo**
Belgium	**Ghent**
Canada	2 sites
Australia	1 site
Japan	2 sites

Clinical trial concept for CTL019



Adapted from Levine, Cancer Gene Therapy, 2015

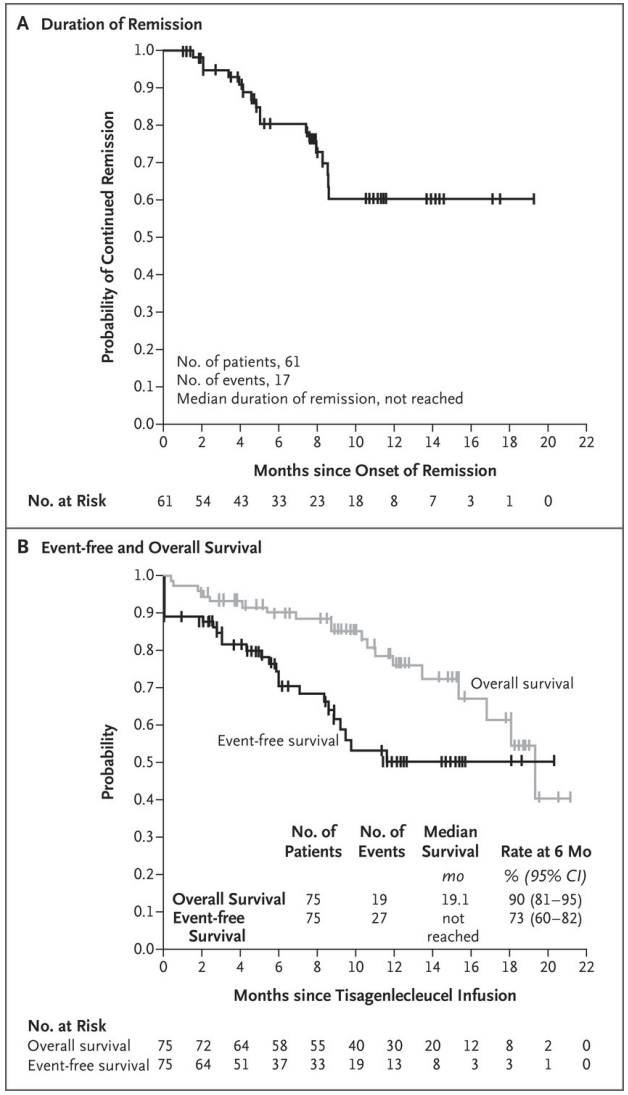
Investigators at Oslo University Hospital

Program Chair for all CTL019 studies in Norway:

Steinar Aamdal (OTM unit at DNR)

- PI Pediatric ALL trial: Jochen Büchner
- PI adult DLBCL trial: Harald Holte
- PI apheresis/cell processing/thawing and infusion CARS: Gunnar Kvalheim

Remission, Event-free Survival, and Overall Survival in pediatric relapsed B-cell ALL treated with CAR CD19



What have we learned from these studies?

Transfer of clinical knowhow to treat severe side effects

Cell collection, processing and freezing of starting cells for CAR production has been optimized

Slots for production of CARS suboptimal

Still to many relapses and further investigations needed to improve outcome !!!!!

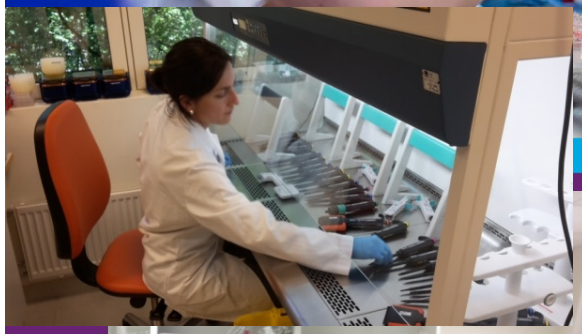
Need of novel B-cell CARS?

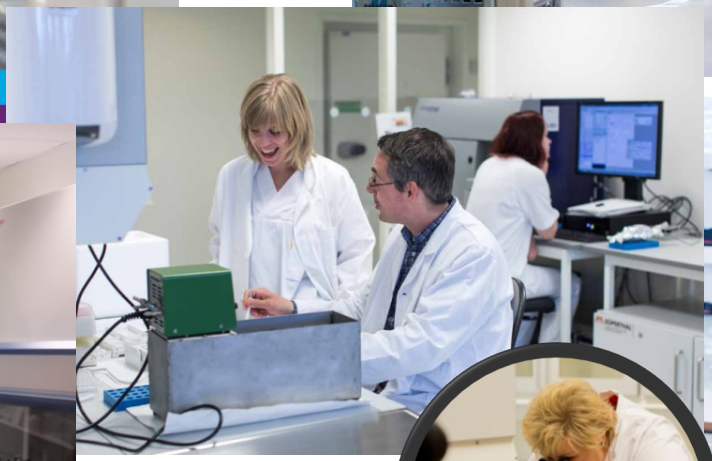
BASIC KNOWHOW AND DEVELOPMENT OF ADOPTIVE T-CELL THERAPY

OSLO CANCER CLUSTER

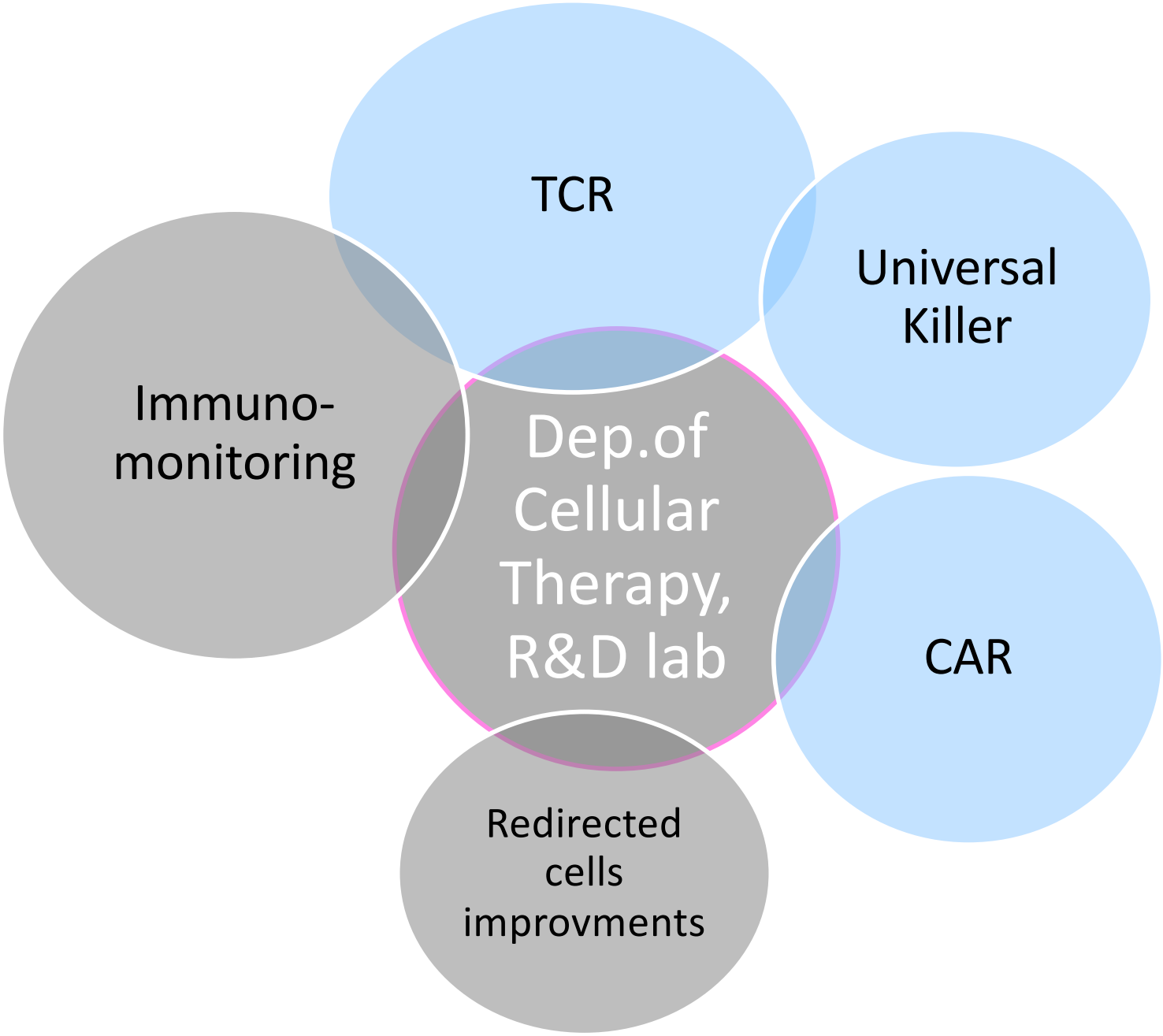
Immunomonitoring and R&D Laboratory
Department of Cellular Therapy

FROM CANCER RESEARCH TO CURE

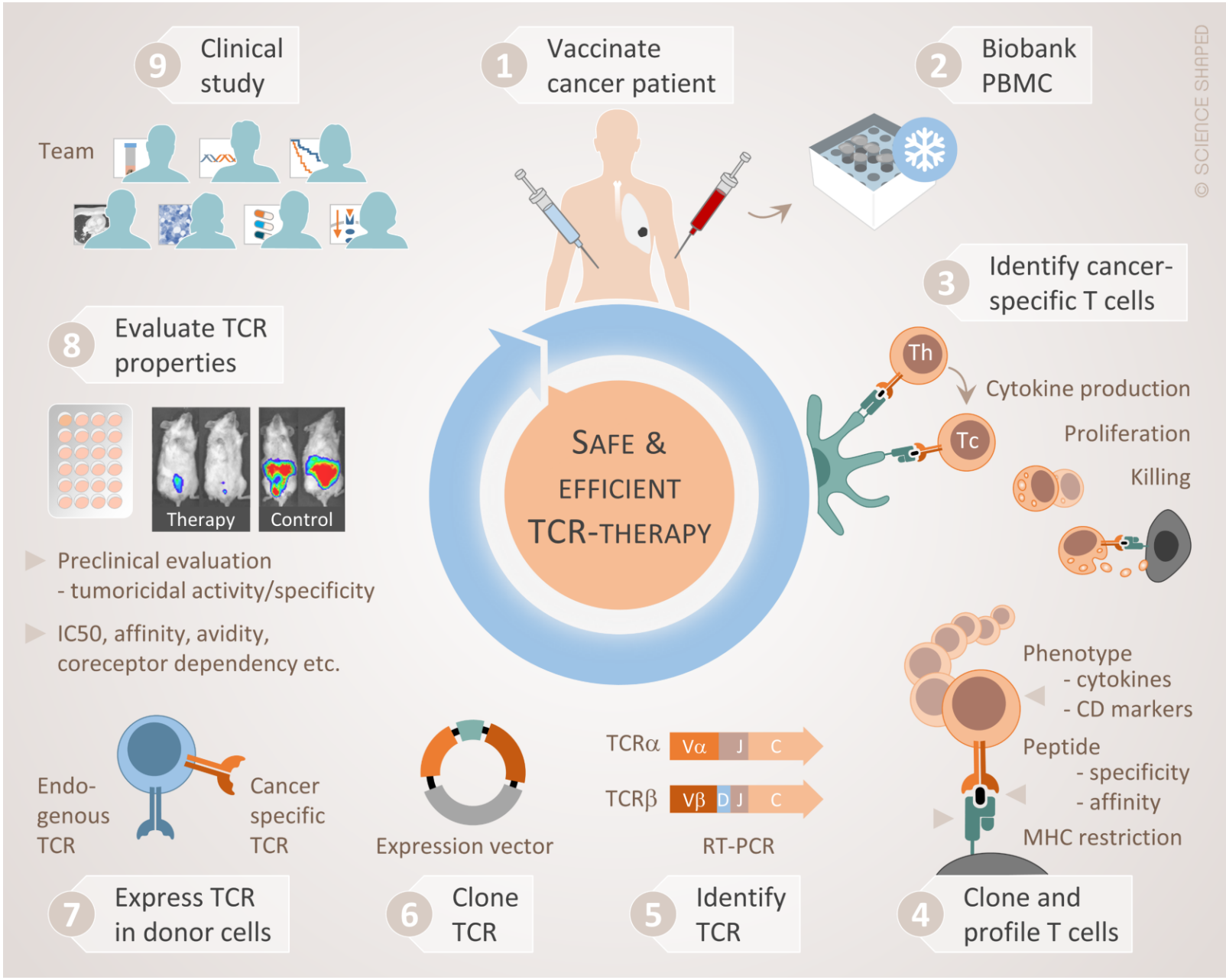




Oslo University Hospital


TCR
Universal Killer
Immuno-monitoring
Dep.of Cellular Therapy, R&D lab
CAR
Redirected cells improvments

TCR platform



Technology base - TCRs

TGFβRII

- MSI+ cancers
- Colorectal cancer (15%)
- Endometrial cancer
- Gastric cancer

hTERT

- >90% of all cancers
- Lung cancer
- Melanoma
- Prostate cancer

KRAS

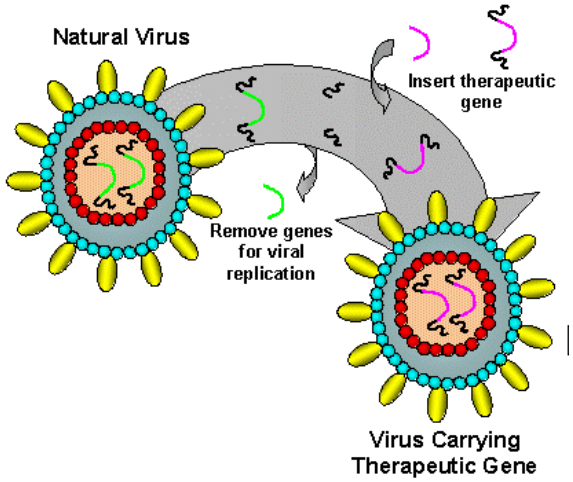
- Pancreatic cancer (98%)
- Colorectal cancer (45%)
- Lung cancer (31%)
- Multiple Myeloma (23%)

- Potential to treat several high unmet need cancers…

- Patents licensed to ZELLUNA IMMUNOTHERAPY

Gene transfer

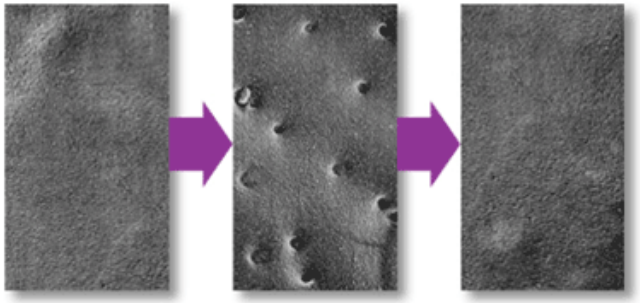
Integrating virus (gammaretro-, lenti-)



- Constitutive expression
- Safety issues
- Regulatory/technologically demanding
- Expensive

- In vivo expansion and differentiation, memory

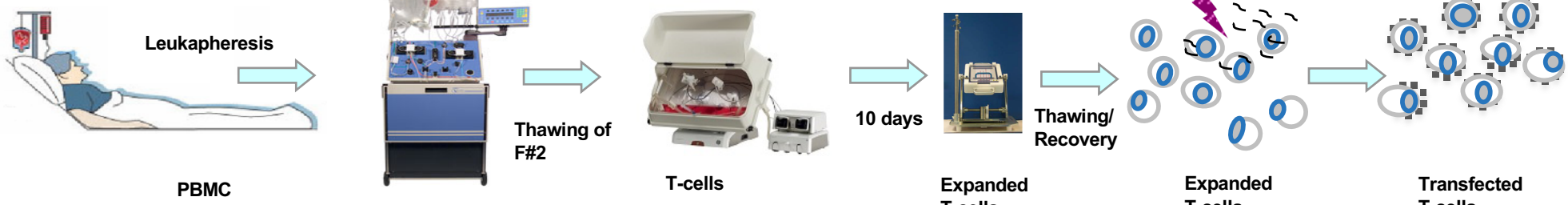
mRNA electroporation



- Transient expression (7-9 days)
- Less risky safety profile
- Regulatory/technol. less demanding
- Less expensive

- No memory

GMP-production platform for CAR/TCR T-cell therapy



PBMC

Cell count
WBC/Monocytes
Viability
Microbiological contamination

T-cells

Cell count
WBC/Lymphocytes
Viability
Microbiological contamination

Expanded T-cells

Cell count
WBC/Lymphocytes
Viability
Microbiological contamination

Expanded T-cells

Cell count WBC/ CD3+ cells
Viability
Residual beads
Microbiological contamination

Expanded T-cells

Cell count WBC
Viability
Microbiological contamination

Transfected T-cells

Cell count WBC/CD3+ cells/other cells
Receptor expression
Viability
Microbiological contamination

Documentation required on cellular therapy products

Investigational Medicinal Product Dossier (IMPD)
(e.g. Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, EMA/CHMP/BWP/534898/2008)

Quality Data *
Non-Clinical Data *

Clinical Data

Study Protocol

Investigator's Brochure

Quality Data

Materials/Equipment

Manufacturing Process

- Cell preparation and culture
- Gene transfer
- Further manufacturing steps
- In process controls
- Process validation

Characterization *

- Identity
- Purity
- Potency

Quality Controls

- Release Criteria

Stability Studies

Rigorous characterization of genetically modified cell medicinal products- issues that should be addressed

- identity, and viability
- sequence and integrity of transgene,
- identity and integrity of vector,
- gene copy number per cell,
- vector integration profile,
- transduction efficiency (e.g. percentage of transduced cells),
- vector/transgenes removal or elimination (when applicable),
- identity and activity of the expressed gene product,
- cell phenotype / morphology,
- homogeneity of the cell population (e.g. percentage of sub-populations),
- proliferation and/or differentiation capacity of the genetically modified cells,
- vector release from cells,
- vector replication competence and possibility of reactivation,
- genetic stability upon in vitro proliferation and/or differentiation

Rigorous characterization of genetically modified cell medicinal products- issues that should be addressed

- identity, and viability
- sequence and integrity of transgene,
- identity and integrity of vector,
- gene copy number per cell,
- vector integration profile,
- transduction efficiency (e.g. percentage of transduced cells),
- vector/transgene removal or elimination (when applicable),
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- vector release from cells,
- vector replication competence and possibility of reactivation,
- genetic stability upon in vitro proliferation and/or differentiation

VECTORS TO BE PRODUCED COMERCIALLY

Documentation required on cellular therapy products

Investigational Medicinal Product Dossier (IMPD)

(e.g. Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, EMA/CHMP/BWP/534898/2008)

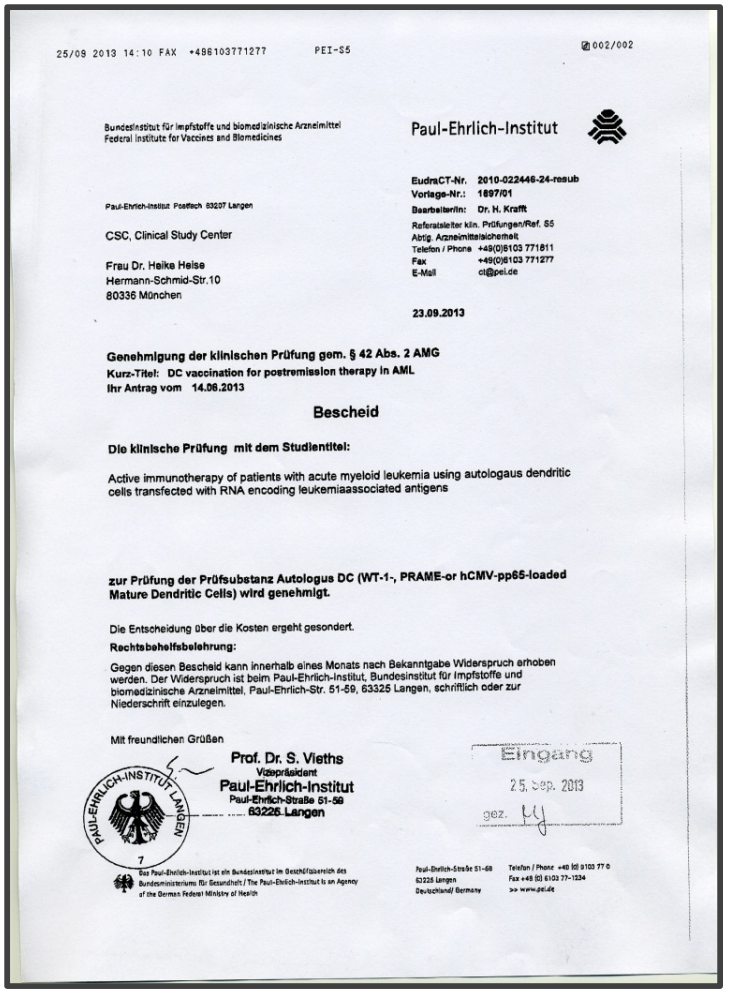
Quality Data *
Non-Clinical Data *

Clinical Data

Study Protocol

Investigator's Brochure

IMPD documentation to the Medicine Agency



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Federal Institute for Vaccines and Biomedicines

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EudraCT-Nr. 2010-022446-24-resub
Vorlage-Nr.: 1897/01
Bearbeiter/in: Dr. H. Krafft
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Telefon / Phone +49(0)6103 771811
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23.09.2013

Genehmigung der klinischen Prüfung gem. § 42 Abs. 2 AMG
Kurz-Titel: DC vaccination for postremission therapy in AML
Ihr Antrag vom 14.06.2013

Bescheid

Die klinische Prüfung mit dem Studientitel:

Active immunotherapy of patients with acute myeloid leukemia using autologaus dendritic cells transfected with RNA encoding leukemiaassociated antigens

zur Prüfung der Prüfsubstanz Autologus DC (WT-1-, PRAME-or hCMV-pp65-loaded Mature Dendritic Cells) wird genehmigt.

Die Entscheidung über die Kosten ergeht gesondert.

Rechtsbehelfsbelehrung:

Gegen diesen Bescheid kann innerhalb eines Monats nach Bekanntgabe Widerspruch erhoben werden. Der Widerspruch ist beim Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Str. 51-59, 63325 Langen, schriftlich oder zur Niederschrift einzulegen.

Mit freundlichen Grüßen

Prof. Dr. S. Vieths
Vizepräsident
Paul-Ehrlich-Institut
Paul-Ehrlich-Straße 51-59
63225 Langen

PAUL-EHRLICH-INSTITUT LANGEN

Eingang
25. Sep. 2013
gez.

7

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit / The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health

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In-Box

22,3 kg

Out-Box

5g

Hospital Exemption

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 13 November 2007
on advanced therapy medicinal products and amending Directive 2001/83/EC
and Regulation (EC) No 726/2004

Parqagraph (6)

*"**Advanced therapy medicinal products** which are **prepared on a non-routine basis** according to specific quality standards, and used within the same Member State in a hospital **under the exclusive professional responsibility of a medical practitioner**, in order to comply with an **individual medical prescription for a custom-made product for an individual patient**, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined."*

Article 28, Parqagraph 2

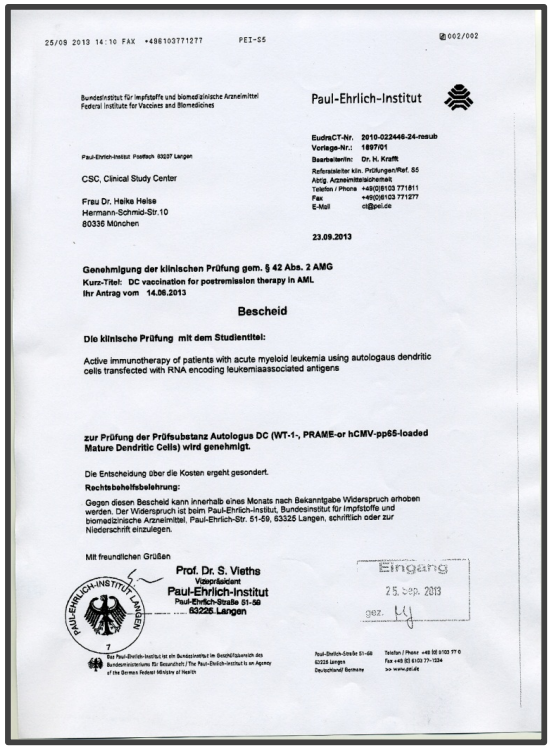
*"Manufacturing of these products shall be **authorised by the competent authority** of the Member State."*

Traceability
Pharmacovigilance
Quality standards
Have to be the **same as for marked level products**

Eligible patients **no other therapeutic options**
urgency/emergency situations
life threatening condition

No marked authorisation **no circulation, product has to stay in the member state**

Hospital Exemption documentation to the Medicine Agency



25/09 2013 14:10 FAX +4961037712?7 PEI-S5 002/002

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Paul-Ehrlich-Institut Postfach 63207 Langen

CSC, Clinical Study Center

Frau Dr. Heike Heise
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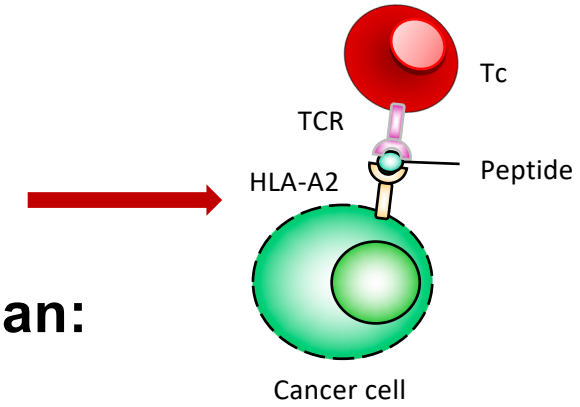
Radium-1 TCR in the clinic

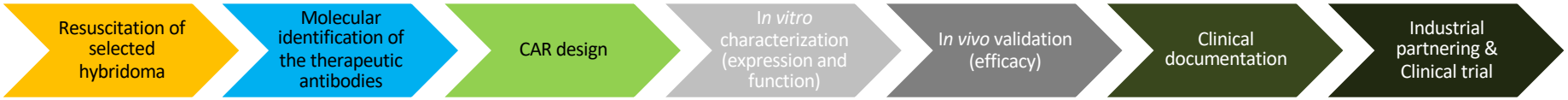


1st clinical TCR therapy in Scandinavia and first-in-man:

T Cell Receptor Based Therapy of Metastatic Colorectal Cancer (TCR-CRC-001), NCT03431311 PI: Svein Dueland

- Patients with metastatic, MSI colorectal cancer, TGFβRII frameshift mutation and HLA-A2+ (MHC I)
- One patient has completed the treatment
- Goal to enroll 3-5 patients under hospital exemption
- Data analysis: Blood chemistry, cellular analyses, cytokine analyses, radiological imaging and biopsy results

CAR pipeline



CD37CAR — 2019Q2 — Köksal, Dillard et al 2019

Bc CAR
OSCAR — 2020Q1

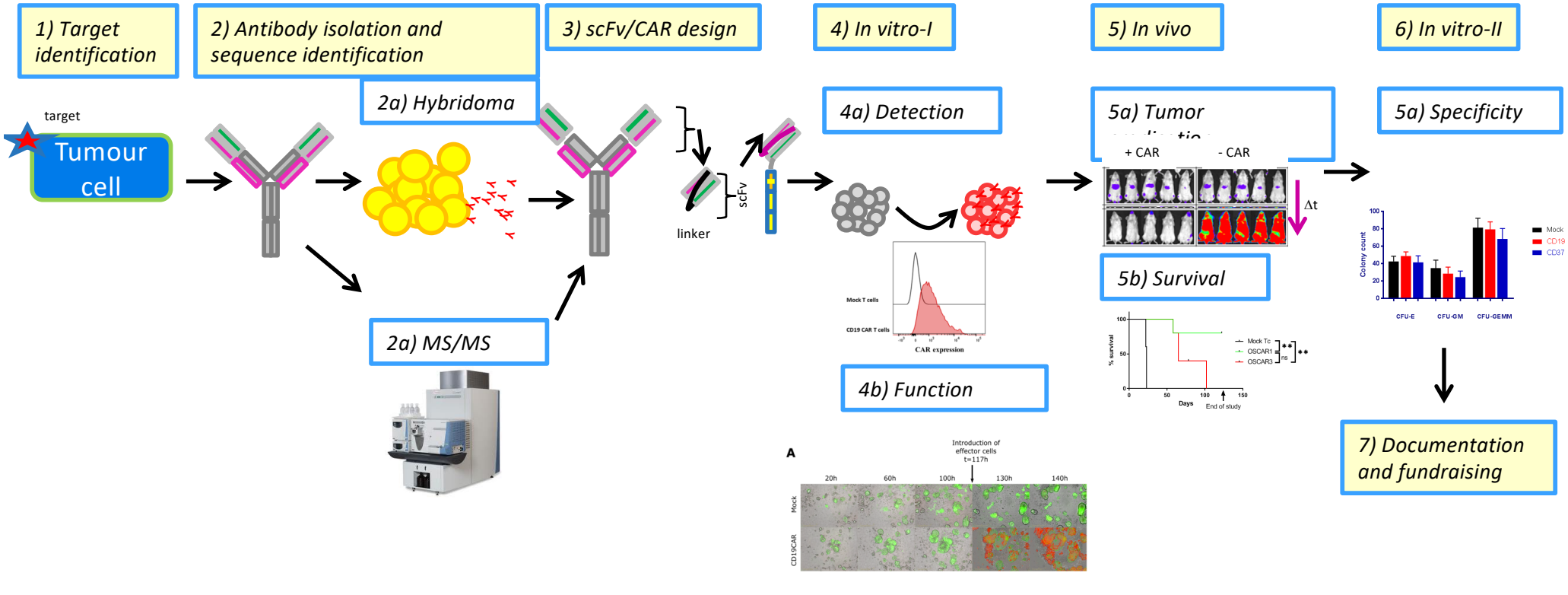
BC CAR

BC CAR
Solid tumour CARs

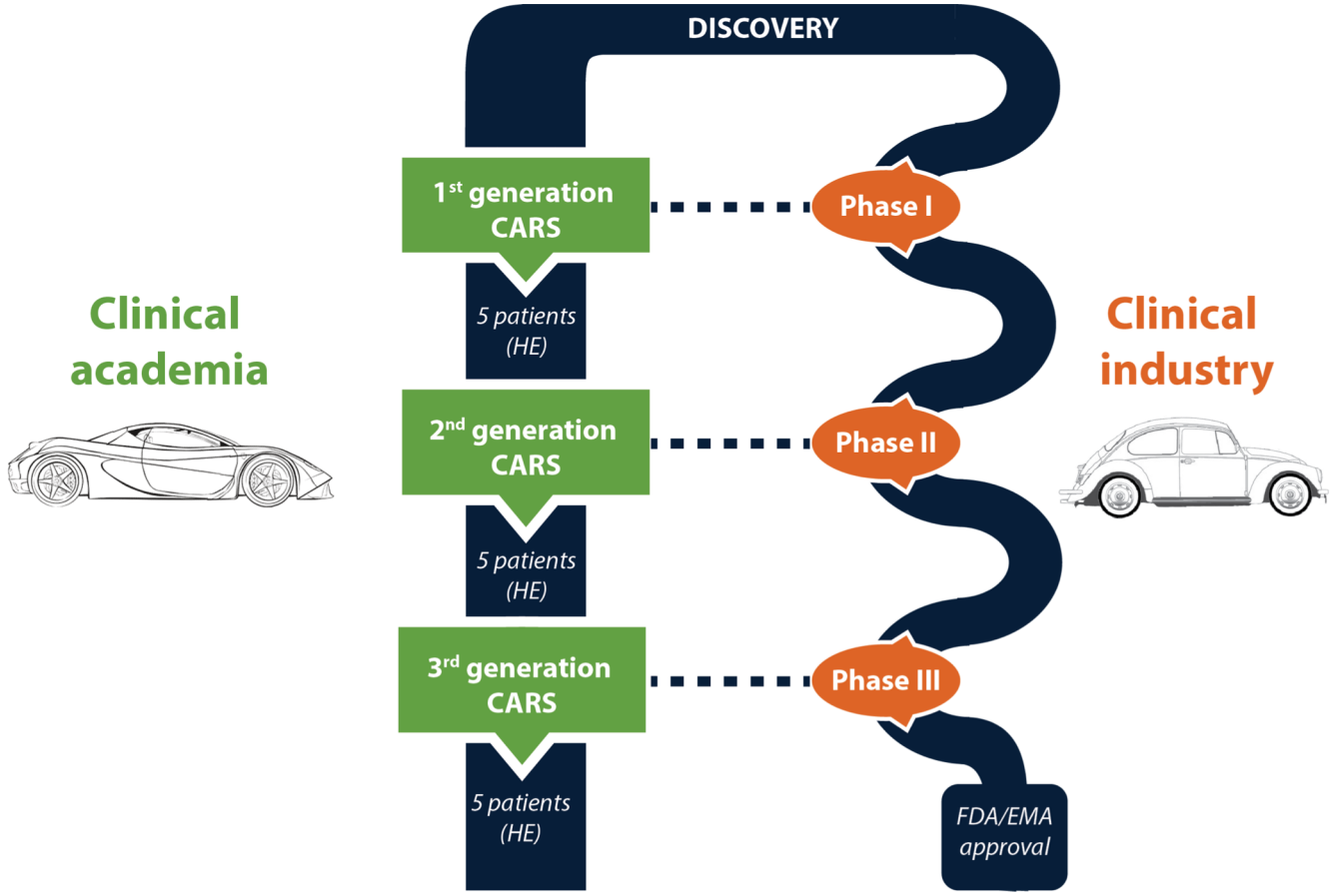
Innovation pipeline:
CAR combination
Affinity maturation

>10 CAR and > 20 hybridoma in the freezers

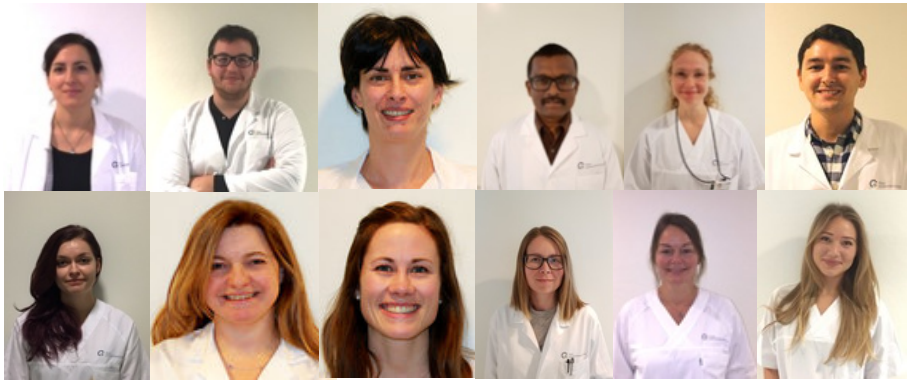
Pre-clinical pipeline



Adoptive T-cell therapy- Industry/ Academia collaborations and how to bring it fast to patients!!!!



Acknowledgements



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Sissel Nygren
Lena Tjeldhorn
Guri Solum
Imran Aydemir-Ay
Jens Andreas Lindin-Jørgensen
Lene Mowinckel

HELSE SØR-ØST

NORWEGIAN CANCER SOCIETY

RADIUMHOSPITALETS LEGATER

invenz

The Research Council of Norway

Sébastien Wälchli
Else Marit Inderberg
Nadia Mensali
Pierre Dillard
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Radiumhospitalets Forskningsstiftelse
THE NORWEGIAN RADIUM HOSPITAL RESEARCH FOUNDATION

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zelluna IMMUNOTHERAPY

Visit: celltherapy.no

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