Why should we make a Nordic Center of Cell & Gene Therapy in Oslo?
Department of Cellular Therapy - for GMP production of cell products - in size one of the largest in Europe ------- a 50 mill NOK investment!!!
INSPECTED AND ACCREDITATED BY:
Norwegian Health and Social Department
EU cell directive (2004/23/EC)
JACIE(FAHCT)
National Marrow Donor Program(NMDP)
Statens Legemiddelverk
GMP production of cell products
(EU directive 2003/94EC/91/412/EC)
Paul Ehrlich Institute, Germany
GMP production of DCs for German AML patients
# Cancer treatments

<table>
<thead>
<tr>
<th>Classical mainstays</th>
<th>Other treatments</th>
<th>Immunotherapy</th>
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</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Hormone therapy</td>
<td>Bone marrow transplantation</td>
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<tr>
<td>Radiation</td>
<td>Small molecule targeted therapy</td>
<td>Immune response Modifiers</td>
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<tr>
<td>Chemotherapy</td>
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<td>Antibody therapy</td>
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<td>Cancer vaccines</td>
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<td>Peptides</td>
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<td><em>Dendritic Cells</em></td>
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<td>Adotive T-cell Therapy</td>
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</tbody>
</table>
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

Commercial 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 paediatric ALL and adult NHL. PI ALL Jochen Buchner, PI NHL Harald Holte
Principle of adoptive T cell immunotherapy

PBMC

isolate immune cells
reactivate expand
gene modify

reinfuse T cells that recognize tumor
CAR and TCR therapy

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

TCR:
- Clinical responses
- Many targets
- Toxicity
- HLA downregulation (tumour escape)

From http://www.adaptimmune.com/technology/
All patients eligible
No need for HLA matching
Offered to young as well as elderly patients
>90% of ALL patients treated with CD19 CARS T-cells in CR

"Engineered T cell therapies likely to replace allogeneic transplantation"
Novartis study

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Site</th>
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<tbody>
<tr>
<td>US</td>
<td>14 sites (running in 13 sites per Oct 2015)</td>
</tr>
<tr>
<td>Spain</td>
<td>Barcelona</td>
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<tr>
<td>France</td>
<td>Paris</td>
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<td>Germany</td>
<td>Frankfurt</td>
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<td>Italy</td>
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<td>Austria</td>
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<td>Norway</td>
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<tr>
<td>Belgium</td>
<td>Ghent</td>
</tr>
<tr>
<td>Canada</td>
<td>2 sites</td>
</tr>
<tr>
<td>Australia</td>
<td>1 site</td>
</tr>
<tr>
<td>Japan</td>
<td>2 sites</td>
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</tbody>
</table>
A Phase II, single arm, multicenter trial to determine the **efficacy** and **safety** of CTL019

- In pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia (04/2015)
- In adult patients with relapsed and refractory high grade B-cell lymphoma (04/2015)

**WHY SHOULD WE NOT OFFER PHARMA TO PRODUCE FOR NORDIC PATIENTS IN OSLO – DO WE HAVE THE KNOWHOW????**
Clinical T-cell platform for CAR/TCR adoptive T-cell therapy

WE HAVE !!!!!!!
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
GMP documentation to the Medical Agency—how to become professional through a Nordic Center for Cell & Gene therapy?

In-Box

22,3 kg

Out-Box

5g
BASIC KNOWHOW AND DEVELOPMENT OF ADOPTIVE T-CELL THERAPY

Department of Cellular Therapy
Immunomonitoring and R&D Laboratory
Department of Cellular Therapy
TCR platform

1. Vaccinate cancer patient
2. Biobank PBMC
3. Identify cancer-specific T cells
4. Clone and profile T cells
5. Identify TCR
6. Clone TCR
7. Express TCR in donor cells
8. Evaluate TCR properties
9. Clinical study

- Preclinical evaluation:
  - Tumoricidal activity/specificity
  - IC50, affinity, avidity, coreceptor dependency etc.

Endogenous TCR
Cancer specific TCR
Expression vector
RT-PCR

TCRα
Vα | J | C

TCRβ
Vβ | D | J | C

Phenotype
- Cytokines
- CD markers

Peptide
- Specificity
- Affinity

MHC restriction

Cytokine production
Proliferation
Killing

Dept of Cellular Therapy
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...

LICENCED TO ZELLUNA IMMUNOTHERAPY AS
CAR pipeline

- Resuscitation of selected hybridoma
- Molecular identification of the therapeutic antibodies
- CAR design
- In vitro characterization (expression and function)
- In vivo validation (efficacy)
- Clinical documentation
- Industrial partnering & Clinical trial

Innovation pipeline: CAR combination, Affinity maturation

>10 CAR and > 20 hybridoma in the freezers
Chimeric Antigen Receptor: pre-clinical platform/necessary steps

Sequence identification

scFv design and CAR building

hybridoma

antibody

CAR assessment

Tc expression:
- In vitro validation
- In vivo validation
- Specificity assessment
Adoptive T-cell therapy - Industry/Academia collaborations and how to bring it fast to patients through a Nordic Center for cell & Gene therapy?
THE RADIUM HOSPITAL INNOVATION CAMPUS

NORDIC CENTER FOR CELL & GENE THERAPY
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Einar Vik-Mo

Visit: celltherapy.no