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- MORGENDAGENS KREFTSELSKAPER
TAM Targeting - New platform technology targeting solid tumors

Kristin Sandereid, Inven2
TAM Targeting
New platform technology targeting solid tumors

Kristin Sandereid
Inven2 AS
TAM Targeting

- TAM - Important part of tumor stroma – required for tumor growth
- Targeted delivery of pro-inflammatory cytokines to the tumor site
  - Induces a potent T and NK-cell based anti-tumor response
- Not personalized – universal strategy
- Potentially applicable to a wide range of tumor types

A. TAM-specific targeting unit
   Linker
   Bioactive unit (e.g. IL15)

B. Tumor-associated macrophage (TAM)

Melanoma  Lung  Colon  Renal  Breast
In vivo proof-of-principle - Myeloma

CD206-RLI: CD206-specific nanobody linked to IL15:IL15Rα(sushi)
Patent protection & status

• The concept of using cytokines to target tumor associated macrophages for cancer treatment is novel and provisional patent application was filed 17.03.2016

• Ongoing Biotek2021 project
  ✓ establishing proof of concept for the concept
  ✓ developing a pipeline
  ✓ testing combinatorial therapy, checkpoint inhibitor
  ✓ safety
  ✓ biodistribution
TAM Targeting

- Novel platform technology
- Universal immunotherapy
- Targeting several indications
- Dependence of effect in different indications it can be used as monotherapy and/or combination therapy
- Induces a potent anti-tumor response
- Exceptionally convincing proof of principle data in mice
Contact information

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Executive Fund & Business Developer
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#2
Tankyrase inhibition in cancer therapy

Jo Waaler, University of Oslo/Oslo university Hospital
Tankyrase inhibition in cancer therapy

Jo Waaler, Stefan Krauss and Mercachem

12.06.2018
What is cancer?

Loss of normal growth control

Frequently caused by altering mutations in **cell signaling pathways**
What is cell signaling?

Sending cell

ligand
What is cell signaling?
What is cell signaling?

- WNT
- Lost growth control
- Resistance against immunotherapy
What is cell signaling?

- WNT signaling is a key pathway in cancer
- World-wide hunt for inhibitors last 20 years
- WNT-induced resistance against immunotherapy found in 13% of tumors
- No WNT inhibitor drug in clinical practice
Tankyrase inhibition in cancer therapy

BIOTARGET – master regulator of WNT signaling
Tankyrase inhibition in cancer therapy

BIOTARGET – master regulator of WNT signaling
Tankyrase inhibition in cancer therapy

TANKYRASE INHIBITOR

NAD^+ → TNKS

ADP-ribose

nicotinamide

BIOTARGET – master regulator of WNT signaling

WNT signaling
Development of benchmark tankyrase inhibitors

2011
Novel Synthetic Antagonists of Canonical Wnt Signaling Inhibit Colorectal Cancer Cell Growth
- JW74: hit compound

2013
Structural Basis and SAR for G007-LK, a Lead Stage 1,2,4-Triazole Based Specific Tankyrase 1/2 Inhibitor
- G007-LK: early lead, highly specific/potent

2017
Discovery of a Novel Series of Tankyrase Inhibitors by a Hybridization Approach
- OD336: optimized lead, good rat/dog PK

2018
- Mix-17 (G007-MP): preclinical lead/candidate
- > 150 compounds tested
- improved ADME properties
- no RED flags so far
Proof-of-concept: single agent

GENETIC COLORECTAL CANCER MODEL

WT

Control

tankyrase inhibitor

COLORECTAL CANCER XENOGRAFT (COLO320DM)

Cancer Research, Lau et al. 2013

human cancer in mice

Cancer Research, Waaler et al. 2012
Proof-of-concept: combination therapy

PROOF-OF-CONCEPT ANTI-MELANOMA EFFICACY

WNT-induced resistance against immunotherapy found in 13% of tumors

Confidential data

tankyrase inhibitor (G007-LK) in combination with drug X

Immunotherapy resistant melanoma model
Proof-of-concept: combination therapy

Unpublished data, Waaler et al.
Experienced project team
Intellectual Property

PCT/US2017/067228
Assignee: OSLO UNIVERSITY HOSPITAL HF
Filing date is 19 December 2017
22 examples

Additional patent application is in preparation
Filing date June 2018
80-90 examples
New optimized compounds will be included
Development scheme

- **Preclinical lead**
  - **Activities**: R&D
  - **Partner**: Mercachem
  - **Funding**: 1 mUSD
  - **Funding source needed**: Public/private

- **IND**
  - **Activities**: POC/safety/tox
  - **Partner needed**:
  - **Funding**: 5 mUSD
  - **Funding source needed**: Private

- **Phase I/II**
  - **Activities**: POC/safety/tox
  - **Partner needed**:
  - **Funding**: 20 mUSD
  - **Funding source needed**: Private
Thank you
Proof-of-concept results (tox)

INTESTINAL TOXICITY UPON G007-LK TREATMENT

*Cancer Research, Lou et al. 2013*

NO TOXICITY UPON TREATMENT WITH drug X + G007-LK

*BiorRes, Norum et al. 2013*
Mix-17 (G007-MP) TPP

- SAR established with >150 compounds!
- Cellular efficacy improved by factor 10-100!
- Solubility improved by factor 10!
- Efflux down to 1!
- Metabolic stability improved!
- Mouse PK of first compound shows greater Cmax!

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mix-17</th>
<th>TPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular IC50 (HEK293)</td>
<td>17 nM</td>
<td>&lt; 25</td>
</tr>
<tr>
<td>Biochemical IC50</td>
<td>4.0 nM</td>
<td>-</td>
</tr>
<tr>
<td>Kin. Solubility: PBS pH=7</td>
<td>95.7 μM</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>CACO2: A-B: P_{app}</td>
<td>39.5 10^{-6} cm/s</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>CACO2: efflux ratio</td>
<td>0.610</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Microsomal stability human: Cl_{int}</td>
<td>t_{1/2}</td>
<td>0.78 μL/min/mg protein</td>
</tr>
<tr>
<td>mouse: Cl_{int}</td>
<td>t_{1/2}</td>
<td>5.59 μL/min/mg protein</td>
</tr>
<tr>
<td>dog: Cl_{int}</td>
<td>t_{1/2}</td>
<td>2.22 μL/min/mg protein</td>
</tr>
<tr>
<td>CYP3A4 inhibition IC50</td>
<td>&gt; 25 μM</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>Mouse plasma stability</td>
<td>t_{1/2} = 880 min</td>
<td>&gt; 240</td>
</tr>
<tr>
<td>Mouse PPB</td>
<td>93.92 %</td>
<td>80 – 99.5</td>
</tr>
<tr>
<td>hERG inhibition IC50</td>
<td>&gt; 25 μM</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>Ames test</td>
<td>Non-genotoxic also for S9 metabolites</td>
<td>-</td>
</tr>
<tr>
<td>Bioavailability: F</td>
<td>107 %</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>PK mouse: t_{1/2}</td>
<td>0.67</td>
<td>&gt; 1.5</td>
</tr>
<tr>
<td>PK mouse: Cl</td>
<td>2.09</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>PK mouse: Vd</td>
<td>2.03</td>
<td>1 - 3</td>
</tr>
</tbody>
</table>
Competitors

- Novartis
- Merck
- Astra Zeneca
- Amgen
- Eisai
A new drug against Acute Myeloid Leukaemia (AML)

Pål Rongved, University of Oslo
Iodinin – from cyanobacteria (Døskeland et al, UiB)

- Selectively killing leukemia cells (AML)
- Strong antibacterial agent

Serious issues:
- Only tiny amounts available (bioprospecting)
- A synthetic method was not known in prior art.
- Described in prior art and is not patentable in itself.
- Efficient prodrug needed.

➢ All solved! HOW???
FIRST: What is AML (acute myeloid leukaemia)?

Crushing out normal blood cells:
- Fatigue
- Bleeding
- Infections
What is the current therapy for AML in the clinic?

Daunorubicin (DNR)

- Old and toxic!
- KOL: High time to replace it!

Observed side effects at clinical doses:
- Short term (CHF)
- Long term: Changes in heart function
Results and potential

We identified:

**IM56**  
Lead candidate

**Membrane penetration** → **Prodrug cleavage** → **Broad-spectrumed antibiotic**

**A. baumannii**

**Selective anti-AML**

**Fluorescent**

**Hypoxia (low oxygen)-selective**

What about tox??

Prof. Kent S. Gates, Univ. Missouri

---

Patient 50 = SS_20170913

Hypoxia (low oxygen)-selective

What about tox??
Results: *in vitro* tox

**First: some definitions:**

Therapeutic index (T.I.) in cancer =  \[ \frac{\text{The dose (EC}_{50}\text{) that kills healthy cells}}{\text{The dose (EC}_{50}\text{) that kills cancer cells}} \]

Cell types used:

- MOLM-13: AML cells (rat)
- NRK cells: Normal Rat Kidney cells
- H2c9 cells: rat cardiomyoblasts

**In vitro results IM56 (normox):**

\[
\begin{align*}
\text{T.I.} & \quad \frac{\text{NRK}}{\text{MOLM-13}} & = 42 \\
\text{T.I.} & \quad \frac{\text{H2c9}}{\text{MOLM-13}} & = 33 \\
\end{align*}
\]

*In vitro* cardiotox: \[ \frac{\text{EC}_{50} \text{ H2c9 IM56}}{\text{EC}_{50} \text{ H2c9 DNR}} = 3.4 \]
Technology status & competitive advantages

Access to sophisticated animal models for AML

a. AML cells isolated from patient bone marrow (BTG, Haukeland Sykehus)

McCormack et al. Blood 2013
What do we want?

1. An exit to a startup/licencing of IPR
2. Continue preclinical development of our lead candidate
3. Financial support for this
4. Identify young business talents to take on as CEO

Present funding:
Key take home messages and summary

1. Seven drugs in late stages of development – MARKET POTENTIAL.
2. KOL: none of the of the new therapies are game-changers.
3. IM56
   - fewer side effects on healthy cells and lower off-target effects on non-leukaemic healthy cells than standard therapy
   - antibacterial and fluorescent
   - high selectivity towards AML cell, even those with genetic markers of poor prognosis, such as FLT-3 or with mutant p53
4. The IPR position is strong and will be strengthened with new patent applications
5. We have a strong interdisciplinary team
WHO ARE WE??

UiB

Prof Herfindal/Døskeland

SYNFAS

UiO

Prof P. Rongved

Haukeland

Prof B.T. Gjertsen

Inven2

BTO

HELESE BERGEN

Haukeland universitetssjukehus

UiO School of Pharmacy

The Faculty of Mathematics and Natural Sciences
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#4
Boosting Immunotherapeutic Cells

Pierre Dillard, Oslo University Hospital
Boosting Immunotherapeutic Cells

Pierre Dillard¹, Theodossis Theodossiou², Sebastien Wächli¹, Else-Marit Inderberg¹

¹Laboratory of Translational Research & Immunomonitoring
Section for Cellular Therapy
Department of Oncology-ÖUS

²Institute for Cancer Research
Department of Radiation Biology-ÖUS
ACT, 3 challenges to overcome
- Length
- Cost
- Efficacy in patients
Boosting killing efficiency

- 12 metabolic modulators tested
- 3 effector cells tested (inc. primary T-cells)
- 7 target cell lines tested
  - Melanoma
  - Colorectal
  - Lymphoma
Relevant TCR T-cells treated with drugs reduced significantly the tumor load and improved overall survival.
Boosting killing specificity

Upon drug treatment, T-cells show reduced killing rate on unspecific target.

Tumor isolated from mice xenograft model showed:
- More TILs for relevant TCR T-cells
- Less TILs for irrelevant TCR T-cells
Upon drug treatment, the growth capacity of T-cells is enhanced both in terms of rate and maximal titration.
New protocol based on metabolic modulators

- Enhance killing efficiency
- Enhance killing specificity
- Enhance growth capacity
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#5
CD37 CAR for cancer immunotherapy

Sébastien Wälchli
CD37 CAR for cancer immunotherapy

Sébastien Wälchli
Laboratory of Translational Research & Immunomonitoring
Section for Cellular Therapy
Department of Oncology-OUS
Cancer Immunotherapy

• Use the immune system to fight cancer
How does immune system kill?

Cytotoxic T cell recognizes complex of viral peptide with MHC class I and kills infected cell

T cell

Cancer cell

Modified from Genaway (Immunobiol) 7th Ed.
What is a Chimeric Antigen Receptor (CAR)
# CD19CAR

## Table 2. CD19 CAR therapy for ALL

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number/age of subjects</th>
<th>Complete remission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentjens, et al. (74)</td>
<td>5 adults</td>
<td>100%</td>
</tr>
<tr>
<td>Grupp, et al. (75)</td>
<td>2 children</td>
<td>100%</td>
</tr>
<tr>
<td>Davila, et al. (76)</td>
<td>16 adults</td>
<td>88%</td>
</tr>
<tr>
<td>Lee et al. (78)</td>
<td>20 children</td>
<td>70%</td>
</tr>
<tr>
<td>Maude, et al. (77)</td>
<td>25 children</td>
<td>90%</td>
</tr>
<tr>
<td>Frey, et al. (107)</td>
<td>5 adults</td>
<td>100%</td>
</tr>
<tr>
<td>Park, et al. (108)</td>
<td>12 adults</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>27 adults</td>
<td>89%</td>
</tr>
</tbody>
</table>

*Sadellain, 2015*

*Novartis, 2017*
Why another CAR?

- **Good kill**
  - CD19+ CD19CAR
  - δt

- **Resistance**
  - CD19- Loss of protein
  - CD19- CD19- Loss of epitope

- **Alternative solutions**
  - CD19 Tc
  - Alternative CAR Tc

Cellular Therapy
Why CD37?

CD37 is a cell surface marker that is associated with certain B cell malignancies. The diagram illustrates the progression of B cells from the bone marrow to the periphery, highlighting the stages where CD37 expression is pertinent. CD19 and CD20 are other B cell markers, and CD37 is positioned between them, indicating its role in cancer research and cellular therapy.

© 2011 American Association for Cancer Research

Cellular Therapy

Oslo University Hospital
CD37 an alternative B-cell lymphoma target

Sektioglu et al. in revision
CD37CAR

Sektioglu et al. in revision

DO NOT POST
CD37CAR

Sektioglu et al. in revision

DO NOT POST
CD37CAR: take home message

- 50% of B-cell lymphoma are not or poorly responding to CD19CAR
- A number of CD19CAR relapse are CD19 negative
- CD37 is a valid alternative solution
Thank you for your attention

Visit: celltherapy.no
Contact: sebastw@rr-research.no
CD37CAR

DO NOT POST

Sektioglu et al. in revision

Cellular Therapy
Backscatter - High data-rate wireless communication for medical implants

Bjarne Tvete, Inven2
Backscatter
High data-rate wireless communication for medical implants

Bjarne Tvete
Business Development Manager

12 juni 2018
215 tusen årlige kolon-kreft dødsfall i Europa kan reduseres ved help av Backscatter teknologien

The most deadly types of cancer in Europe in 2012

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Deaths in Thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>254.4</td>
</tr>
<tr>
<td>Colon and rectum cancer</td>
<td>113.4</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>92.2</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>61.6</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>52.0</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>131.2</td>
</tr>
<tr>
<td>Colon and rectum cancer</td>
<td>101.5</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>99</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>51.9</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>43.7</td>
</tr>
</tbody>
</table>

Source: European Journal of Cancer / J. Ferlay

113,400 menn + 101,500 kvinner = 215 tusen personer

Michigan stadium: 107,601 x 2 = 215 tusen personer
Energiforbruk og båndbredde begrenser dagens bruk av sensorer/implantater i kroppen
Backscatter reflekterende kommunikasjonsteknologi gir lavere energiforbruk og høyere båndbredde

Eksisterende kommunikasjons-enhet

- Mottaker
- Sender
- Elektronikk
- Sensorer

"Backscatter" kommunikasjons-enhet

- Refleksjonerende antenne
- Switch
- Elektronikk
- Sensorer
Ingen annen kommunikasjonsteknologi har lavt energiforbruk og høy datarate inne i kroppen

<table>
<thead>
<tr>
<th>Teknologi</th>
<th>Dybde i kroppen</th>
<th>Høy data rate (HD video mulig)</th>
<th>Lavt energiforbruk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tradisjonell aktiv sender</td>
<td>Inntil 150 mm</td>
<td>Inntil 300 kbps</td>
<td>15-45 mW</td>
</tr>
<tr>
<td>RFID</td>
<td>Inntil 20 mm</td>
<td>Inntil 10 kbps</td>
<td>30 nW</td>
</tr>
<tr>
<td>Refleksjon</td>
<td>Inntil 180 mm</td>
<td>Inntil 10 Mbps</td>
<td>30 nW</td>
</tr>
</tbody>
</table>
Treating lymphoma with TCR modified T cells

Arne Kolstad, Inven2
Treating lymphoma with TCR-modified T cells

Arne Kolstad
Dept of Oncology, OUH,
Chairman, Norwegian Lymphoma Group
Partner, KG Jebsen Center for Cancer
Immunotherapy, UiO
Identification of high-potency TCRs from healthy donor T cells (Johanna Olweus group)

Donor T cell

Patient HLA

Normal self Peptide (CD20p)

Donor TCR

Kumari et al.

Patient TCR


Kumari et al., PNAS 2014, Stronen et al., Science 2016

Research agreement Kite Pharma 2017-19
FDA-approved cell therapy in lymphoma: Chimeric antigen receptors (CARs) targeting the B-cell antigen CD19

- High initial response rate in lymphoma and leukemia patients
- In spite of 40-50% durable complete responses the cancer frequently comes back and often with decrease or loss of surface CD19 expression
Possible advantages and opportunities for TCRs

TCR

Cancer cell

CAR

Target localization

Target density

Signal
Novel cell product: A CD20-targeted T-cell receptor (TCR) for treatment of B-cell lymphoma

1. Patient T cells harvested
2. Retroviral stable permanent insertion of cancer-targeted TCR (DNA) in the lab
3. Re-infusion into patient for long-term killing of cancer cells

Target patient population: Relapsed incurable Non-Hodgkin B-cell lymphoma
CD20-specific TCRs kill patient leukemia and lymphoma cells

ORIGINAL ARTICLE

Targeting B cell leukemia with highly specific allogeneic T cells with a public recognition motif

IW Abrahamsen¹,²,³, E Stronen¹,²,³, S Wål, G Tjonnfjord³,⁴, M Toebes⁵, TN Schumacher⁶,⁷,⁸, and Johann Olweus⁹,¹⁰

T cells raised against allogeneic HLA-A2/CD20 kill primary follicular lymphoma and acute lymphoblastic leukemia cells

Shraddha Kumari¹,², Sébastien Wälchli¹,², Lars-Egil Fallang¹, Weiwen Yang¹,², Frida Ton N. Schumacher⁶,⁷,⁸, and Johann Olweus⁹,¹⁰

Alloreactive cytotoxic T cells provide decipher the immunopeptidome and a plethora of tumor-associated self-e

PNAS

Targeting B-cell neoplasia with T-cell receptors recognizing a CD20-derived peptide on patient-specific HLA

CD20-specific TCRs cures lymphoma in mice

3-4 wk

SLF (CD20p) → TCR-1

MC703 → HHD

TCR-2

T cells

TCR-1

Rejection: 9/9

TCR-2

Rejection: 8/8
Commercialization strategy

• Currently evaluating multiple commercialization strategies:
  - industrial co-development agreement (multiple interested parties)
  - establishing a company around this and other novel TCR development programs

• Orphan drug protection as primary market exclusivity strategy

• Potential for «method of use» patent protection
### Development plan

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
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<tbody>
<tr>
<td></td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>GMP production &amp; qualification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trial design &amp; regulatory approval</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation of first in man trial</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- First-in-man study to be performed at OUH for patients with relapsed incurable non-Hodgkin’s lymphoma (PI Arne Kolstad) starts 2020/21

- 8.0 MNOK funding obtained from NFR BIOTEK program.
- Seeking additional 2.0 MNOK private funding to complete financing of preclinical development stage
Key take home messages

• Highly innovative product

• Spectacular preclinical data

• Strong interest from pharma companies

• Project team with world-leading competence

• Large un-met medical need in patients with non-Hodgkin`s lymphoma
Principal Investigators K.G. Jebsen Center for Cancer Immunotherapy

Johanna Olweus – Director and PI
Ton Schumacher – PI
Fridtjof Lund-Johansen – PI
Kjetil Tasken – PI
Karl-Johan Malmberg - PI
Arne Kolstad – PI
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