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

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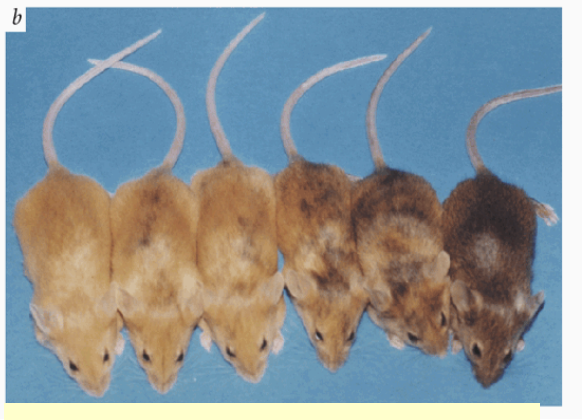
Epigenetics

- **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)

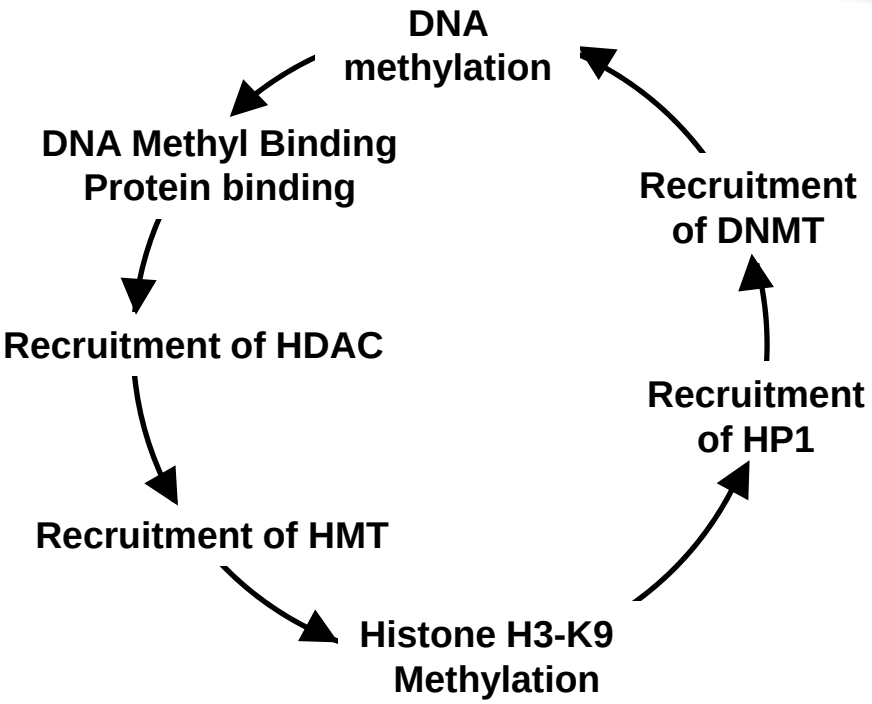
The epigenome: Signals that are necessary (? sufficient) to establish and/or perpetuate an epigenetic state

Evidence for Cancer as an Epigenetic Disease

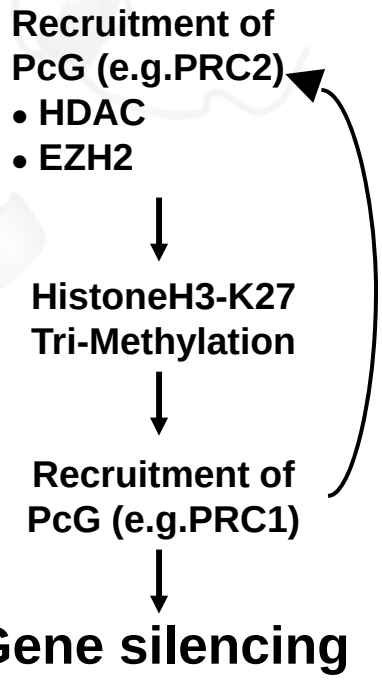
- The marks are abnormal: DNA methylation and histone patterns
  - Variable in different cancers
  - Affect critical genes
- The readers/writers are genetically targeted in some cancers
  - DNA methylation regulators (DNMT3a, TET2, ? IDH1/2)
  - Histone modifiers (MLL1-3, UTX2, EZH2 etc.)
  - Chromatin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



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**

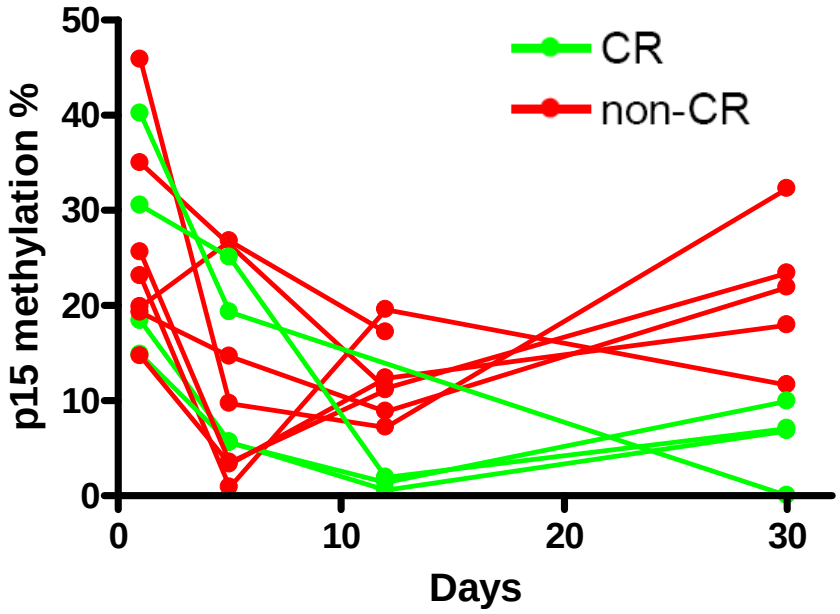
Issa, CCR 2009

Decitabine

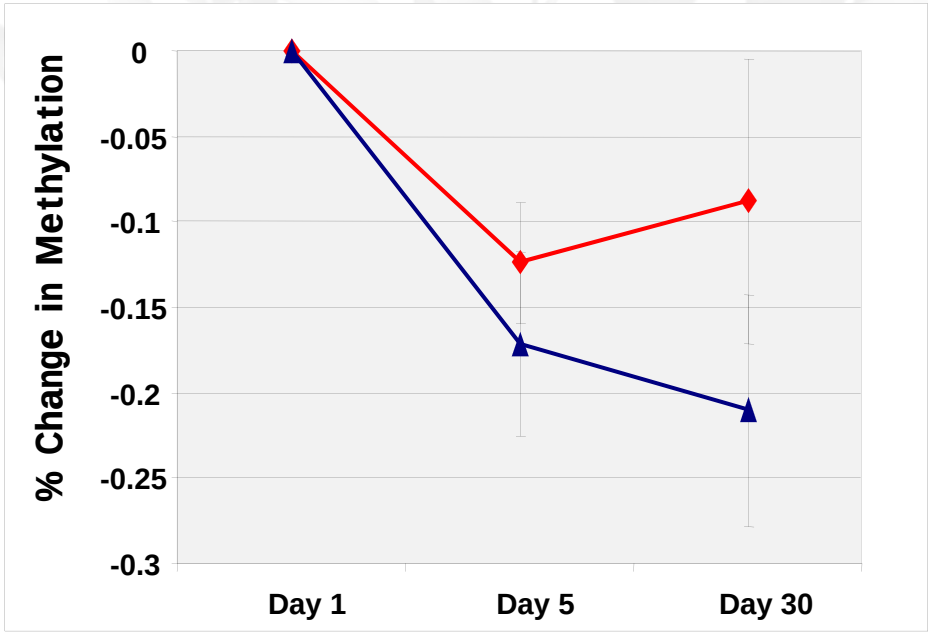
- **Hypomethylation is induced in nearly every patient**
  - **Only sustained hypomethylation correlates with response**

- **Gene expression induction is variable**
  - **Correlates with response**

Hypomethylation After Decitabine



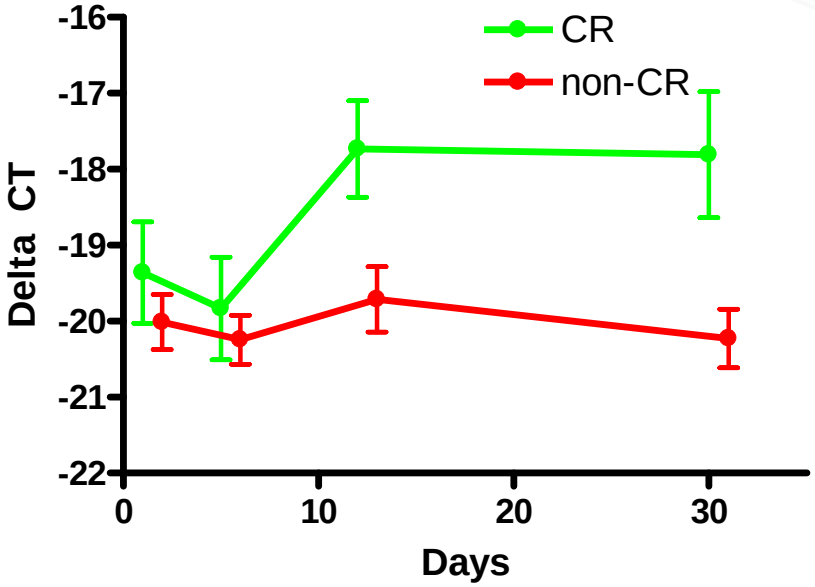
P15/CDKN2B



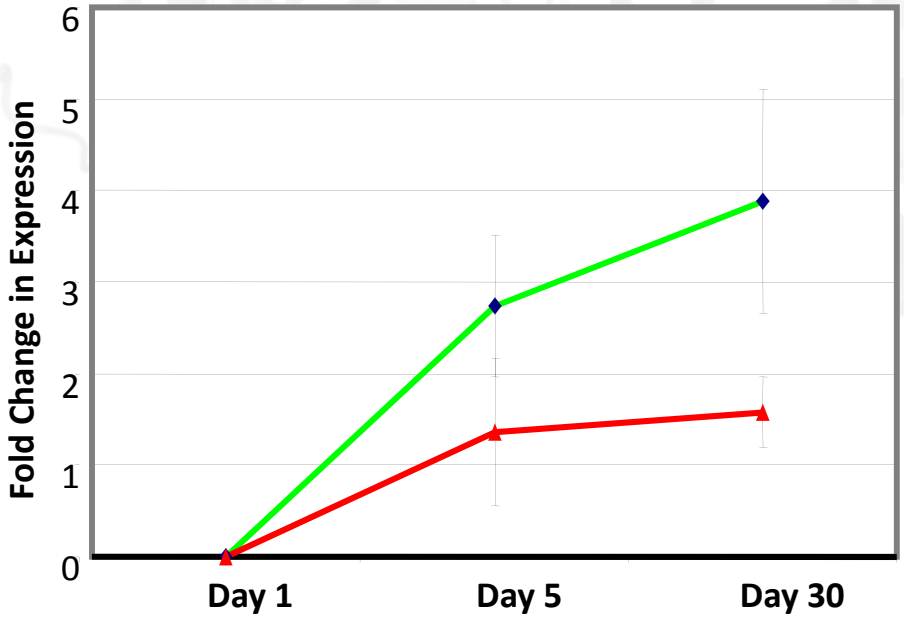
MiR124a

Oki, Blood 2007; Castoro, submitted

Gene Induction After Decitabine



P15/CDKN2B

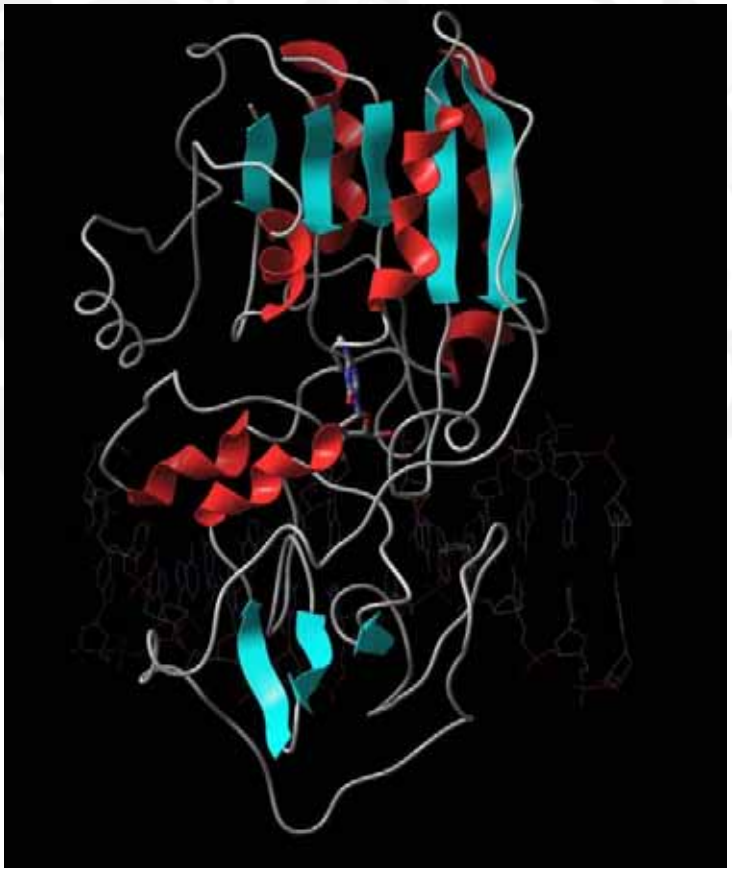


MiR124a

Oki, Blood 2007; Castoro, submitted

SGI-110: Background

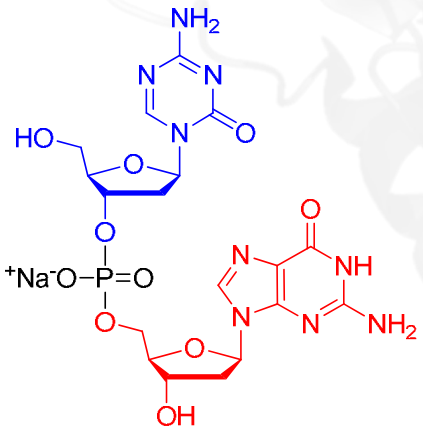
- Decitabine is a potent, well-characterized hypomethylating agent.
- Lacks optimal drug stability: rapidly eliminated in plasma by Cytidine Deaminase (CDA). This limits drug exposure time to cancer cells *in vivo*.
- SGI-110 was designed to increase the *in vivo* efficacy of decitabine by incorporating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



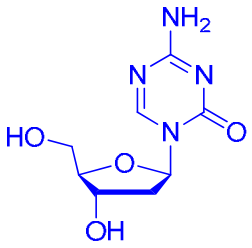
DNMT1
Target for decitabine activity

SGI-110 Structure

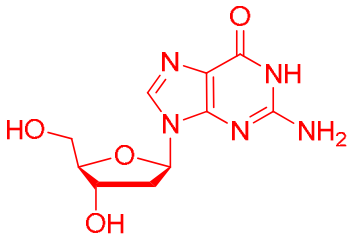
- Dinucleotide of Decitabine and Deoxyguanosine



SGI-110



Decitabine



Guanosine

SGI-110 Improves Stability of Decitabine

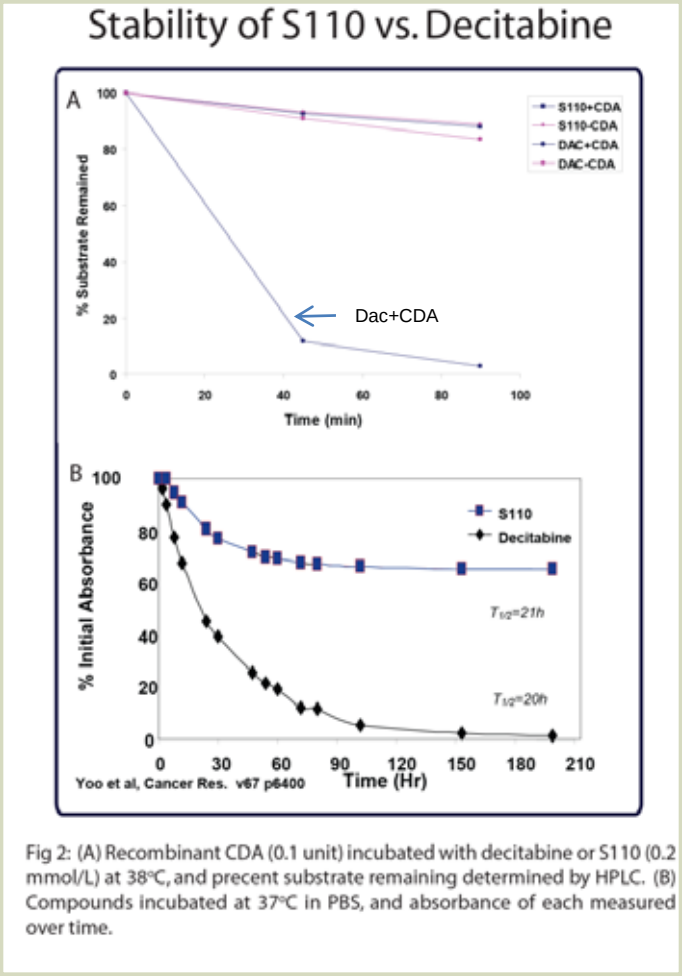


Fig 2: (A) Recombinant CDA (0.1 unit) incubated with decitabine or S110 (0.2 mmol/L) at 38°C, and precent substrate remaining determined by HPLC. (B) Compounds incubated at 37°C in PBS, and absorbance of each measured over time.

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

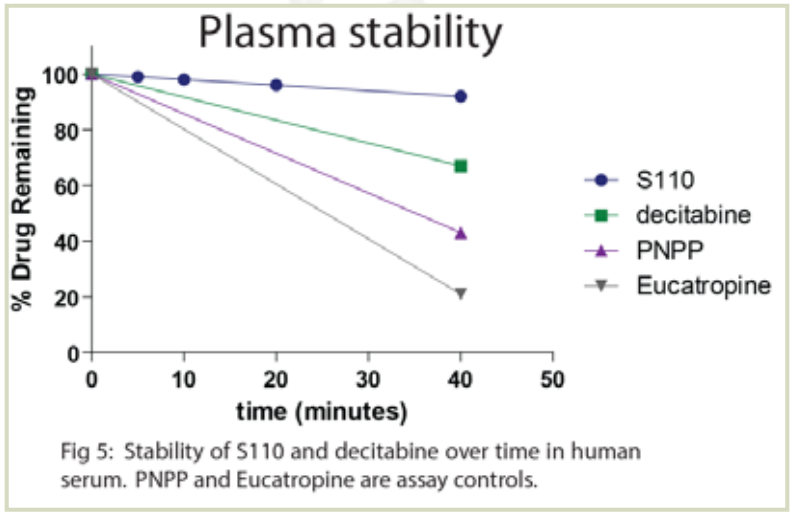


Fig 5: Stability of S110 and decitabine over time in human serum. PNPP and Eucatropine are assay controls.

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

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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

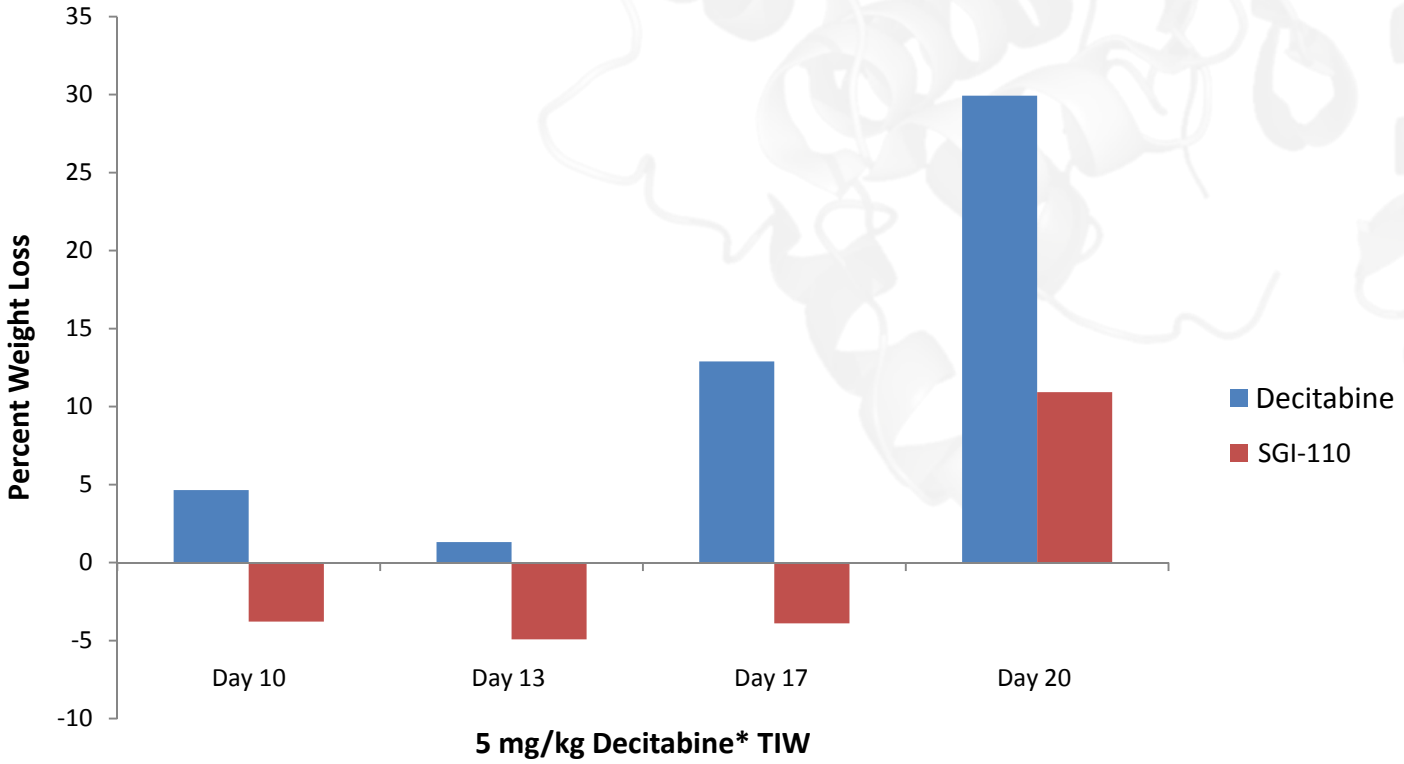
	SGI-110 Lyophile reconstituted with	
Composition	Water For Injection	Non-aqueous formulation
SGI-110 solubility in diluent	~20 mg/mL	~130 mg/mL
Injection volume, @ 25 mg dose given subcutaneously	> 1 mL	< 1 mL
Stability of reconstituted solution	Unstable, degrades even at refrigerated conditions	Stable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

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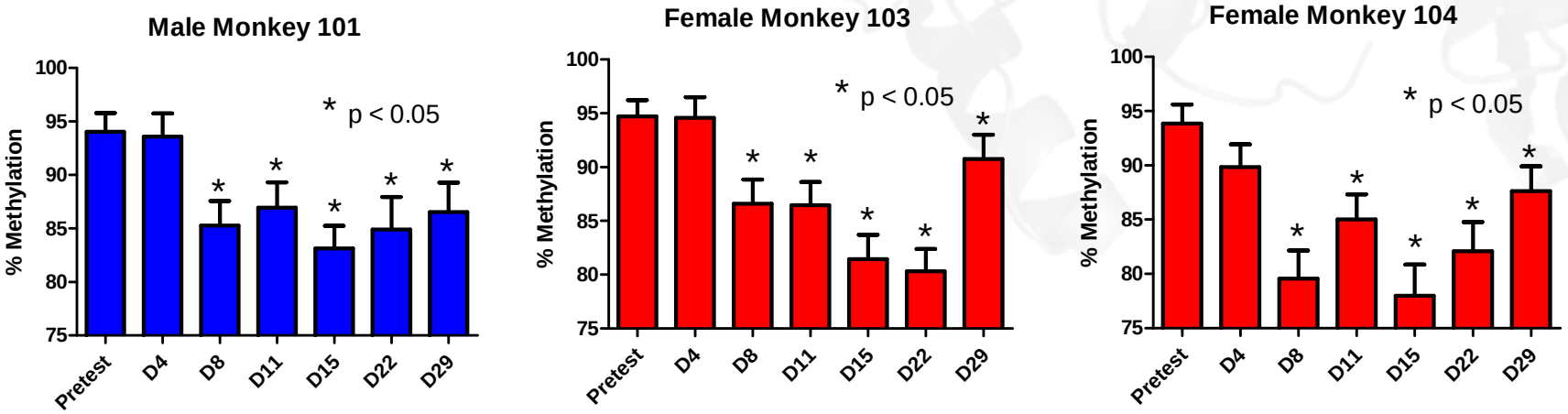
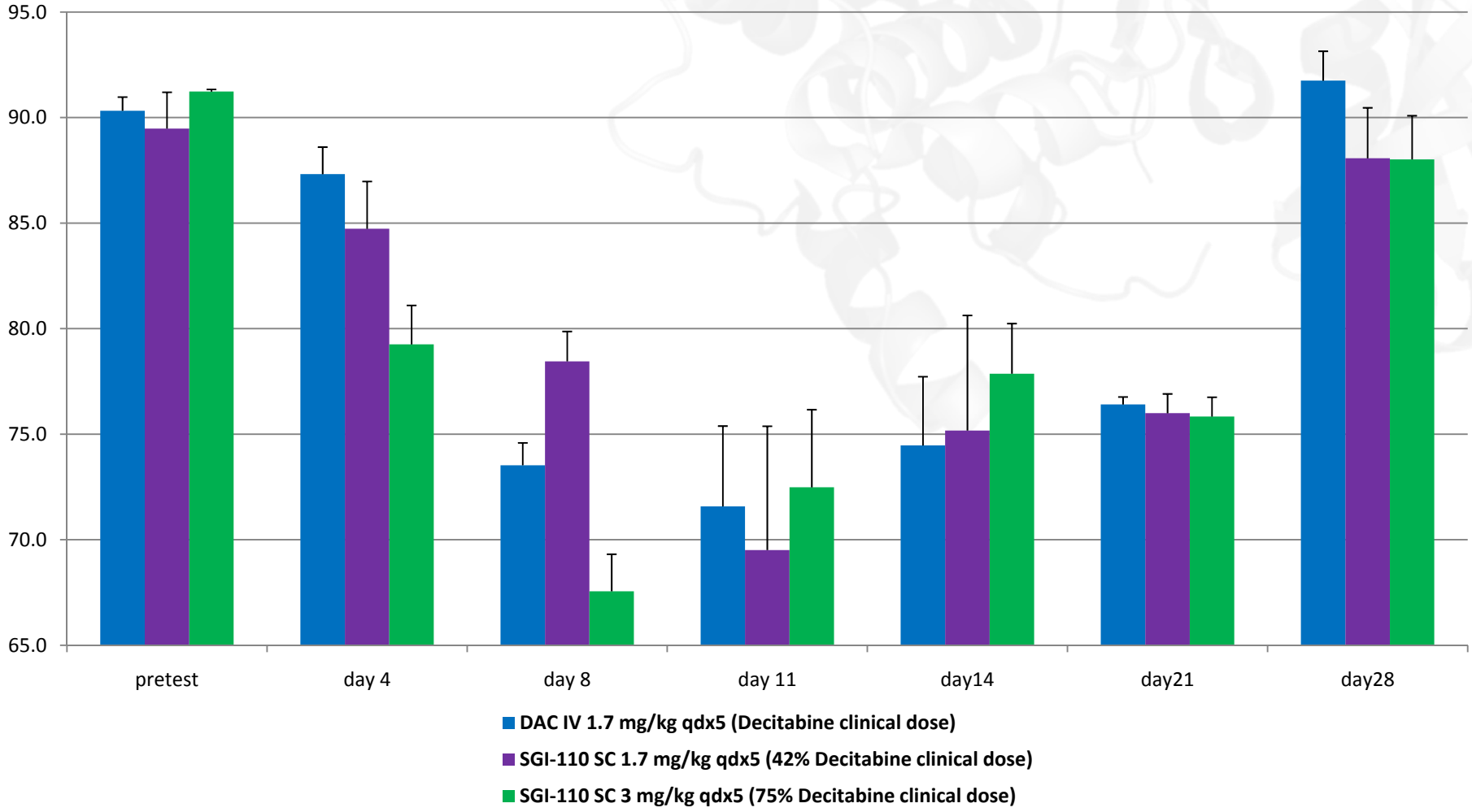
Sustained Hypomethylation, Less Frequent Administration

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



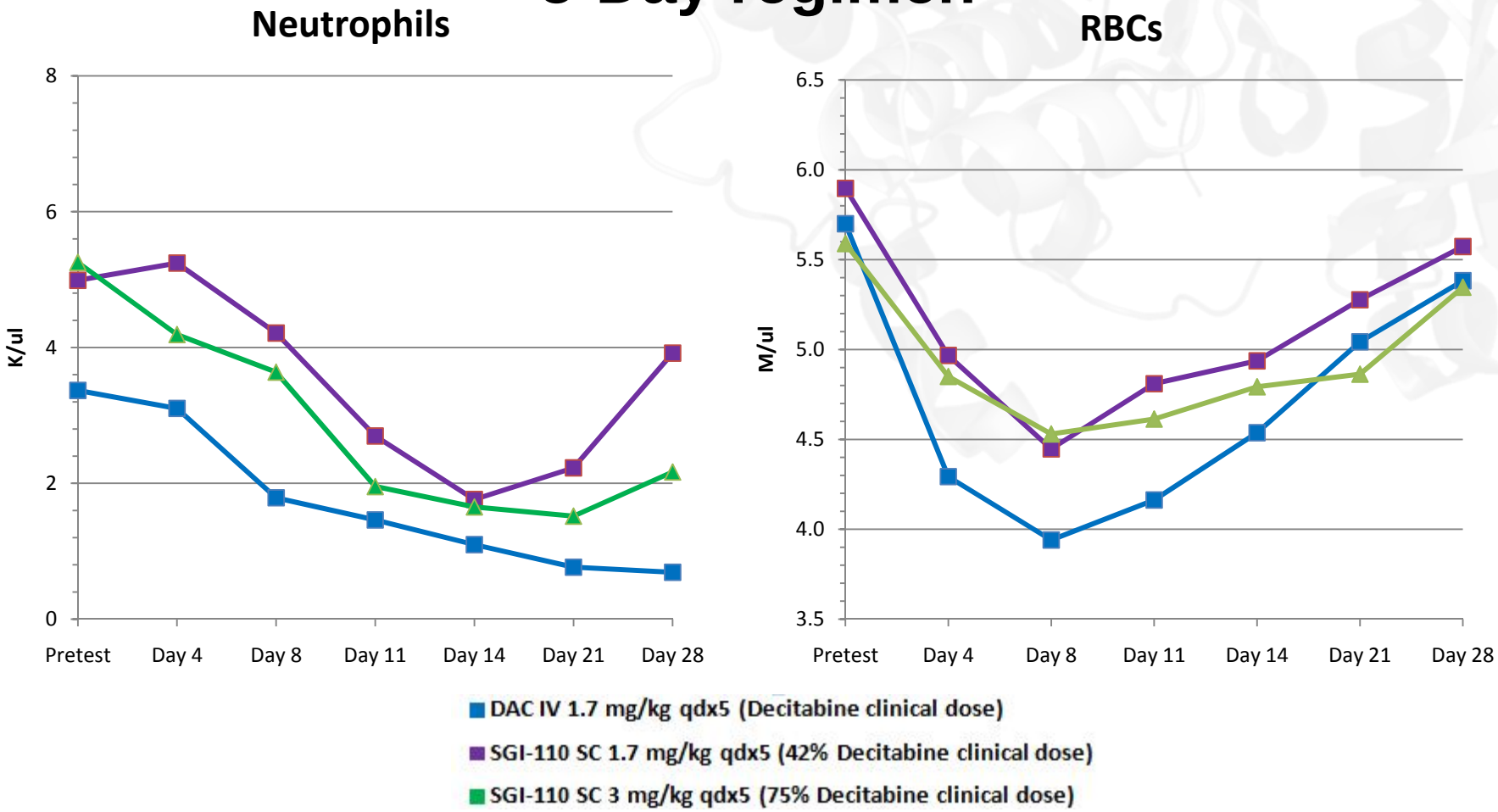
- Significant decrease ($p<0.05$) in global methylation with once weekly dosing for up to 4 weeks
- Recovery trend 14 days after third dose

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



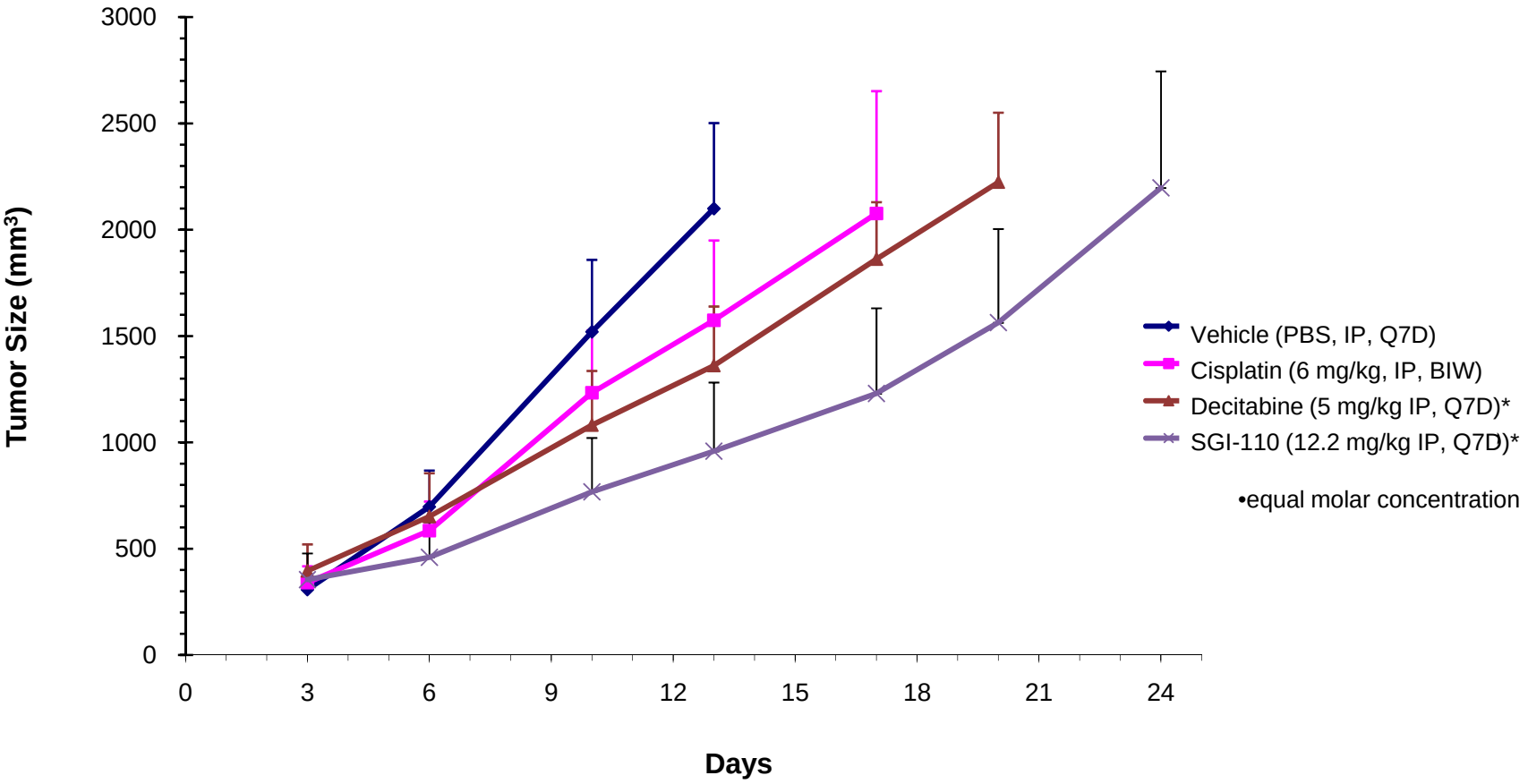
Similar or better hypomethylation with SGI-110 at lower doses

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)

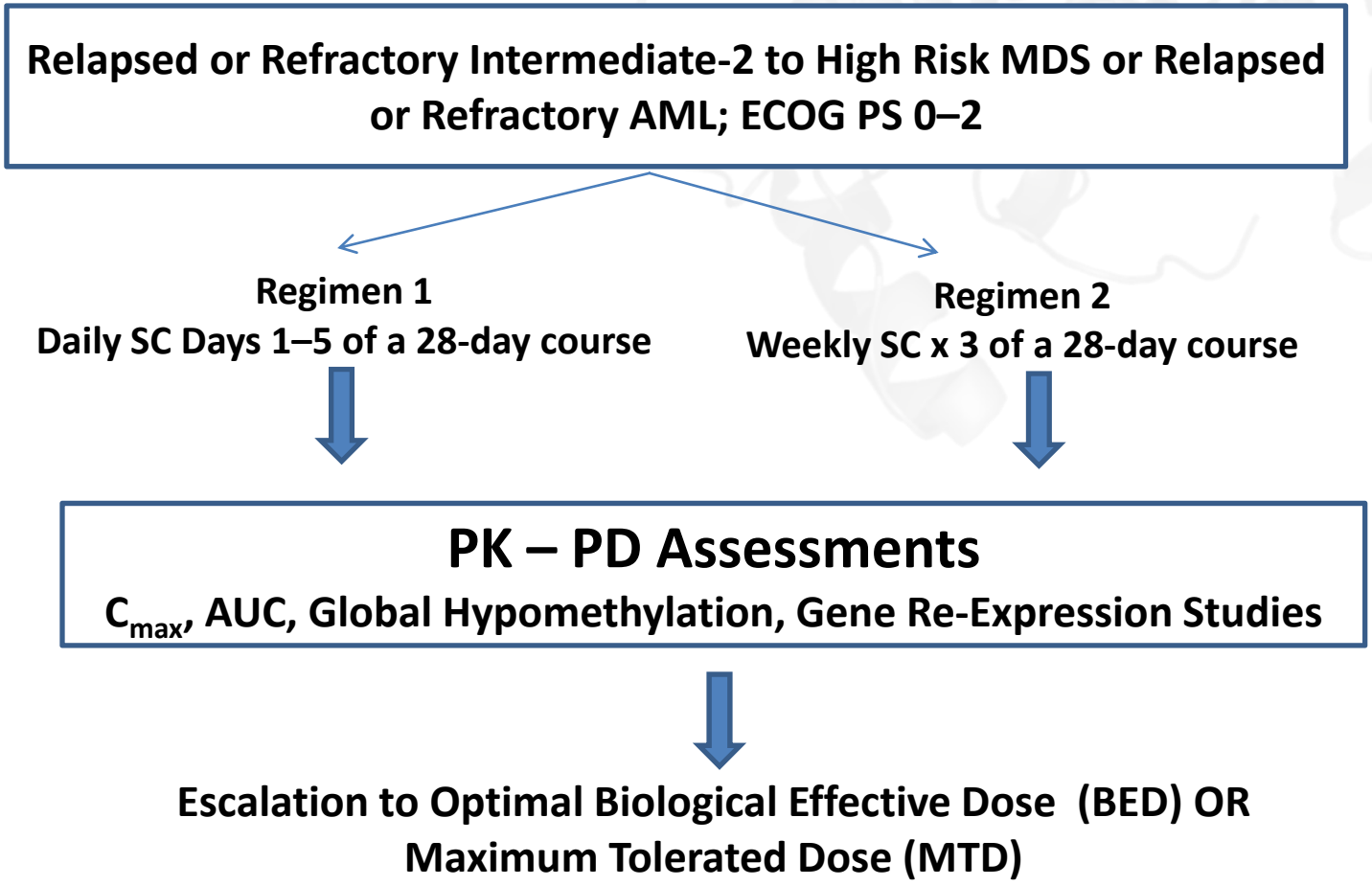
Study Design

- 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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