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

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Disclosure Information

Jean-Pierre Issa

I have the following financial relationships to disclose:

- Consultant for: *GSK, Syndax*
- Speaker's Bureau for: NA
- Grant/Research support from: *Eisai, Celgene, Merck, Supergen*
- Stockholder in: NA
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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**

Morgan *et al. Nat Genetics* 23, 314 (1999)

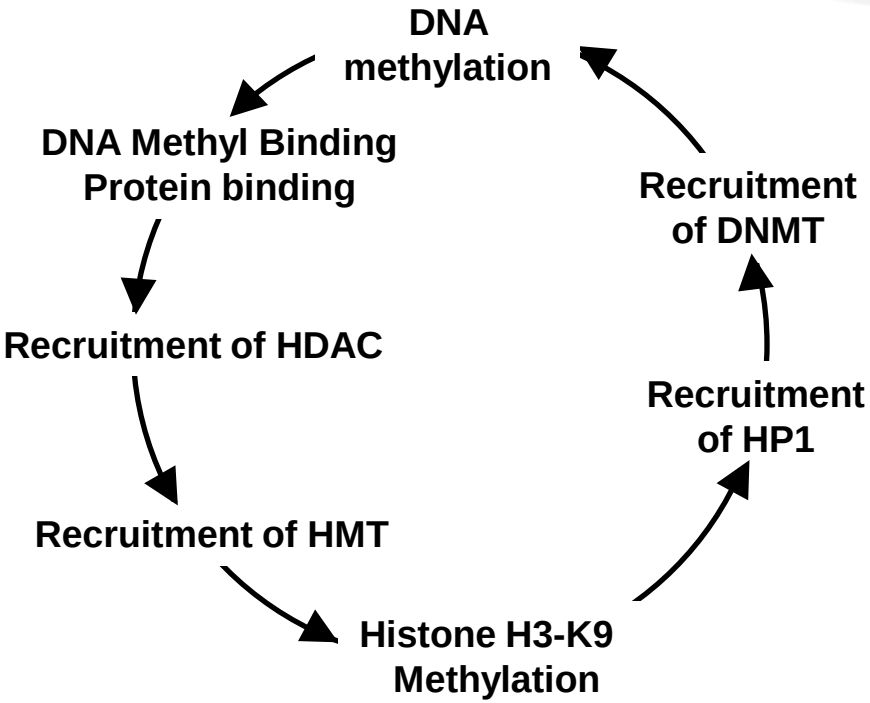
The epigenome: Signals that are necessary (? sufficient) to establish and/or perpetuate an epigenetic state; DNA methylation, histone marks

Evidence for Cancer as an Epigenetic Disease

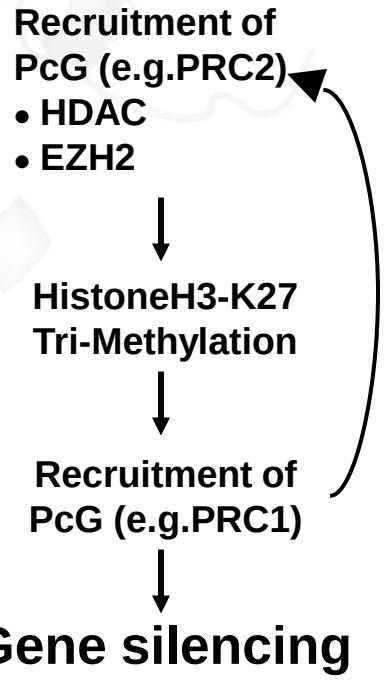
- The marks are abnormal: DNA methylation and histone patterns
  - Variable in different cancers
  - Affect critical genes
- The readers/writers are genetically targeted in some cancers
  - DNA methylation regulators (DNMT3a, TET2, ? IDH1/2)
  - Histone modifiers (MLL1-3, UTX2, EZH2 etc.)
  - Chromatin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

Epigenetic Silencing Mechanisms

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



Histone H3-K27 Tri-Methylation Dependent Gene Silencing



Yutaka Kondo, Cancer & Metastasis Rev., 2007

DNA Methylation Inhibitors

Inhibitor	Trade Name	Mechanism of Inhibition	Clinical Trials (Cancer)	FDA Approval
5-aza-2'-deoxycytidine SuperGen/Esai	Dacogen	DNMT; incorporation into DNA (IV delivery)	Yes	Yes
5-azacytidine Celgene	Vidaza	DNMT; incorporation into RNA & DNA (IV delivery)	Yes	Yes
Decitabine dinucleotide SuperGen	SGI-110	DNMT (SC delivery)	Yes	No
Zebularine (NCI)		DNMT (oral delivery)	No (preclinical)	No
Procainamide		Unknown (CpG-rich sequences?)	No (preclinical)	Yes (antiarrhythmic)
Procaine		Unknown (CpG-rich sequences?)	No (preclinical)	Yes (anesthetic)
Hydralazine		Unknown (DNMTs and other enzymes?)	Yes	Yes (vasodilator)

Epigenetic Therapy: Clinical Results

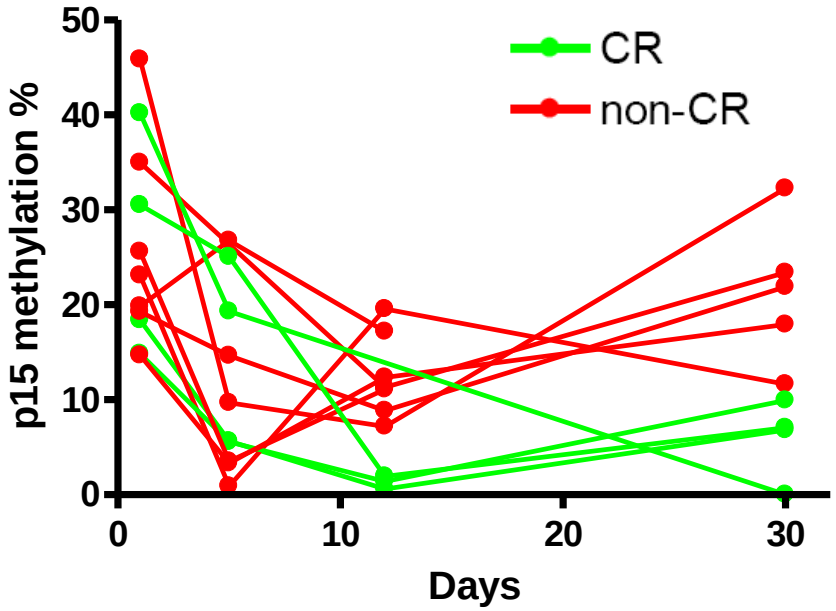
- **DNA methylation inhibitors**
  - **Response rates of 10-70% in MDS, AML and CML; Side-effects primarily myelosuppression**
  - **Prolong survival in MDS compared to supportive care or chemotherapy**
  - **Anecdotal responses in solid tumors – response rate not well defined yet**

Issa, CCR 2009

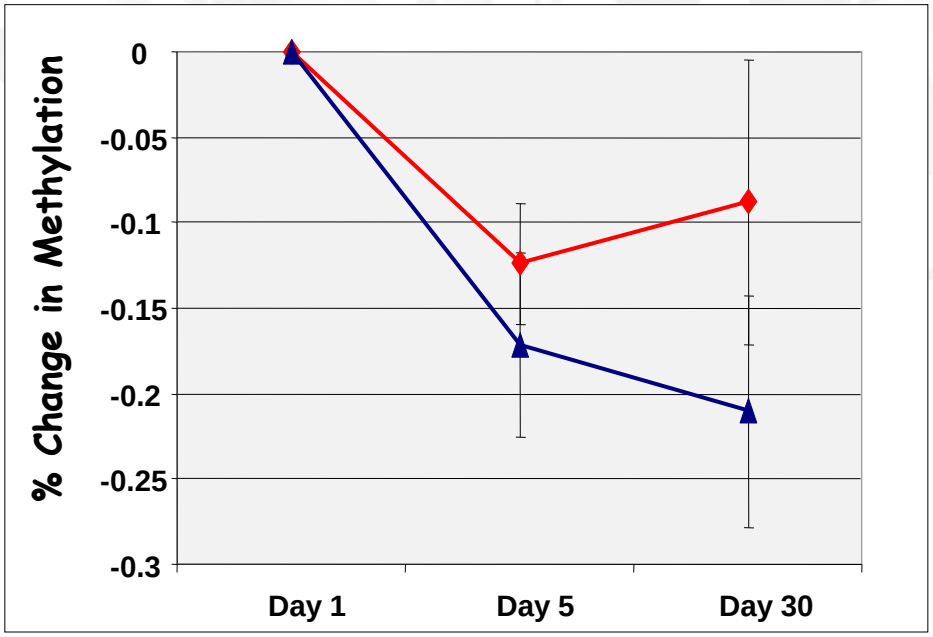
Decitabine

- **Hypomethylation is induced in nearly every patient**
  - **Only sustained hypomethylation correlates with response**
- **Gene expression induction is variable**
  - **Correlates with response**

Hypomethylation After Decitabine



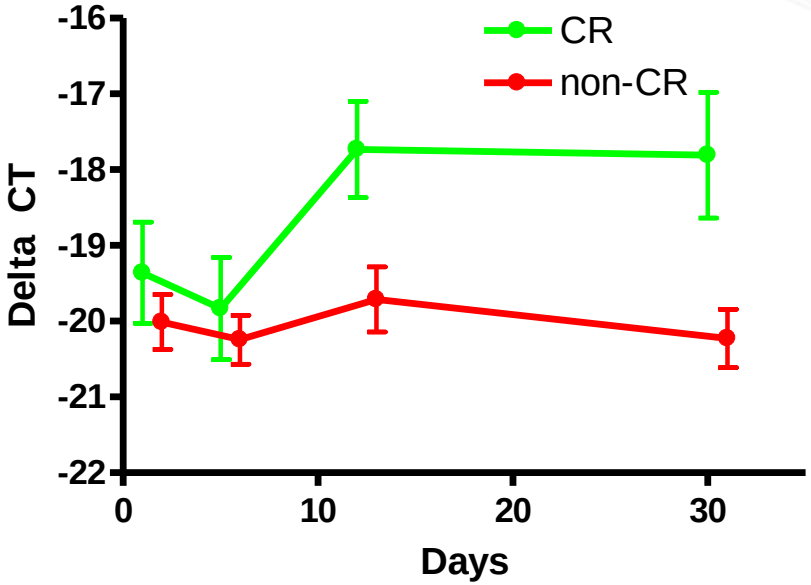
P15/CDKN2B



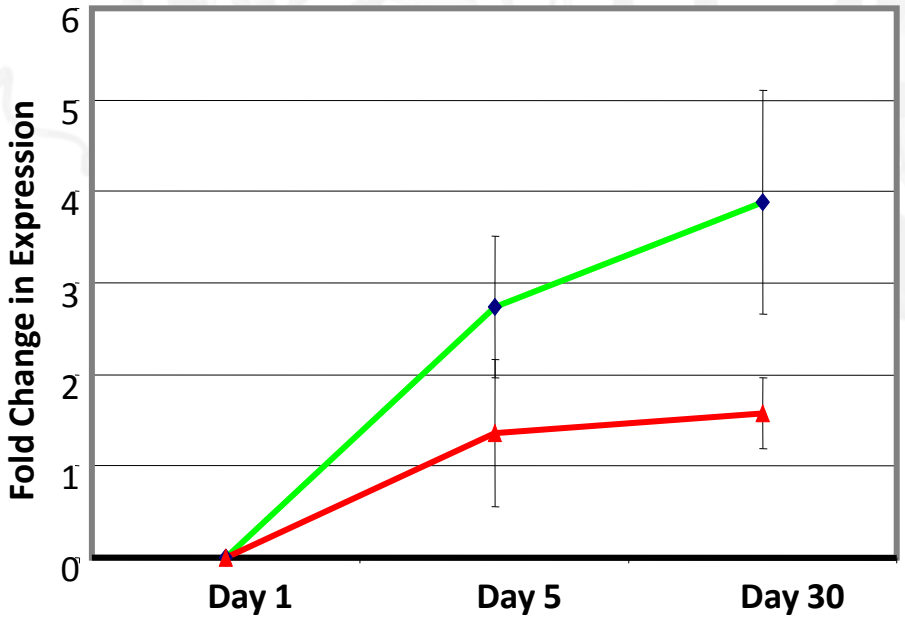
MiR124a

Oki, Blood 2007; Castoro, submitted

Gene Induction After Decitabine



P15/CDKN2B

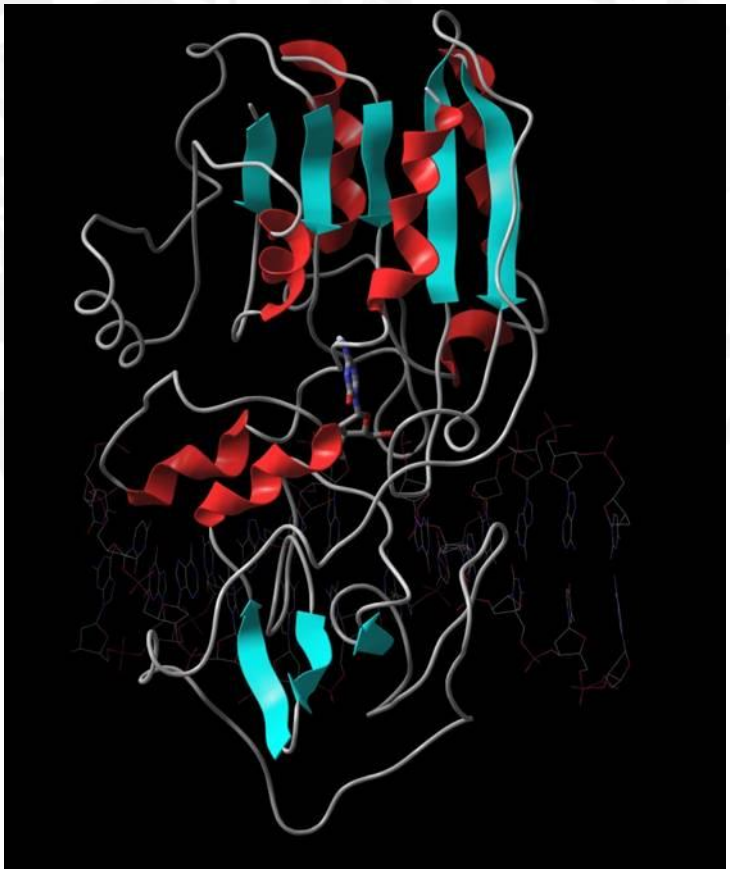


MiR124a

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 *in vivo*.
- SGI-110 was designed to increase the *in vivo* efficacy of decitabine by incorporating it into a guanine dinucleotide



DNMT1
Target for decitabine activity

SGI-110 Structure

- Dinucleotide of Decitabine and Deoxyguanosine

SGI-110 Improves Stability of Decitabine

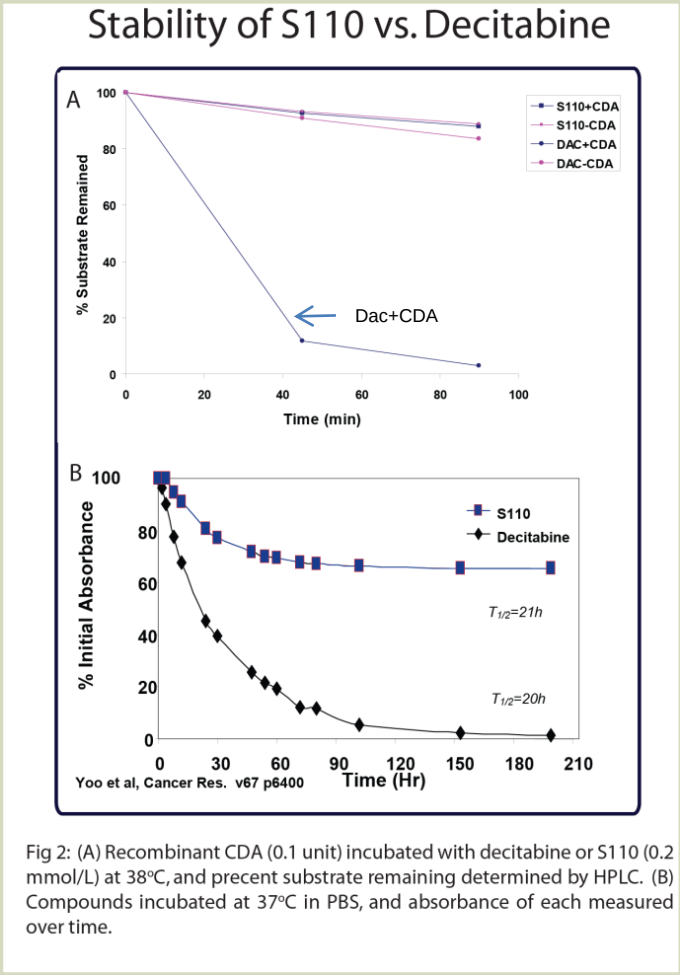


Fig 2: (A) Recombinant CDA (0.1 unit) incubated with decitabine or S110 (0.2 mmol/L) at 38°C, and precent substrate remaining determined by HPLC. (B) Compounds incubated at 37°C in PBS, and absorbance of each measured over time.

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

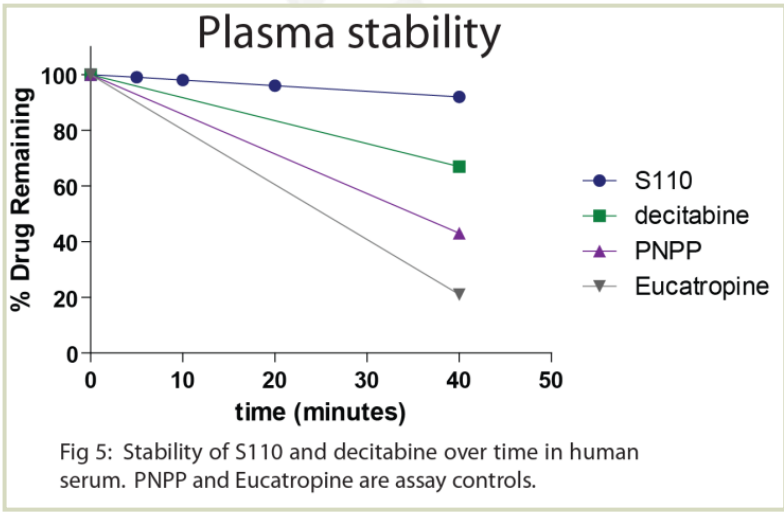


Fig 5: Stability of S110 and decitabine over time in human serum. PNPP and Eucatropine are assay controls.

Yoo C B et al. Cancer Res 2007;67:6400-6408

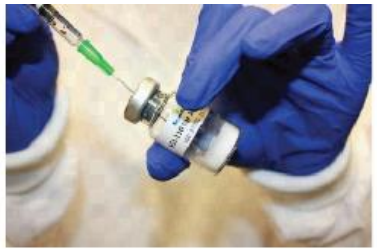
American Association for Cancer Research

SGI-110: Better Formulation Development

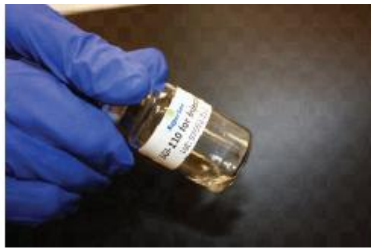
- Two-vial kit – “Ready to Reconstitute” product
- Easy reconstitution and solubility
- Designed for SQ injection
- Safe composition: all excipients are *GRAS*
- Very small Injection volume: 100 mg/mL
- Stability: solution stable for 1 month

	SGI-110 Lyophile reconstituted with	
Composition	Water For Injection	Non-aqueous formulation
SGI-110 solubility in diluent	~20 mg/mL	~130 mg/mL
Injection volume, @ 25 mg dose given subcutaneously	> 1 mL	< 1 mL
Stability of reconstituted solution	Unstable, degrades even at refrigerated conditions	Stable for a month in the refrigerator

Two vial kit - SGI-110 powder and diluent

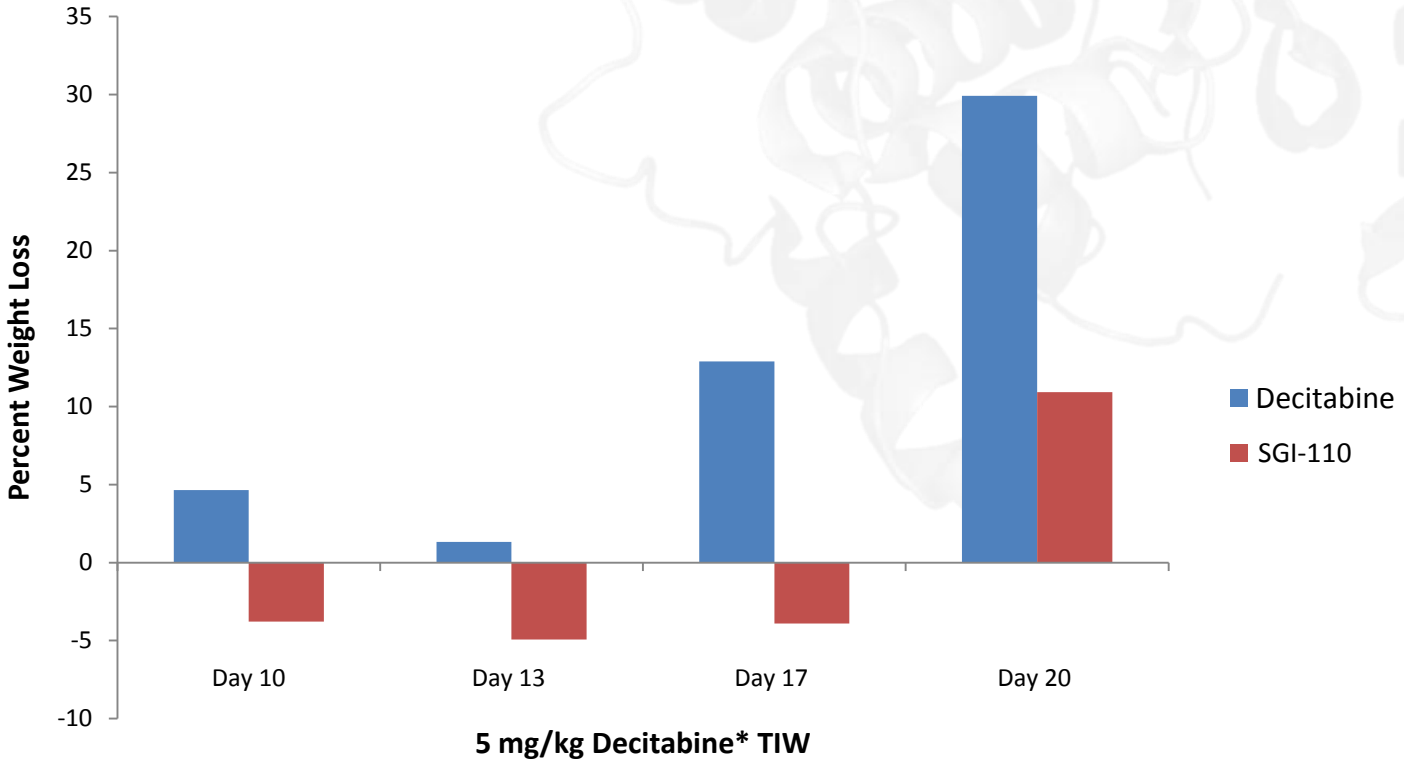


Diluent added to SGI-110 powder to make up to 100 mg/mL solution



Stable solution formed

SGI-110 Improves Tolerability *In Vivo*



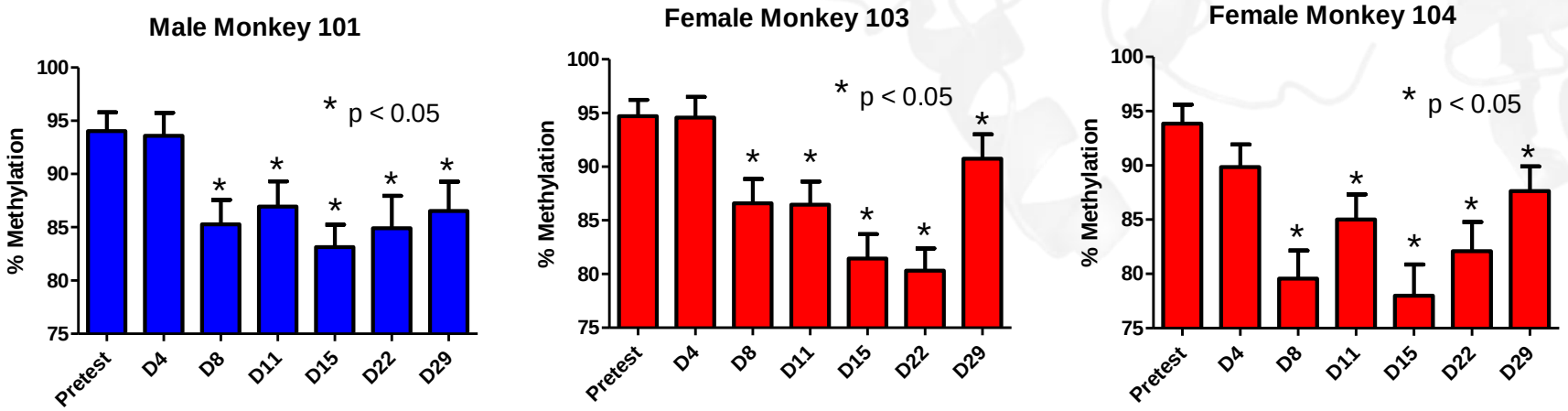
•Concentration value of SGI-110 given in molar equivalent of Decitabine.
(6 mice dosed 3 times weekly IV)

Chuang et al. 2010 Molecular Cancer Therapeutics

American Association for Cancer Research

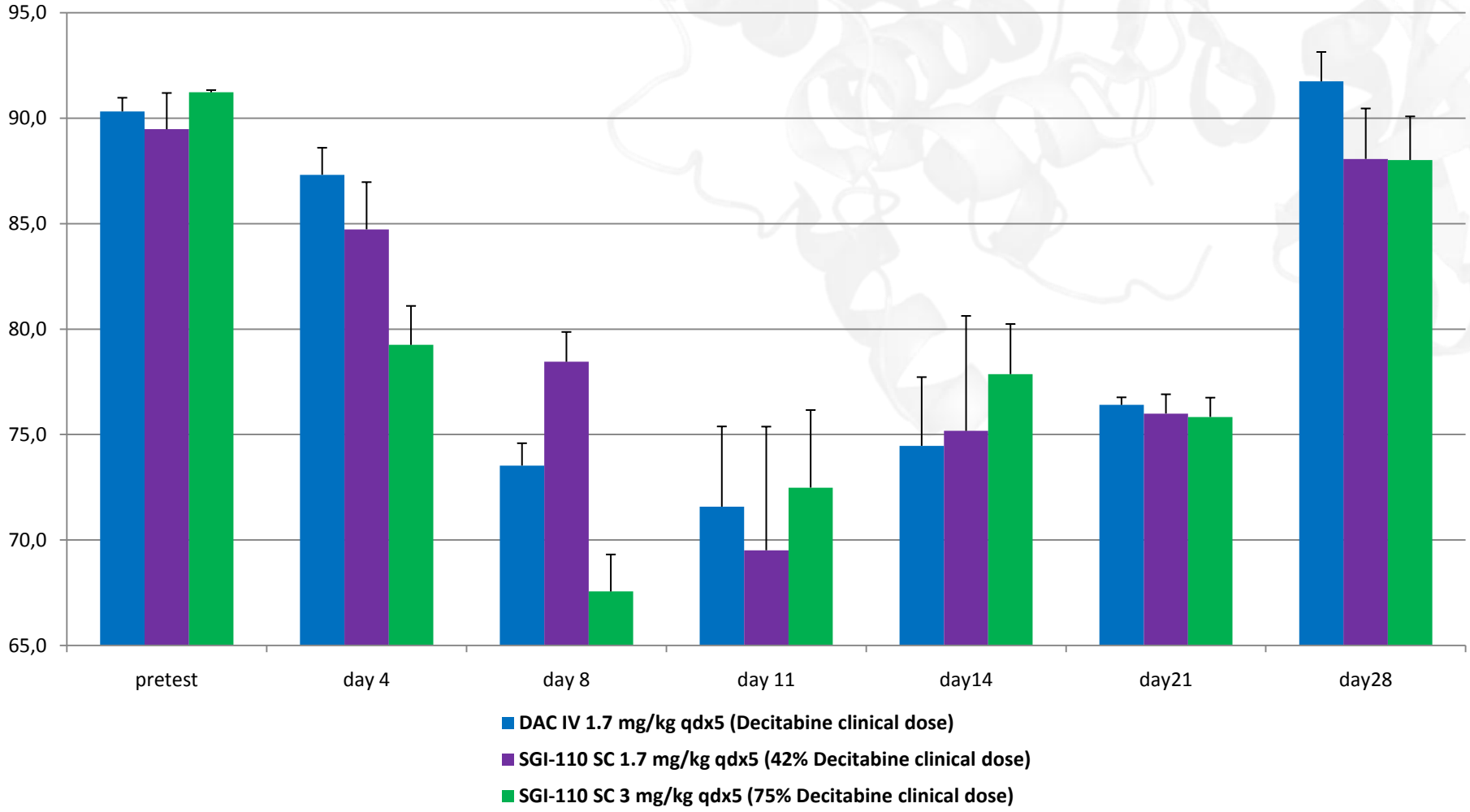
Sustained Hypomethylation, Less Frequent Administration

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



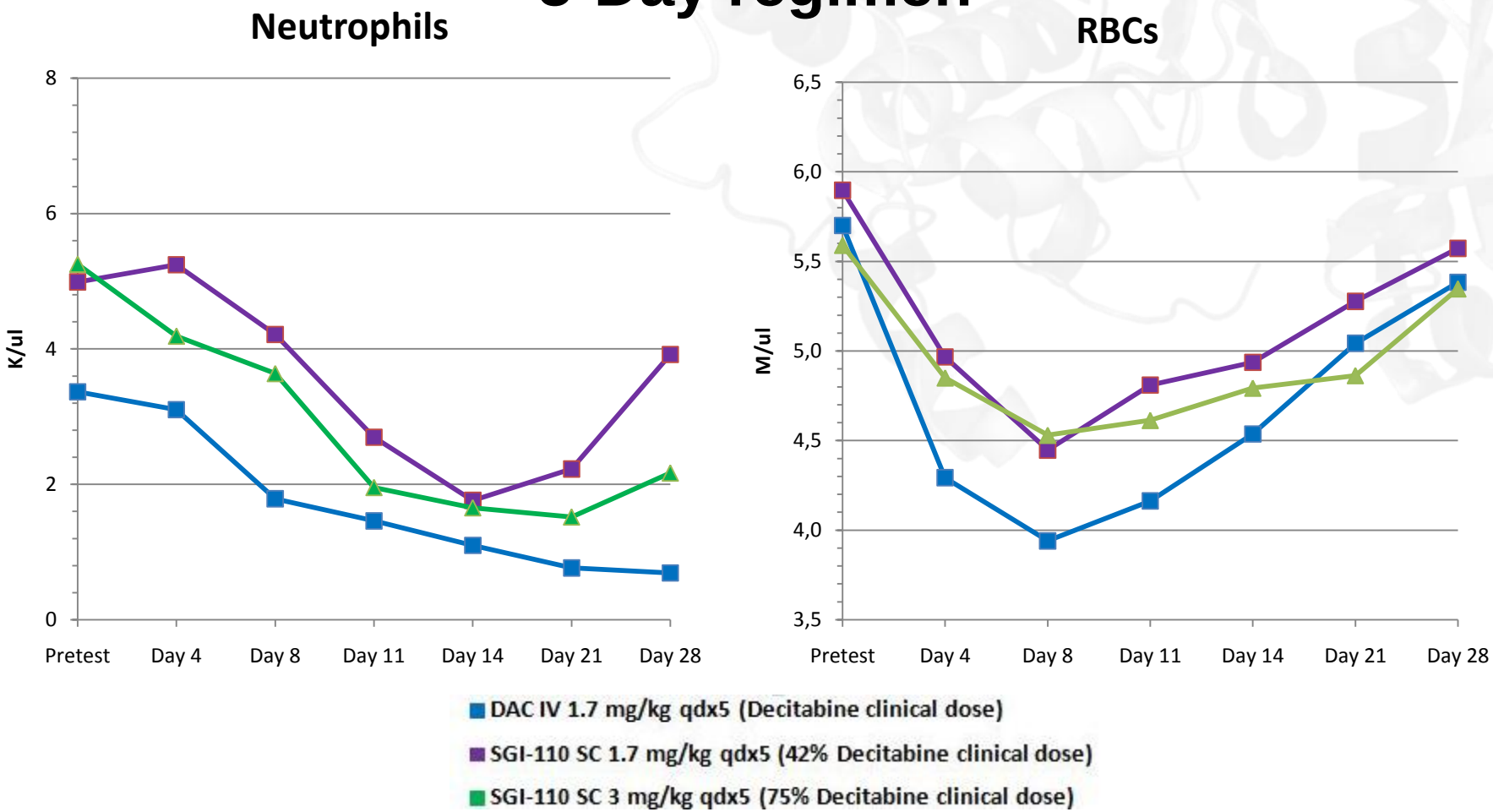
- Significant decrease ($p<0.05$) in global methylation with once weekly dosing for up to 4 weeks
- Recovery trend 14 days after third dose

SGI-110 vs Decitabine: Methylation in Monkeys 5-Day regimen



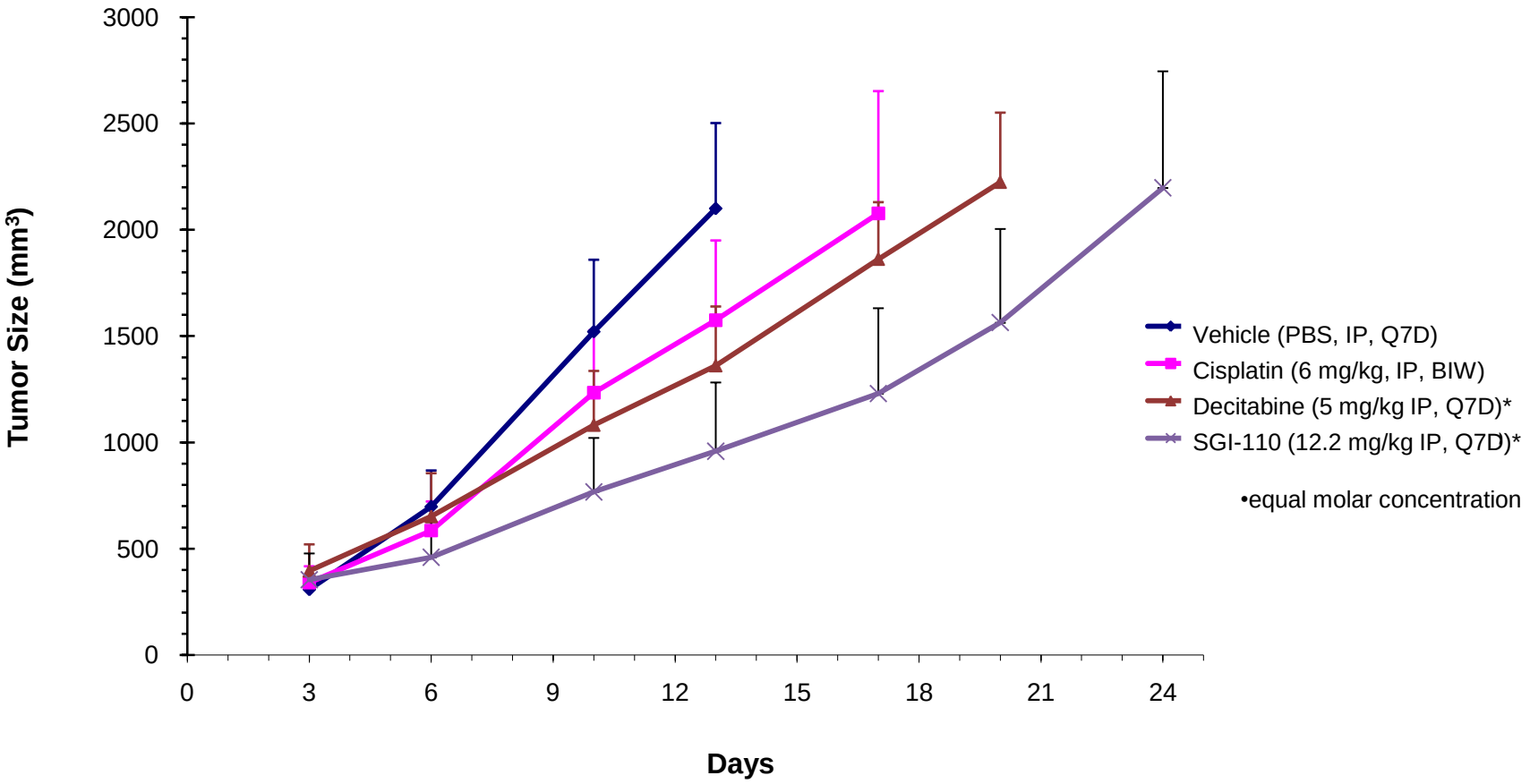
Similar or better hypomethylation with SGI-110 at lower doses

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)



SGI-110 Clinical Program

SGI-110-01

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)

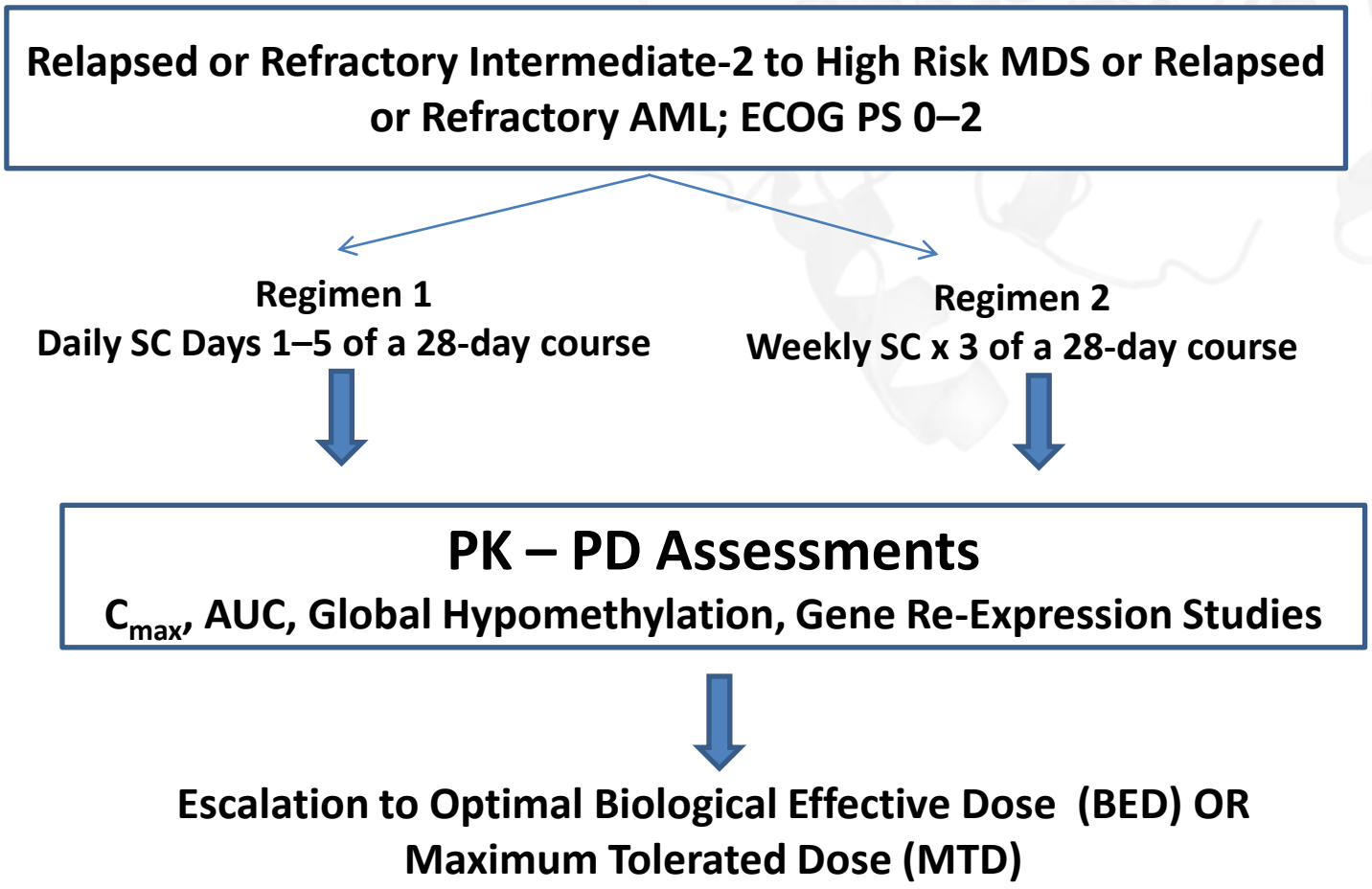
Study Design

- 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



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

	Total	AML	MDS-Int 2	MDS-HR
Weekly	7	3	3	1
Daily	4	3	1	0

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

Acknowledgments

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