Genistein-SSDH*)

A phase II ready compound

Potential utility in the treatment of pancreatic cancer

US BIO 2014

*)crystalline genistein sodium salt dihydrate
Why develop genistein for pancreatic cancer?

• Genistein: a well studied and safe compound
• Genistein is efficacious in animal models of pancreatic cancer either as monotherapy or in combination with gemcitabine
  – Decreases size of primary tumor & enhances the effects of gemcitabine
  – Inhibits metastasis
• Multi-targeted mechanism of action
  – ERβ a tumor suppressor gene
  – Multikinase inhibitor
  – NF-κB, matrix metalloproteinases, topoisomerase II

Competitive advantage: a unique multi-targeted mechanism of action
Pathophysiology of pancreatic cancer requires a multi-targeted approach

- Highly heterogeneous disease
- Successive genetic mutations over time
- On average 63 genetic mutations
- Up to 12 key signalling pathways affected
- Current treatments largely ineffective

Mono-targeted therapies unlikely to be efficacious

Poor pharmaceutical properties of the native crystalline form of genistein have hampered development efforts

• Poorly soluble in aqueous solutions/buffers
• Dissolution rate properties not optimal
• Poor oral bioavailability

Pharmacological effect of native genistein limited by low exposure levels
A comprehensive solid form screen identified genistein-SSDH as a clinical development candidate

• Water solubility substantially increased
• Stable at room temperature & not hygroscopic
• Straight forward large scale manufacturing process already in place
• US patent already granted on genistein-SSDH and PCT applications of 10 more solid forms in national phases in major markets
• Oral bioavailability improved 5-fold over native crystalline form

The novel crystalline form removes the limitations of native genistein
Summary of pre-clinical data
Preclinical tox studies have demonstrated that genistein is a safe compound

- Genetic toxicity
  - Genistein is not mutagenic or clastogenic.

- Rats
  - Genistein daily for 1 year NOAEL\(^\text{1)}\) not reached at 50mg/kg/day\(^\text{2)}\)

- Dogs
  - Genistein daily for 1 year NOAEL\(^\text{1)}\) not reached at 500 mg/kg/day\(^\text{3)}\)

- Swedish Medicinal Products Agency
  - No safety / tox data needed for initiation of Axcentua phase Ib/IIa trial

\(^{1)}\text{No Adverse Effect Level}\)

\(^{1)}\) McClain R.M. et al., (2006), Genetic toxicity studies with genistein. Food and Chemical Toxicology; 44: 42-55


Genistein have chemosensitizing properties enhancing the effect of gemcitabine

A

ICR SCID mice (Female; 4 - 6 wks. old; n = 56)
COLO 357/L3.8pl (2 x 10⁶ cells / 20µl, orthotopic)

Rx schedule:

- Gemcitabine
- Gemcitabine
- Gemcitabine

Day-1  Day-3  Day-5  Day-10  Day-13  Sacrifice

Genistein

B

COLO 357

L3.8pl

Pancreas wt (gms)

Control  Gemcitabine  Genistein  Gemcitabine + Genistein

n = 5  n = 6  n = 7  n = 6

n = 7  n = 7  n = 5  n = 7

n denotes the number of tumors analysed in each group

*P < 0.01, combination treatment vs single agent and untreated control.

Conclusions pre-clinical studies

- Genistein is a safe compound
- Genistein is efficacious in animal models of pancreatic cancer either as monotherapy or in combination with gemcitabine
  - Decreases size of primary tumor & enhances the effects of gemcitabine
  - Inhibits metastasis
- Genistein-SSDH shows increased oral bioavailability (AUC and Cmax) in a comparative dog study with native form of genistein
How does this translate to humans?
Phase Ib study out-line

Phase Ib/IIa trial in pancreatic adenocarcinoma
Genistein-SSDH (G-SSDH) in combination with gemcitabine

Pre-treatment
- G-SSDH**)

Chemosensitization
- Gemcitabine*)
- G-SSDH**)

Chemoprevention
- Gemcitabine*)
- G-SSDH**)

*) i.v. once a week
**) p.o. twice a day

#) http://clinicaltrials.gov/ct2/show/NCT01182246?term=Axcentua&rank=1
Majority of **hematologic** adverse events of only mild or moderate severity*

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>None Grade 0</th>
<th>Mild Grade 1</th>
<th>Moderate Grade 2</th>
<th>Severe Grade 3</th>
<th>Life-threatening Grade 4</th>
<th>Total</th>
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<tbody>
<tr>
<td>Granulocytes</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1a)</td>
<td>16</td>
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<tr>
<td>Hemoglobin</td>
<td>0</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>16</td>
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<tr>
<td>Leucocytes</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>16</td>
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<tr>
<td>Platelets</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Percentage</td>
<td>33%</td>
<td>28%</td>
<td>28%</td>
<td>9%</td>
<td>2%</td>
<td>100%</td>
</tr>
</tbody>
</table>

a) One brief episode of granulocytes = 0.2 without fever

*Study on-going. Data from 16 patients evaluated in June 2014. Three patients still receiving treatment.
No life-threatening non-hematologic adverse events*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>None Grade 0</th>
<th>Mild Grade 1</th>
<th>Moderate Grade 2</th>
<th>Severe Grade 3** (patient number, #)</th>
<th>Life-threatening Grade 4</th>
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</thead>
<tbody>
<tr>
<td>Anorexia</td>
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<td>0</td>
<td>1</td>
<td>1 (#108)</td>
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</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>1 (#108)</td>
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<tr>
<td>Vomiting</td>
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<td>1</td>
<td>0</td>
<td>1 (#109)</td>
<td>0</td>
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<tr>
<td>Fatigue</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>1 (#108)</td>
<td>0</td>
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<tr>
<td>Infection</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>1 (#201)</td>
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<tr>
<td>Cholangitis</td>
<td>13</td>
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<td>0</td>
<td>1 (#102)</td>
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<td>Ascites</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>1 (#201)</td>
<td>0</td>
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</table>

*Study on-going. Data from first 14 patients.
** Four out of 14 patients account for all grade 3 toxicities.
Genistein-SSDH shows early signs of efficacy in Phase Ib study

- Sixteen patients enrolled
- Dose escalation of genistein-SSDH from 400 mg to 1600 mg in combination with gemcitabine
- Seven patients had a time to progression (TTP) > 3 months* (range 3.5 to 10.9 months). Tumor progression still not obtained in three patients
- Six patients had an overall survival (OS) > 6 months* (range 6.3 to 18.3 months).

*Study on-going. Data from first 14 patients. Time to progression (TTP) and overall survival (OS) with gemcitabine mono-therapy typically 3 and 6 months, respectively.
The improved bioavailability of genistein-SSDH enables the targeting of multiple pathways\(^1\)

**Kinases**
- EGFR
- PDGFR
- PDGFRB
- c-KIT

**ERβ**
- Low plasma levels

**NF-κB**
- Low plasma levels

**MMPs**

\(^1\) PK analysis. Cmax and AUC calculated from Axcentua phase Ia clinical trial data (on file)
Key takeaways – genistein-SSDH

• Unique mechanism of action
  – Multi-targeted affecting several key targets implicated in pancreatic cancer (ERβ, topoisomerase II, c-Kit, EGFR, PDGFRA, PDGFRB kinases, MMPs, NF-κB)
  – Shown in pre-clinical animal studies to enhance the effect of gemcitabine decreasing the size of primary tumor and inhibiting metastasis
• Favorable toxicity profile in pre-clinical animal models
• US patent granted
• Straight forward manufacturing of API and capsules or tablets
• Safe and well-tolerated with early signs of efficacy in Axcentua’s clinical phase Ib study

Continued clinical evaluation warranted
Next step: A Phase IIa study already approved by Swedish Medical Product Agency¹)

- **Objective**
  - Provide efficacy and safety data to permit planning of a possible randomized phase IIb trial.

- **Study design**
  - **Open-labeled study**: assess the effect of genistein-SSDH in combination with gemcitabine.
  - **Primary efficacy endpoint**: overall survival (OS).
  - **Secondary efficacy endpoints**: time to progression (TTP) and objective response (OR).
  - **Safety**: incidence of treatment-related adverse events (AEs) and serious adverse events (SAEs).

- **No of patients**
  - 20 new patients permitting an evaluation of efficacy based on altogether 36 patients.

- **Cost and time-line**
  - Trial related costs: $1-1.5 Million
  - Patient enrolment 18 months assuming 2 sites in Sweden

¹) [https://clinicaltrials.gov/ct2/show/NCT01182246?term=axcentua&rank=1](https://clinicaltrials.gov/ct2/show/NCT01182246?term=axcentua&rank=1)
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Thank you!