Cellular based therapy programs at Radiumhospitalet
Oslo University Hospital
Department of Cellular Therapy

Head of Department and Production Site, Qualified Person
Prof. Gunnar Kvalheim
Substituted by: Dag Josefsen

Head of Staff: Merete Djupedal

Head of Quality Management
Merete Djupedal

Cleanroom Facility
Facility Manager: Bente Woldseth

Analysis Laboratory
Responsible Biomedical Scientists: Sissel Nygren Marianne Dyr-Haug

Leukapheresis
Production Leader: Grete Andreassen
Biomedical Scientists

DC Production
Production Leader: Hege Haakenstad
Biomedical Scientists

T-cell Production
Production Leader: Marianne Lundby
Biomedical Scientists

RNA Production
Production Leader: Stein Sæbøe-Larssen
Biomedical Scientists

Immune Monitoring
Head: Else Marit I. Suso
Biomedical Scientists

Research and Development
Head: Gunnar Kvalheim
Research Scientists Biomedical Scientists
Department of Cellular Therapy - for GMP production of cell products – in size one of the largest in Europe.
INSPECTED AND ACCREDITATED BY:
Norwegian Health and Social Department
EU cell directive (2004/23/EC)
JACIE
National Marrow Donor Program (NMDP)
Statens Legemiddelverk
GMP production of cell products
(EU directive 2003/94EC/91/412/EC)
Translational research and clinical activities at Department of Cellular Therapy

Cellular based Personalized Immunotherapy

• DC vaccination with autologous mRNA from tumor in Glioblastoma Multiforme, Prostate, Melanoma, Ovarian;
• Adotive T-cell Therapy.

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 cells. Clinical program on non-healing chronic wounds following curative radiotherapy and in breast reconstruction after radiotherapy… clinical 2013.
Oslo University Hospital

Dept. of Cellular Therapy
Gunnar Kvalheim
Kirsti Hønnåshagen
Anne-Merete Tryggestad
Stein Sæbøe-Larssen
Jon Amund Kyte
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Dept. of Neurosurgery
Iver Langmoen
Einar Wiik-Moe

Dept. of Surgery-Radiumhospitalet
Karol Axcrona
Bjørn Brennhovd

Dept. of Hematology
Geir E. Tjønnfjord
Ingunn Dybedal

Dept. of Clinical Cancer Research
Steinar Aamdal
Svein Dueland
Paal Brunsvig
Study coordinators/nurses

Dept. of Cancer Therapy
Wolfgang Lilleby
Estimated Cancer Deaths in USA 2012

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>29%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Cancer Facts & Figures 2012. American Cancer Society
Acute Lymfatisk Leukemi (ALL)

- Mest vanlige type leukemia hos barn
- 15% av akutte leukemier hos voksne
Allotransplant

The Allogeneic Transplant Process

1. Collection
   Stem cells are collected from the patient's bone marrow or blood.

2. Processing
   Bone marrow or peripheral blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process.

3. Cryopreservation
   Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient’s bloodstream.

4. Chemotherapy
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. Infusion
   Thawed stem cells are infused into the patient.

Donor

Patient
Acute Lymphoblastic Leukemia Overall Survival
Unrelated Transplantation with Bone Marrow for Pediatric Patients, by Disease Status at Transplant (2000-2009)

SOURCE: Data and analysis on NMDP-facilitated transplants through CIBMTR®, the research arm of the NMDP.
Acute Lymphoblastic Leukemia Overall Survival
Unrelated Transplantation with PBSC for Adult Patients,
by Disease Status at Transplant (2000-2009)

SOURCE: Data and analysis on NMDP-facilitated transplants through CIBMTR®, the research arm of the NMDP.
Critical issues that affect outcome after allo-SCT

1. Patient-related features (age, gender, serostatus, comorbidities…)

2. Prior therapy (type of chemo, high dose chemo…)

3. Conditioning regimen

4. GVHD prophylaxis

5. Stem Cell Source

6. Supportive care

-6 -5 -4 -3 -2 -1 0 +14 +21 +100 >180

Graft

Disease-related features (lym. vs. myl., stage, kinetics…)

Department of Cellular Therapy
Impact of a graft-versus-host disease (GVHD) on post-hematopoietic cell transplantation outcomes

Acute GVHD

Chronic GVHD


©2005 by American Society of Clinical Oncology
Genmodifiserte T celler i behandling av leukemi og lymfom
Adoptiv T-celleterapi

PBMC

Isolere immunceller
Reaktivere disse
Ekspandere antallet
Genmodifisere for å dirigere spesifisitet mot leukemi/lymfom

Tilbakeføre store mengder modifiserte T celler for å eliminere leukemi/lymfomceller

Hilde Almåsbak hilde.almasbak@rr-research.no
T-celler med kimær antigen reseptor (CAR)

Antistoff som binder tumor

T-cell reseptor

TCR complex

CAR

Genmodifisert T celle (virusvektorer)

leukemicelle

CD19 molekyll

Anti-CD19
tumordrap

Adapted from Chekmasove et al. Discovery Medicine 2010

Hilde Almåsbak hilde.almasbak@rr-research.no
CAR i prekliniske studier rundt i verden

Kreftform:
- Leukemi
- Lymphom
- Ovaria cancer
- Melanom
- Brystkreft
- Myelom
- Glioblastom
- Prostatakreft
### Table 1 | Summary of published anti-CD19 CAR clinical trial results

<table>
<thead>
<tr>
<th>Institution</th>
<th>Gene-transfer vector used</th>
<th>Antibody*</th>
<th>Co-stimulatory domain in CAR</th>
<th>Chemotherapy administered before cell infusion</th>
<th>Normal B-cell depletion‡</th>
<th>Regression of malignancy reported?</th>
<th>Cytokine-release-type toxicities§ reported?</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor College of Medicine48</td>
<td>Gamma-retrovirus</td>
<td>FMC63</td>
<td>CD28 or none</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>City of Hope81</td>
<td>Plasmid electroporation</td>
<td>FMC63</td>
<td>None</td>
<td>Fludarabine before some T cell infusions</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Center80,81</td>
<td>Gamma-retrovirus</td>
<td>SJ25C1</td>
<td>CD28</td>
<td>None or cyclophosphamide</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
</tr>
<tr>
<td>National Cancer Institute33,44</td>
<td>Gamma-retrovirus</td>
<td>FMC63</td>
<td>CD28</td>
<td>Cyclophosphamide and fludarabine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>University of Pennsylvania34,51</td>
<td>Lentivirus</td>
<td>FMC63</td>
<td>4-1BB</td>
<td>Variable</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3</td>
</tr>
</tbody>
</table>

*The antibody that CAR antigen-recognition moiety was derived from. ‡Reported for >3 months. §For example, hypotension. Abbreviation: CAR, chimeric antigen receptor.

**Alle I USA**

Kurerte kreft med HIV-virus

CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia
Renier J. Brentjens et al.
Sci Transl Med 5, 177ra38 (2013);
DOI: 10.1126/scitranslmed.3005930

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia
David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.
Behandling med CD19 CAR T celler på UPENN

Kronisk Lymfatisk Leukemi

9 pasienter behandlet,  
Resistente mot annen terapi

4 pasienter CR  
2 pasienter PR 3-5 mnd varighet  
3 pasienter NR (T-cellene ikke overlevd)

1-2 kg tumorceller eliminert

Akutt Lymfoblastisk leukemi

2 barn behandlet,  
7 år gammel jente, 2 tilbakefall, kjemoterapi uten videre virkning, forhindret allo-SCT  
10 år gammel jente, 2 tilbakefall etter navlestrangsblodtransplantasjon

Begge pasienter i morfologisk remissjon 1 mnd etter T celler (<0.01% MRD)  
7 åringen fremdeles uten påviselig sykdom (>11 mnd)  
10 åringen i tilbakefall med CD19-negative blaster
All patients eligible
No need for HLA matching
Offered to young as well as elderly patients

"Engineered T cell therapies likely to replace allogeneic transplantation"
B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells


Table 1. Patient data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Malignancy</th>
<th>No. of prior therapies</th>
<th>Total no. infused cells/kg, ×10^7</th>
<th>Percentage of infused cells CAR⁺</th>
<th>No. of infused CAR⁺ cells/kg ×10^7</th>
<th>Infused cells CD4/CD8 ratio</th>
<th>Doses of IL-2 administered</th>
<th>Response and time since treatment, mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a‡</td>
<td>47</td>
<td>Follicular lymphoma</td>
<td>4</td>
<td>0.5</td>
<td>64</td>
<td>0.3</td>
<td>29/63</td>
<td>8</td>
<td>PR (7)</td>
</tr>
<tr>
<td>1b‡</td>
<td>48</td>
<td>Follicular lymphoma</td>
<td>5</td>
<td>2.1</td>
<td>63</td>
<td>1.3</td>
<td>19/71</td>
<td>10</td>
<td>PR (18+)</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>Follicular lymphoma</td>
<td>5</td>
<td>0.5</td>
<td>65</td>
<td>0.3</td>
<td>23/73</td>
<td>9</td>
<td>NE (died with influenza)</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>CLL</td>
<td>3</td>
<td>2.5</td>
<td>45</td>
<td>1.1</td>
<td>35/53</td>
<td>2</td>
<td>CR (15+)</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>Splenic marginal zone lymphoma</td>
<td>3</td>
<td>2.0</td>
<td>53</td>
<td>1.1</td>
<td>72/24</td>
<td>4</td>
<td>PR (12)</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>CLL</td>
<td>4</td>
<td>0.6</td>
<td>50</td>
<td>0.3</td>
<td>87/12</td>
<td>2</td>
<td>SD (6)</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>CLL</td>
<td>7</td>
<td>5.5</td>
<td>30</td>
<td>1.7</td>
<td>37/57</td>
<td>1</td>
<td>PR (7)</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>CLL</td>
<td>4</td>
<td>5.4</td>
<td>51</td>
<td>2.8</td>
<td>58/41</td>
<td>2</td>
<td>PR (7+)</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>Follicular lymphoma</td>
<td>7</td>
<td>4.2</td>
<td>71</td>
<td>3.0</td>
<td>54/43</td>
<td>5</td>
<td>PR (8+)</td>
</tr>
</tbody>
</table>
Cell-Based Therapeutics: The Next Pillar of Medicine

Michael A. Fischbach, Jeffrey A. Bluestone, Wendell A. Lim

Two decades ago, the pharmaceutical industry—long dominated by small-molecule drugs—was revolutionized by the advent of biologics. Today, biomedicine sits on the cusp of a new revolution: the use of microbial and human cells as versatile therapeutic engines. Here, we discuss the promise of this “third pillar” of therapeutics in the context of current scientific, regulatory, economic, and perceptual challenges. History suggests that the advent of cellular medicines will require the development of a foundational cellular engineering science that provides a systematic framework for safely and predictably altering and regulating cellular behaviors.
Adoptive T-celle terapi i Norge

- Internasjonalt forskningssamarbeide etablert (CAR 19 - EU-grant CHILDEHOPE)
- Preklinisk studier
- Translasjon pågynt
- Klinisk i bruk Høst 2013/2014
Gene transfer

Integrating virus (gammaretro-, lenti-)

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

mRNA electroporation

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

• In vivo expansion and differentiation, memory
• No memory

hilde.almasbak@rr-research.no
Overview over the process

mRNA expression vector → IVT CAR mRNA → Electroporation → CD3CD28 Dynabeads activated and expanded T cells

In vitro assays for CAR expression and functionality

Formulation for i.v. injection in NSG mice

hilde.almasbak@rr-research.no
Low *in vivo* anti-leukemia activity despite excellent in vitro functionality; modified CAR format significantly better.
Adoptive T-celle terapi i Norge

- Internasjonalt forskningssamarbeide etablert (CAR 19 - EU-grant CHILDEHOPE)
- Preklinisk studier
- Translasjon pågynt
- Klinisk i bruk Høst 2013/2014
Adoptive T-celle terapi kostnader

Allo transplant
- DRG+

CD19 CARS
- DRG-

Avdeling for blodsykdommer
Avdeling for celleterapi

Oslo University Hospital
Financing

Health authorities

Universities

Norwegian Research Council

Translational research T1

Pre clinical research

Clinical trials

Phase 1

Phase 2

Phase 3

Others: Industry, Cancer Society

T2