Discovery and Development of Next Generation Epigenetic DNMT Inhibitors: Development of SGI-110, a novel DNMT inhibitor

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- Employee of: NA

I will discuss off label use and/or investigational use in my presentation.
Epigenetics

• Mitotically stable changes in gene expression, thought to be irreversible
• Differentiation, stem cells vs. committed cells, X-inactivation, imprinting, germ cell restriction
• Phenotypic differences

The epigenome: Signals that are necessary (?) sufficient) to establish and/or perpetuate an epigenetic state; DNA methylation, histone marks

Evidence for Cancer as an Epigenetic Disease

• The marks are abnormal: DNA methylation and histone patterns
  • Variable in different cancers
  • Affect critical genes
• The readers/writers are genetically targeted in some cancers
  • DNA methylation regulators (DNMT3a, TET2, ? IDH1/2)
  • Histone modifiers (MLL1-3, UTX2, EZH2 etc.)
  • Chromatin regulators (SNF5 etc.)
Epigenetic Silencing Mechanisms

DNA Methylation and Histone H3-K9 Methylation Dependent Gene Silencing Loop

- DNA methylation
- DNA Methyl Binding Protein binding
- Recruitment of HDAC
- Recruitment of HMT
- Histone H3-K9 Methylation
- Recruitment of DNMT
- Recruitment of HP1
- Histone H3-K27 Tri-Methylation

Histone H3-K27 Tri-Methylation Dependent Gene Silencing

- Recruitment of PcG (e.g. PRC2)
  - HDAC
  - EZH2
- Histone H3-K27 Tri-Methylation
- Recruitment of PcG (e.g. PRC1)
- Gene silencing

Yutaka Kondo, Cancer & Metastasis Rev., 2007
<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Trade Name</th>
<th>Mechanism of Inhibition</th>
<th>Clinical Trials (Cancer)</th>
<th>FDA Approval</th>
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<td>5-aza-2’-deoxycytidine SuperGen</td>
<td>Dacogen</td>
<td>DNMT; incorporation into DNA (IV delivery)</td>
<td>Yes</td>
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<td>5-azacytidine Celgene</td>
<td>Vidaza</td>
<td>DNMT; incorporation into RNA &amp; DNA (IV delivery)</td>
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<td>Decitabine dinucleotide SuperGen</td>
<td>SGI-110</td>
<td>DNMT (SC delivery)</td>
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<td>Zebularine (NCI)</td>
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<td>No (preclinical)</td>
<td>Yes (antiarrhythmic)</td>
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<tr>
<td>Procaine</td>
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<td>Yes (anesthetic)</td>
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<td>Hydralazine</td>
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<td>Unknown (DNMTs and other enzymes?)</td>
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<td>Yes (vasodilator)</td>
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Epigenetic Therapy: Clinical Results

• DNA methylation inhibitors
  • Response rates of 10-70% in MDS, AML and CML; Side-effects primarily myelosuppression
  • Prolong survival in MDS compared to supportive care or chemotherapy
  • Anecdotal responses in solid tumors – response rate not well defined yet

Issa, CCR 2009
Decitabine

• Hypomethylation is induced in nearly every patient
  • Only sustained hypomethylation correlates with response

• Gene expression induction is variable
  • Correlates with response
Hypomethylation After Decitabine

Days
\[\text{p15 methylation \%} \]

\[\text{P15/CDKN2B} \quad \text{MiR124a} \]

% Change in Methylation

Oki, Blood 2007; Castoro, submitted
Gene Induction After Decitabine

**P15/CDKN2B**

- CR
- non-CR

**MiR124a**

*Oki, Blood 2007; Castoro, submitted*
SGI-110: Background

- Decitabine is a potent, well-characterized hypomethylating agent.
- Lacks optimal drug stability: rapidly eliminated in plasma by Cytidine Deaminase (CDA). This limits drug exposure time to cancer cells \textit{in vivo}.
- SGI-110 was designed to increase the \textit{in vivo} efficacy of decitabine by incorporating it into a guanine dinucleotide.
SGI-110 Structure

• Dinucleotide of Decitabine and Deoxyguanosine
SGI-110 Improves Stability of Decitabine

- Increases half-life
- Improves bioavailability
- Lowers dose requirement
- Prevents degradation by CDA

Stability of S110 vs. Decitabine

Fig 2: (A) Recombinant CDA (0.1 unit) incubated with decitabine or S110 (0.2 mmol/L) at 38°C, and percent substrate remaining determined by HPLC. (B) Compounds incubated at 37°C in PBS, and absorbance of each measured over time.

Plasma stability

Fig 5: Stability of S110 and decitabine over time in human serum. PNPP and Eucatropine are assay controls.

SGI-110: Better Formulation Development

- Two-vial kit – “Ready to Reconstitute” product
- Easy reconstitution and solubility
- Designed for SQ injection
- Safe composition: all excipients are GRAS
- Very small Injection volume: 100 mg/mL
- Stability: solution stable for 1 month

<table>
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<tr>
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<th>SGI-110 Lyophile reconstituted with</th>
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<tr>
<td>Composition</td>
<td>Water For Injection</td>
</tr>
<tr>
<td>SGI-110 solubility in diluent</td>
<td>~20 mg/mL</td>
</tr>
<tr>
<td>Injection volume, @ 25 mg dose given subcutaneously</td>
<td>&gt; 1 mL</td>
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<tr>
<td>Stability of reconstituted solution</td>
<td>Unstable, degrades even at refrigerated conditions</td>
</tr>
<tr>
<td></td>
<td>Non-aqueous formulation</td>
</tr>
<tr>
<td></td>
<td>~130 mg/mL</td>
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<tr>
<td></td>
<td>&lt; 1 mL</td>
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- Stable solution formed
SGI-110 Improves Tolerability * * 

In Vivo

![Graph showing percent weight loss over days with Decitabine and SGI-110.]

- Concentration value of SGI-110 given in molar equivalent of Decitabine.
- (6 mice dosed 3 times weekly IV)

Chuang et al. 2010 Molecular Cancer Therapeutics
Sustained Hypomethylation, Less Frequent Administration

Methylation Results in Monkeys
(Weekly SQ Regimen on D1, D8, D15)

- Significant decrease (p<0.05) in global methylation with once weekly dosing for up to 4 weeks
- Recovery trend 14 days after third dose
SGI-110 vs Decitabine: Methylation in Monkeys 5-Day regimen

Similar or better hypomethylation with SGI-110 at lower doses
SGI-110 vs Decitabine: Hematology in Monkeys
5-Day regimen

Less hematological suppression with SGI-110 at lower doses
Better Antitumor activity of SGI-110 in Solid Tumors Cisplatin-Resistant Ovarian Xenografts (A2780/CP70)

![Graph showing tumor size over days for different treatments.]

- **Vehicle (PBS, IP, Q7D)**
- **Cisplatin (6 mg/kg, IP, BIW)**
- **Decitabine (5 mg/kg IP, Q7D)**
- **SGI-110 (12.2 mg/kg IP, Q7D)**

*equal molar concentration*
A Phase 1, Dose Escalation, Multicenter Study of Two Subcutaneous Regimens of SGI-110, a DNA Hypomethylating Agent, in Subjects with Intermediate-2 or High-Risk Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML)
Study Design

• Multicenter
• Open Label, Randomized, Dose Escalation and Dose Expansion Segments (PK-PD Adaptive Escalation)
• Primary Objectives:
  - **Dose Escalation Segment**
    Population: Relapsed or refractory intermediate-2 or high-risk MDS or relapsed or refractory AML patients
    - Determine safety profile, including DLT’s
    - Determine the dose and regimen(s) for the dose expansion segment
    - Determine MTD or Biologically Effective Dose (BED)
  - **Dose Expansion Segment**
    Population: Relapsed or refractory MDS and AML (as above) and Treatment naïve MDS and Treatment naïve elderly AML (≥65 yrs)
    - Treatment naïve AML subjects must also meet additional specific entry criteria
    - Evaluate the activity of SGI-110 as measured by overall remission rate
Study Design

Relapsed or Refractory Intermediate-2 to High Risk MDS or Relapsed or Refractory AML; ECOG PS 0–2

Regimen 1
Daily SC Days 1–5 of a 28-day course

Regimen 2
Weekly SC x 3 of a 28-day course

PK – PD Assessments
C_{max}, AUC, Global Hypomethylation, Gene Re-Expression Studies

Escalation to Optimal Biological Effective Dose (BED) OR Maximum Tolerated Dose (MTD)
Study Design – Unique Features

• Randomization between 2 schedules

• Rapid dose escalation based on pharmacokinetics of both SGI-110 and decitabine

• Dose escalation stops at MTD or Biologically Effective Dose (whichever comes first)

• BED defined based on hypomethylation induction (LINE1, P15, miR124) and gene activation (P15, miR124)
Trial Status Update

As of 7 March 2011

• 3 active sites (MDACC, USC, Cornell)
• First Cohort Regimen 1 and Regimen 2 fully enrolled
  • No DLTs; PK allows further escalation
• Cohort 2 opened 02 Mar 2011
  • Two subjects in Cohort 2 dosed
  • One additional subject consented

<table>
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<tr>
<th></th>
<th>Total</th>
<th>AML</th>
<th>MDS-Int 2</th>
<th>MDS-HR</th>
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<td>Weekly</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Daily</td>
<td>4</td>
<td>3</td>
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Next Generation DNMT Inhibitor
SGI-110 Summary

• Intelligent design of a nucleotide for better more stable release of decitabine in vivo
• Several areas of potential improvement (based on preclinical data):
  - More convenient low volume SQ formulation
  - Less frequent administration
  - Sustained hypomethylation
  - Potential improvement in efficacy and/or safety
  - Potential development in solid tumors
  - Potential development as immunotherapy
• Clinical Phase I/II trial initiated
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