Harnessing Adaptive NK Cells in Cancer Immunotherapy

Karl-Johan Malmberg, MD. PhD. Prof.
“Immunotherapy against cancer is like drying an ocean with an hairdryer”
Challenge

To decipher the cellular and molecular mechanisms underlying immune failure and exploit this knowledge to convert clinical non-responders to responders.
Regulation of NK cell function by killer cell immunoglobulin-like receptors (KIR)

Malberg and Ljunggren, Nature Reviews Immunology 2007
Variegated KIR expression confer tolerance and broad specificities in missing-self recognition.
Haploidentical NK cell therapy -
Preliminary results from a Phase I/II trial at the Karolinska Institute
NK cell therapy across HLA barriers – missing self in the new host!
Protocol Design –
Refractory AML or MDS

Escalating dose of total lymphoid irradiation (TLI) and addition of Cyclosporine A

Infusion of over night IL-2 activated Haploidentical NK cells

Fludarabine 25mg/m2 (Day -7 to -4)
Cyclophosphamide 25mg/kg (Day -3 to -2)
TLI 2-4 Gy (Dose Level 1 and 2) (Day -1)
Cyclosporin A (Dose Level 3) Target conc 75ng/ml (Day 0 until end of study 3 months)
6/16 patients reaching CR or PR becoming eligible for stem cell transplantation

<table>
<thead>
<tr>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
</tr>
<tr>
<td>☀</td>
<td>⬀</td>
<td></td>
</tr>
<tr>
<td>⬀</td>
<td>⬀</td>
<td></td>
</tr>
<tr>
<td>☀</td>
<td>⬀</td>
<td></td>
</tr>
<tr>
<td>☀</td>
<td>⬀</td>
<td>⬀</td>
</tr>
</tbody>
</table>

- RAEB-2
- MDS/AML
- AML

- CR/mCR/CRI start
- mCR/PR start
- Stable disease
- Response end
- Continued response
- SCT
- DLI
- Chemotherapy
- NK
- 2nd NK-treatment
- PTLD in CR
- Diseased

Table: 1 year Q1: ☀, Q2: ⬀, Q3: ⬀, Q4: ⬀. 2 years Q1: ☀, Q2: ⬀, Q3: ☀, Q4: ⬀. 3 years Q1: ⬀, Q2: ⬀, Q3: ⬀, Q4: ⬀.
Reduction of CD34+ blast counts

Frequency live lin-CD34+

Non-responder  Responder

0.0480
Role for NK cells in the therapeutic effect?
NK cell micro-chimerism at day 7-14 correlates with clinical responses

\[
p = 0.03
\]
Immunoediting – higher levels of HLA class I on residual blasts in responders

**HLA class I**

- Non-responder: 0.0177
- Responder: 0.0025

**HLA E**

- Non-responder: 0.0025
- Responder: 0.0025

**Graphs:**

1. **HLA class I**
   - Non-responder
   - Responder

2. **HLA E**
   - Non-responder
   - Responder
Harnessing the power of adaptive NK cells
Not all NK cells are equal

CyTOF: $10^5$

CMV

SCT

CMV

CNV

Beziat et al., *Blood*, 2013b
Beziat et al., *Blood*, 2013a
Björklund et al., *Blood*, 2010
Andersson et al., *Blood*, 2009
Björkström et al., *Blood*, 2012

CD8

NK

CD56^{bright} NKG2A^+ CD57^+ KIR^+ 

CD56^{dim} 

# of KIRs
CMV is associated with a clonal-like expansion of adaptive NK cells

Beziat V. et al. Blood 2013
Expanding tumor-reactive NK cells
CD2 provides signal 2 in antibody-driven adaptive NK cell responses
Expansion platforms

NKG2C
HLA-E
Feeder Cell

aKIR
Ig coated Bead

CD16
mAb
Balancing numbers and specificity

A

Natural Repertoire

CD56bright  NKG2A+KIR-  Non-Self KIR+  Self KIR+ (Educated)  Adaptive

B

Cytokine-stimulated


C

Guided Differentiation


D

Selective Expansion
## Acknowledgements

<table>
<thead>
<tr>
<th>Malmberg group</th>
<th>Karolinska Institutet</th>
<th>Oslo University Hospital (OUH) and UiO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per Ljungman</td>
<td>Johanna Olweus</td>
</tr>
<tr>
<td></td>
<td>Eva Hellström-Lindberg</td>
<td>Arne Kolstad</td>
</tr>
<tr>
<td></td>
<td>Petter Höglund</td>
<td>Eivind Hovig</td>
</tr>
<tr>
<td></td>
<td>Klas Kärre</td>
<td>Andreas Brecht</td>
</tr>
<tr>
<td></td>
<td>Sten Linnarsson</td>
<td>Harald Stenmark</td>
</tr>
<tr>
<td></td>
<td>Björn Önfelt</td>
<td>Kjetil Taskén</td>
</tr>
<tr>
<td></td>
<td>Sören Lehman</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Björn Wahlin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hans-Gustaf Ljunggren</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Funding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KI/SLL Theme Centers:</td>
<td>Regenerative Medicine and IMTAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Swedish Research Council</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Swedish Cancer Foundation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Swedish Children's Cancer Foundation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Swedish Royal Society of Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oslo University Hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Norwegian Cancer Society</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Univ. of Minnesota</th>
<th>KG Jebsen Foundation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jeffrey Miller</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarah Cooley</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Univ. of Cambridge</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>John Trowsdale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>James Traherne</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Stanford University</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amir Horowitz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peter Parham</td>
<td></td>
</tr>
</tbody>
</table>