Reprogramming cancer
4SC-202 and resminostat are impacting tumor antigen presentation and overcoming immune tolerance

July 23rd 2015
EPIGENETIC REPROGRAMMING OF CANCER CELLS WITH RESMINOSTAT AND 4SC-202

RESMINOSTAT AND 4SC-202

Change of gene transcription

TUMOR CELL

Targeting “Cancer Stem Cells”

Combination therapy (e.g. with sorafenib in HCC)

Immune priming (e.g. together with PD-1/PD-L1)

Monotherapy of haematological cancers (e.g. in CTCL)
RESMINOSTAT – TARGETING IN PARTICULAR HDAC 6

IC50 in molar [M]

Resminostat

1,00E-08
1,00E-07
1,00E-06
1,00E-05

HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7, HDAC8, HDAC9, HDAC10, HDAC11
**Niche indication CTCL**
- **Goal:** 1st HDAC inhibitor in EU, potential filing for conditional approval in 2019
- **Planned 4SC study:** reduced risk, fast to EU market opportunity

**Blockbuster indication HCC**
- **Data from Yakult’s ongoing Phase II in HCC & NSCLC in Japan**
- **Basis for potential pivotal HCC study in Western patients**

**Upside potential: immune priming**
- **Goal:** Development of resminostat in combo with checkpoint inhibitor(s)

**Near term goal**

**Mid term value option**

**The future**
RESMINOSTAT CLINICAL SAFETY SHOWN IN MORE THAN 250 PATIENTS TO DATE

- Resminostat was well tolerated in general
- The most frequent adverse events were GI disorders (nausea, vomiting, diarrhoea), fatigue, and thrombocytopenia
- The majority of adverse events were mild to moderate, manageable and reversible
- So far, no significant effect of resminostat on the cardiovascular system was observed
RESMINOSTAT CLINICAL EFFICACY – PHASE II

Monotherapy

<table>
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<tr>
<th>Combination Therapies</th>
<th>Hodgkins Lymphoma (HL)</th>
<th>Liver Cancer (HCC) 2nd line</th>
<th>Liver Cancer (HCC) 1st line</th>
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<tr>
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- **Resminostat efficacy in monotherapy**
  - Relapsed Hodgkin’s lymphoma: 34% ORR (1 CR, 11 PR*), 54% disease control rate
    - 69% reduction in tumor lesions

- **Resminostat efficacy in combination with sorafenib**
  - Relapsed/refractory HCC: 62.5% PFS rate after 6 treatment cycles,
    - median TTP 6.5 mths, median OS 8.0 mths

- **Biomarker ZFP64 shows potential to predict resminostat responses**
  
* Including partial metabolic responders
Tumor lesion reductions in 69% of patients,
- 1 CR and 11 PR*,
- disease control rate of 54%

* Including partial metabolic responders
### RESMINOSTAT: GLOBAL ROADMAP FOR BROAD DEVELOPMENT

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- **Phase II (OS & ZFP64), Asia**
- **Phase III, Japan & Asia**
- **Pivotal (incl ZFP64), EU & US**
- **Phase I/II, Japan**
- **Phase I/II, Japan**
- **Phase III**

* Estimation for Yakult trials by 4SC Management

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* Estimation for Yakult trials by 4SC Management

- **Ongoing studies**
- **In preparation**
- **Further potential studies**
- **Potential Filing for Conditional Approval**
Normal somatic cells must undergo extensive and complex changes in order to gain the ability to initiate cancer.

Epigenetic mechanisms are able of concurrent and concerted regulation of many cellular processes ➔ epigenetic mutations can account for a significant part of cancer hallmarks at once.
Additionally to tumor cells solid tumors are comprised of fibroblasts and immune cells:

- Tumor promoting (MDSC, TAM, Treg)
- Potentially tumoricidal (CTL, NK cells), but in suppressed state
### IMMUNOTHERAPY OF CANCER

#### Challenges

**LOW IMMUNOGENICITY**
- Poor systemic anti-tumoral response

**Pronounced immunosuppression**
- Unspecific mechanisms: e.g. IDO, ARG
- T cell brakes, e.g. immune check points

#### Therapy Approach

- **Enhancement of NK cell recognition and killing**
- **Enhancement of tumor specific T cell response**
- **Inhibition of IDO, ARG**
- **Immune check point inhibitors**

- **PD1/PD-L1 antibodies** block the inhibitory T cell signaling allowing anti-tumoral attack by *existing* but suppressed tumor specific T cells

**Challenges:**

- Low or non-existent anti-tumoral T cell response
- Unspecific immunosuppressive mechanisms in tumor microenvironment
Resminostat has demonstrated the ability to:

- Enhance expression of tumor associated antigens
- Enhance recognition and killing of tumor cells by NK cells
- Increase anti-tumoral immune response
- Reduce unspecific immunosuppression
- Allow attack on tumor by activated tumor-specific T cells
RESMINOSTAT AS A PRIMING AGENT FOR PD1/PD-L1 BLOCKADE

- Resminostat has demonstrated the ability to:
  - Enhance expression of tumor associated antigens
  - Enhance recognition and killing of tumor cells by NK cells
- Increase anti-tumoral immune response
  - Reduce unspecific immunosuppression
- Allow attack on tumor by activated tumor-specific T cells
Tumor associated antigens (TAA) are expressed on tumor cells but silent in normal tissue

Anti-tumoral T cell response can be enhanced by up-regulation of TAA expression

<table>
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<tr>
<th>selected TAA</th>
<th>A549 lung</th>
<th>HepG2 liver</th>
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RESMINOSTAT IS ABLE TO ENHANCE EXPRESSION OF TUMOR ASSOCIATED ANTIGENS IN TUMOR CELL LINES OF VARIOUS ORIGIN
RESMINOSTAT ENHANCES MHC CLASS I EXPRESSION

- TAA have to be presented to T cells on MHC class I molecules (HLA A-F)
- Anti-tumoral T cell response can be enhanced by up-regulation of TAA presentation on MHC class I molecules

RESMINOSTAT IS ABLE TO ENHANCE EXPRESSION OF MHC CLASS I MOLECULES
RESMINOSTAT ENHANCES NK CELL RECOGNITION

- NK cells recognize tumor cells by expression of NKG2D ligands (MICA/B, ULBP1-3)
- Increased expression of NKG2D ligands enhance recognition and killing of tumor cells by NK cells

RESMINOSTAT UPREGULATES EXPRESSION OF NKG2D LIGANDS ON VARIOUS TUMOR CELL LINES
RESMINOSTAT ENHANCES NK CELL KILLING

- Increased expression of NKG2D ligands enhances recognition and killing of tumor cells by NK cells

RESMINOSTAT STRONGLY BOOSTS NK CELL MEDIATED CELL CYTOTOXICITY
RESMINOSTAT UPREGULATES MHC CLASS II AND COSTIMULATORY MOLECULES ON TUMOR CELLS

- Co-Expression of MHC class II (HLA-DO, -DP and -DM) and co-stimulatory molecules for T cells (4-1BBL, CD70) has the potential to convert tumor cells into “unprofessional” APC → induction and enhancement of tumor-specific CD4\(^+\) T cell response

RESMINOSTAT IS ABLE TO ENHANCE EXPRESSION OF MHC CLASS II AND CO-STIMULATORY MOLECULES POTENTIALLY CONVERTING TUMOR CELLS INTO “UNPROFESSIONAL” APC
Resminostat has demonstrated the ability to:

- Enhance expression of tumor associated antigens
- Enhance recognition and killing of tumor cells by NK cells
- Increase anti-tumoral immune response
- Reduce unspecific immunosuppression
- Allow attack on tumor by activated tumor-specific T cells
RESMINOSTAT REDUCES IDO AND ARGINASE EXPRESSION

- IDO and arginase deplete the surroundings of Trp and Arg, respectively; both amino acids are essential for T cell function

<table>
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<tr>
<th>RESMINOSTAT IS ABLE TO REDUCE ARGINASE1 AND INDUCIBLE AS WELL AS CONSTITUTIVE EXPRESSION OF IDO1 IN VARIOUS TUMOR CELL LINES</th>
<th>IDO</th>
<th>ARG</th>
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<td>A549 lung</td>
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RESMINOSTAT BIASES T HELPER STATUS TO TH1

- TH1 (IFN-\(\gamma\)) response is beneficial, whereas TH2 (IL-4), and Treg (Foxp3, IL-10) responses are adverse for cancer therapy

RESMINOSTAT BIASES PBMC TOWARDS TH1 BY ENHANCING TH1 AND REDUCING TH2 AND Treg SIGNATURE
SUMMARY: RESMINOSTAT AS IMMUNE PRIMING AGENT FOR CANCER IMMUNOTHERAPY
SUMMARY: RESMINOSTAT AS IMMUNE PRIMING AGENT FOR CANCER IMMUNOTHERAPY

RESMINOSTAT ENHANCES NK CELL RECOGNITION AND KILLING, TAA EXPRESSION AND PRESENTATION, AND REDUCES UNSPECIFIC IMMUNOSUPPRESSIVE MECHANISMS
SUMMARY: RESMINOSTAT AS IMMUNE PRIMING AGENT FOR CANCER IMMUNOTHERAPY

RESMINOSTAT ENHANCES TUMOR IMMUNOGENICITY ➔ NON/LOW IMMUNOGENIC TUMORS BECOME IMMUNOGENIC
HOWEVER: UPREGULATION OF PD-L1 IS A COMMON ESCAPE MECHANISM FOR IMMUNOGENIC CANCER
SUMMARY: RESMINOSTAT AS IMMUNE PRIMING AGENT FOR CANCER IMMUNOTHERAPY

COMBINATION OF PD-1/PD-L1 BLOCKADE WITH RESMINOSTAT:

- INCREASE THE EFFICACY OF PD-1/PD-L1 BLOCKADE
- EXPAND INDICATIONS TO NON/LOW-IMMUNOGENIC TUMORS
Increase the rate of durable remissions in patients with only limited anti-tumoral response by combination of resminostat and immunotherapies

- Diagnosis
- Immuno Priming by Resminostat
- Immunotherapy
- Response

E.g. potential in HL, renal, NSCLC, melanoma

Broaden the spectrum of indications to render non-immunogenic tumors more responsive by combination of resminostat and immunotherapies

- Diagnosis
- Immuno Priming by Resminostat
- Immunotherapy
- Response

E.g. potential in CRC, HCC, further indications
4SC-202 inhibits LSD1 activity
- Alpha-screen
- (Sub)micromolar IC50

4SC-202 specifically inhibits HDAC1/2/3
- Submicromolar IC50

LSD1 Activity (Alpha-screen)

IC50 = 1.2µM

4SC-202 – IC50
LSD1 INTERACTION AND INHIBITION

- 4SC-202 binds to LSD1 (model) and completely inhibits LSD1 activity in LSD1/CoREST complex
  - More physiological conditions in complex
Complete response in patient with T-NHL (AITL)

Patient on study medication for 28 months
4SC-202 IS A POTENT INHIBITOR OF HH SIGNALING

- SMO dependent medulloblastoma cell line (DAOY)
  - Stimulation by SHH or SAG
  - Vismodegib and 4SC-202 are active

Western Blot
SMO-INDEPENDENT HH SIGNALING

- 4SC-202 is a potent inhibitor of smo-independent HH signaling
  - mRNA and protein level; SUFU depleted cells (smo-independent activity)
4SC-202 IN VITRO PD - STEMNESS

- 4SC-202 blocks clonogenic capacity of HepG2 cells when pre-treated with IC50 concentrations on 2D layer for 2 days

Pre-treatment with 4SC-202 inhibits clonogenic growth of HepG2 cells.
4SC-202 has the potential to change our view of cancer therapies.

Treatment targeting cancer stem cells offer a broad range of novel therapeutic opportunities in hematological and solid cancer types for:

- Combination therapies
- Adjuvant therapy
- Neo-adjuvant therapy

Targeting long-term survival and quality of life of cancer patients.
EPIGENETIC REPROGRAMMING OF CANCER CELLS WITH RESMINOSTAT AND 4SC-202

- Targeting “Cancer Stem Cells”
- Combination therapy (e.g. with sorafenib in HCC)
- Monotherapy of haematological cancers (e.g. in CTCL)
- Change of gene transcription

4SC-202
Resminostat

Immune priming (e.g. together with PD-1/PD-L1)
Resminostat and 4SC-202
Resminostat and 4SC-202
THANK YOU VERY MUCH!

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