IL1RAP as a therapeutic target

Göran Forsberg, CEO
Cantargia

- Specialized in antibody therapy/immunology, with initial focus on oncology
- Lead antibody CAN04 (nidanilimab) in clinical development
- Listed on Nasdaq Stockholm, approximately 5000 shareholders
- Based in Lund, Sweden at Medicon Village Science park
- Virtual company, with strong academic and corporate collaborations
IL-1 blockade - recent intriguing clinical data

CANTOS trial (>10000 pat)

- Canakinumab (anti-IL-1β)
- Reduced lung cancer incidence by 67% and death by 77%.

Canakinumab NSCLC phase 3 trials

Adjuvant NSCLC
After surgery, no mets, placebo control
1500 patients, recruitment ongoing
Completion 2021/22

First line (CANOPY-1)
Untreated locally advanced/metastatic
Combination Pembrolizumab/Platinum doublet
627 patients, start Dec 2018
Completion 2021/22

Second line metastatic (CANOPY-2)
Previously treated loc adv/metastatic
Combination Docetaxel
240 patients, start Dec 2018
Completion 2021

Source clinicaltrials.gov
CANTOS additional findings (from Canakinumab)

<table>
<thead>
<tr>
<th>CANCER decreased risk of death with treatment (high dose)</th>
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<tbody>
<tr>
<td>Lung cancer</td>
<td>77 %</td>
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<tr>
<td>Non-lung cancer</td>
<td>37 %</td>
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<table>
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<tr>
<th>Decreased incidence of inflammatory disease (all doses)</th>
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<tr>
<td>Arthritis</td>
<td>32%</td>
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<tr>
<td>Ostheoartritis</td>
<td>28%</td>
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<tr>
<td>Gout</td>
<td>53%</td>
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<td>Cardiovascular</td>
<td>12%</td>
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<tr>
<th>Biomarker levels (reduction)</th>
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<tr>
<td>CRP</td>
<td>26-41%</td>
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<tr>
<td>IL-6</td>
<td>25-43%</td>
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IL-1 is a “broad-spectrum” cytokine implicated in a number of inflammatory diseases

- IL-1 is released by tissues or the innate immune system to induce inflammation, IL-1 has highly pro-inflammatory properties and affect a large number of cells
- IL-1 is involved in several autoimmune diseases and is the dominant cytokine in autoinflammatory diseases
- Blocking drugs are on the market (anakinra, rilonacept, canakinumab)

Next step in IL-1 blockade?

- IL-1 blockade can be used to treat disease
- Approved for autoimmune/inflammatory disease
- Promising clinical data for cancer treatment/prevention
- Is IL-1β the optimal target?
- Advantages of receptor targeting?
- Antibodies against IL1RAP.
IL1RAP – IL-1 Receptor Accessory Protein

Low expression of IL1RAP on normal cells

- Low reactivity on monocytes and lymphocytes
- No significant tissue reactivity seen on normal tissue (frozen tissues FDA/EMA panel)
- Low-to-moderate expression on monocytes

- The highest expression is found on cancer cells
IL1RAP

- Three different systems signal through IL1RAP
- These systems contribute to various inflammatory diseases
- Can be blocked by antibodies against IL1RAP
The IL-33 and IL-36 signaling pathways - novel targets for several diseases

- IL-33 and IL-36 are barrier-associated cytokines highly expressed in skin and mucosal tissues.
- IL-33 is involved in allergic inflammation and Th2-responses
- IL-36 is heavily upregulated in inflamed skin and mediates e.g. certain psoriatic conditions
- No approved product on the market but several projects in preclinical or clinical phase
  - Allergy
  - Asthma
  - Atopic Dermatitis
  - Rhinosinusitis
  - Pustular psoriasis
  - Palmo-Plantar Pustulosis
  - Ulcerative Colitis
  - Crohn’s Disease
Unique binding properties of IL-1 and IL-33

Günther et al, Immunity 2017, 47, 510-523
<table>
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<th>Project</th>
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<td>CAN04</td>
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<td>Non-small cell lung cancer</td>
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CAN04 and CAN03 both inhibit IL-1β and IL-33 signaling but with different properties.

**CAN04**
Potent IL1β and IL33 inhibitor, but only blocks IL33 signaling partially.

**CAN03**
Less potent, but the binding mode allows full inhibition of IL1β and IL33 signaling.
CAN04 and CAN03 bind different domains of IL1RAP

Measurement of binding affinities to IL1RAP by SPR

<table>
<thead>
<tr>
<th>Antibody</th>
<th>$ka$ (1/M•s)</th>
<th>$kd$ (1/s)</th>
<th>$K_D$ (M)</th>
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<tbody>
<tr>
<td>CAN03</td>
<td>2.26E+05</td>
<td>7.25E-05</td>
<td>3.21E-10</td>
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<tr>
<td>CAN04</td>
<td>4.27E+05</td>
<td>4.72E-05</td>
<td>1.10E-10</td>
</tr>
</tbody>
</table>

Epitope mapping in collaboration with Eric Sundberg, University Maryland

Wang et al., 2010, Nature Immunology, 11, 905-912.
IL1RAP as a target in cancer
The original finding:
IL1RAP - a novel target on cancer cells

Leukemic cells from patients
Genomics & Bioinformatics
IL1RAP identified as upregulated on CML leukemia stem cells
Isolation of CML leukemia stem Cells based on IL1RAP expression

Production of a polyclonal anti-IL1RAP antibody (KMT1)
Selective killing of leukemia stem cells using antibodies
IL1RAP expressed in several tumor forms

Size of each indication corresponds to annual deaths in USA
Tumor inflammation – key to cancer progression

Enablers

Genomic instability and mutation (2000)

Tumor-promoting inflammation (2011)

Cancer hallmarks

Deregulating cellular energetics
Sustaining proliferative signaling
Evading growth suppressors
Resisting cell death
Enabling replicative immortality
Inducing angiogenesis
Activating invasion and metastasis
Avoiding immune destruction

The inflammatory cytokine IL-1
– Well established role in cancer progression:

Tumor cells
- Signaling/proliferation of cancer cells
- Chemoresistance

Tumor microenvironment
- Metastasis
- Crosstalk between tumor cells and stroma
- Inflammation and local suppression of the immune system


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CAN04 has generally been well tolerated

• 6 mg/kg is safe.

• Biomarker results (IL-6 and CRP) support target engagement already after two doses of CAN04.

• In a heavily pre-treated patient population, 5 of 13 patients (38%) had SD. One patient with NSCLC had SD for 6 months.

• Recently 10 mg/kg was shown to be safe (Dec 2018)
Phase I/IIa trial - NSCLC and pancreatic cancer

- Norway, Denmark, Netherlands and Belgium
- 22 patients treated, good safety
  - NSCLC, pancreatic cancer, colon cancer, triple negative breast cancer
- Phase IIa: focused on NSCLC and pancreatic cancer (appr 20 centres)
  - Monotherapy
  - Combination with standard therapy
    - NSCLC Cisplatin/Gemcitabine
    - Pancreatic cancer Gemcitabine/nab-paclitaxel

Details on www.clinicaltrials.gov

Q4 2018

Early 2020
Receptor blockade vs IL-1β blockade

Canakinumab
- Antibody directed against one of the two IL-1 ligands, IL-1β

CAN04
- Binds the common signaling receptor and counteracts both ligands
- Induce killing via the immune system (ADCC)
CAN04 - immuno-oncology mechanism with antitumor effect

- Antitumor effects in NSCLC PDX models
- CAN04 stimulates immune cells to infiltrate tumor
- (CAN04 not cross reactive with mIL1RAP)
Activity in AML

Blocking proliferation ex vivo

![Graph showing fold proliferation for AML5 and AML6 with isotype and mAb3F8.]

Treating AML (PDX) in vivo

![Graph showing % leukemic cells in BM with isotype and mAb81.2.]

AML5 AML6

0 1 2 3

Fold proliferation

Isotype mAb3F8

p=0.006 p=0.033

p<0.0001

p=0.006

p=0.033

p<0.0001
Inflammation and metastasis

- Cancer cells (seeds) need a good soil to form a metastasis
- The IL-1 system (inflammation) can provide such environment (soil)

A tumor can create its own “seed and soil”
CAN04 attacks several cell types in the tumor

Cancer cells

Tumor promoting immune cells

Metastatic cells
IL-1 and resistance to therapy

Interleukin-1 blockade overcomes erlotinib resistance in head and neck squamous cell carcinoma

Aditya Stanam1,2, Katherine N. Gibson-Corley1,5,6, Laurie Love-Homan2, Nnamdi Ihejirika1, Andrea L. Simons1,2,4,5,6

(Author list)

[Research article from 2002]

Autocrine Production of Interleukin-1β Confers Constitutive Nuclear Factor-kB Activity and Chemoresistance in a Novel Role for the Interleukin-1 Receptor Axis in Resistance to Anti-EGFR Therapy

Alexander Arlt1,2, Jens Vorndamm1,2, Susanne Heiner Schäfer1

Valerio Gelfo1,2,10, Martina Mazzeschi1,1, Giada Grilli1, Moshit Lindze1, Gabriele D’Uva6,8, Balázs Győrffy7,8, Andrea Ardizzone1, Yosef Yarden1,3, Mattia Lauriola1,2,3,9

Vassilis Georgoulas8, Rinat Zaynageldinov2,3,10,11 and Timothy S. Blackwell1,5,8,10

IRAK1 is a therapeutic target that drives breast cancer

Zhen Ning Wei1, Puay Leng Lee1, Dave S.B. Ho1

Neutrophil-Derived IL-1β Impairs the Efficacy of NF-κB Inhibitors against Lung Cancer

Alyson G. McLoed1, Taylor P. Sherrill2, Dong-Sheng Cheng2, Wei Han2, Jamie A. Saxon1, Linda A. Gleaves2, Pingsheng Wu2, Vassilis V. Polosukhin2, Michael Karin4, Fiona E. Yull1,5, Georgios T. Stathopoulos2,6,7,3,10,11

Vassilis Georgoulas8, Rinat Zaynageldinov2,3,10,11 and Timothy S. Blackwell1,5,8,10,11

Constitutive Prognosis and Chemoresistance in Pancreatic Ductal Adenocarcinoma

Daoxiang Zhang1, Lin Li1, Hongmei Jiang1, Brett L. Knolhoff1, Albert C. Lockhart1, Andrea Wang-Gillam1, David G. DeNardo1, Marianna B. Ruzinova2, and Kian-Huat Lim1

Serum levels of IL-6 and IL-1β can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer

S Mitsunaga1,2, M Ikeda1, S Shimizu1, I Ohno1, J Furuse2, M Inagaki3, S Higashi4, H Kato5, K Terao6 and A Ochiai7

Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlpr3 inflammasome and promotes tumor growth

Melanie Bruchand1,2,6, Grégoire Mignot1,2,3, Valentin Derangère1,2, Fanny Chalmin1,2, Angélique Chevriaux1,2,3,4,5, Wilfrid Boireau1, Benoît Simon3, Bernhard Ryffel1, Jean Louis Condat5, Jos2, François Martin1,2, Cédric Rébé3, Lionel Apetoh1,3,8 and François Ghiringhelli1,3,8

Dry cytokines defines resistance of inhibitors

María Teresa Rodía1,2, Michela Pucci1, Massimiliano Dall’Ora1,2, Rossella Solmi1, Lee Roth1, Moshit Lindzen1, Massimiliano a Bertotti1, Elisabetta Caramelli1, Pier-Luigi Lollini1, Livio Trusolino1, Fabrice D’Uva1,2,3,4,5,6 and Mattia Lauriola1,2,4,5,6

Cantargia
NSCLC CAN04/Cisplatin combination

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<th></th>
<th>Control</th>
<th>CAN04</th>
<th>Cisplatin</th>
<th>Combination</th>
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<tbody>
<tr>
<td>Animals withdrawn</td>
<td>20 % (Tumor)</td>
<td>0 %</td>
<td>50 % (Toxicity)</td>
<td>20 % (Toxicity)</td>
</tr>
<tr>
<td>Tumor reduction</td>
<td>N/A</td>
<td>14%</td>
<td>18%</td>
<td>52 %</td>
</tr>
<tr>
<td>Comment</td>
<td>Highest tumor burden</td>
<td>Best safety</td>
<td>Highest toxicity</td>
<td>Superior efficacy and reduced toxicity</td>
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Combination CAN04/Cisplatin superior to individual agents
- Reduction in severe toxicity
- Increased efficacy
# Cantargia pipeline

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Three different systems signal through IL1RAP. These systems contribute to various inflammatory diseases and can be blocked by antibodies against IL1RAP.

Cantargia partnership with Panorama Res Inc (Sunnyvale, CA)
IL1RAP summary

• IL1RAP is a novel target for antibody therapy
• IL-1, IL-33 and IL-36 use IL1RAP for signaling
• IL-1 and IL-33 function through distinct binding
• Generating antibodies blocking various function of these cytokines
• CAN04 is entering phase IIa clinical trials in NSCLC and pancreatic cancer