



Scale up and development of a process for a low volume subcutaneous formulation of SGI-110, a potent hypomethylating agent

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DISCLOSURE INFORMATION
AACR Annual Meeting 2012, Chicago, IL
Sanjeev Redkar

I have the following financial relationships to disclose

- **Stockholder in Astex Pharmaceuticals, Inc.**
- **Employee of Astex Pharmaceuticals, Inc.**

I will discuss the following investigational use in my presentation:

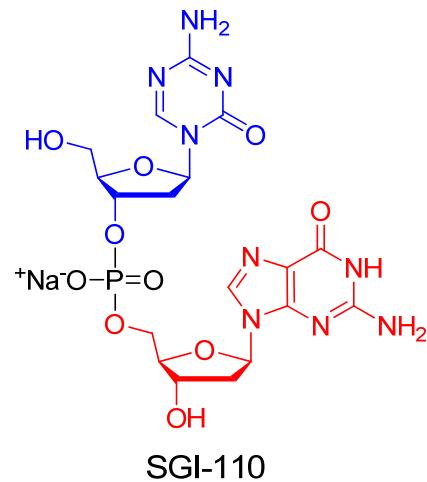
MDS/AML

Agenda

- **SGI-110 Introduction**
- **History of SGI-110 and Challenges**
- **Nonclinical Data**
- **Clinical Data**

SGI-110 Structure

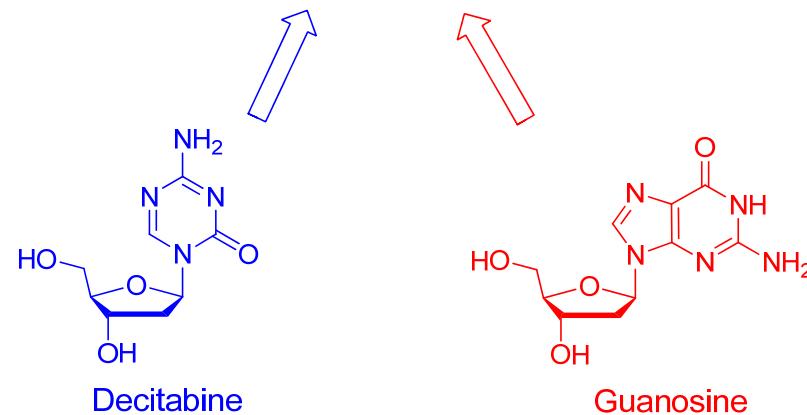
- Dinucleotide of Decitabine and Deoxyguanosine



MW 579.4 Da

Log D 0.98

pKa 3.22, 7.06, 9.98

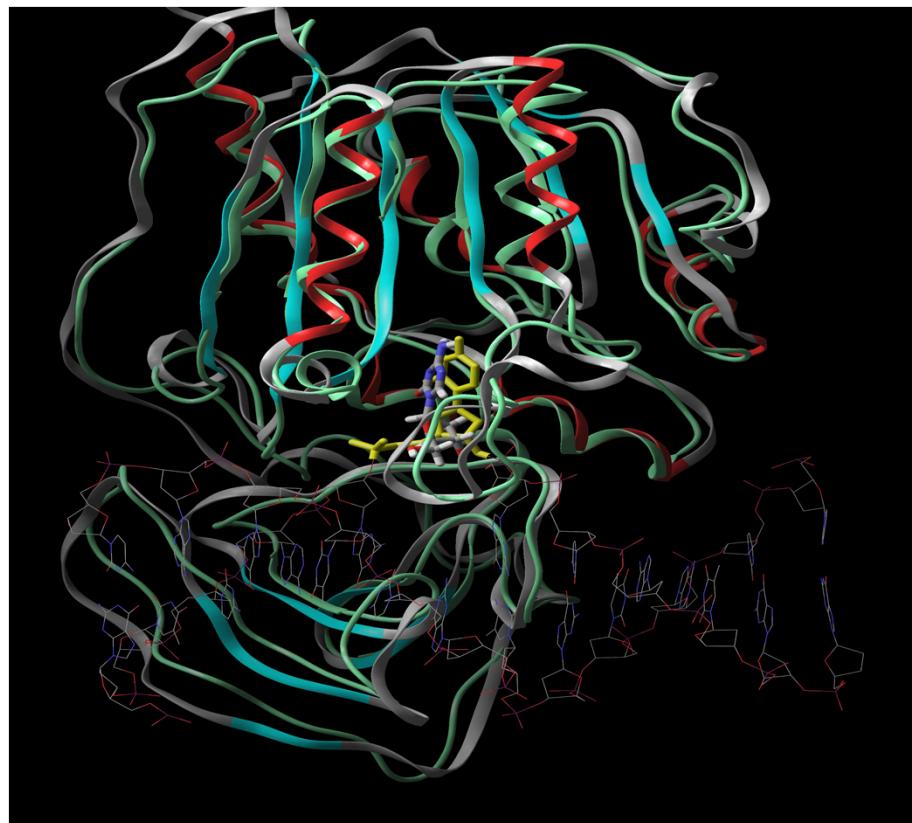
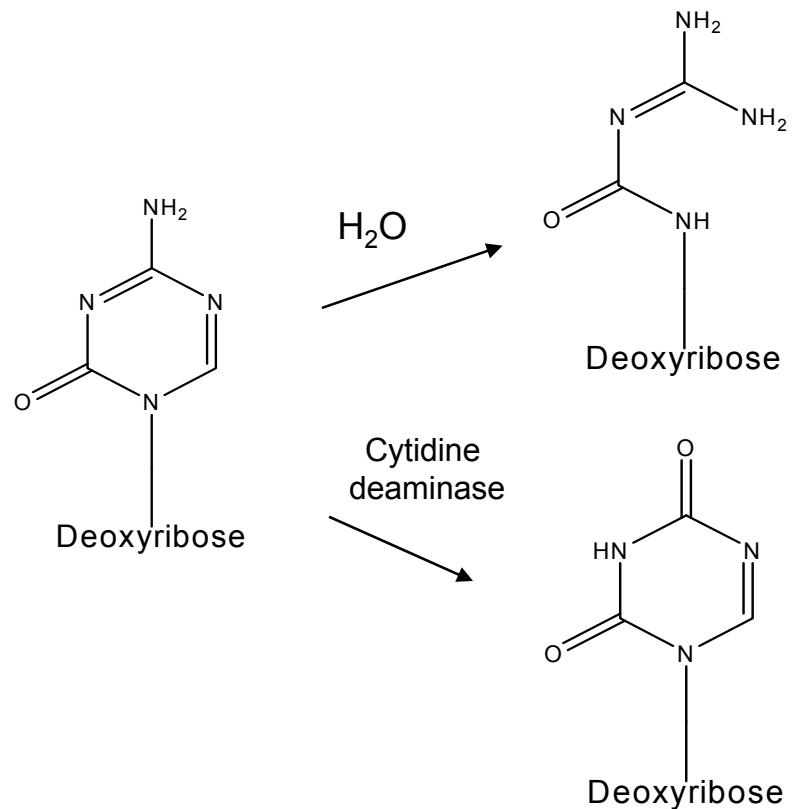


Overview

- **Molecular target: DNMT inhibitor**
- **Increase *in vivo* exposure / efficacy of decitabine by protecting it from de-amination**
- **Disease areas:**
 - Hematology: MDS & AML
 - Solid tumors: Epigenetic Therapy
- **Stage of project: Phase 1/2 MDS and AML**

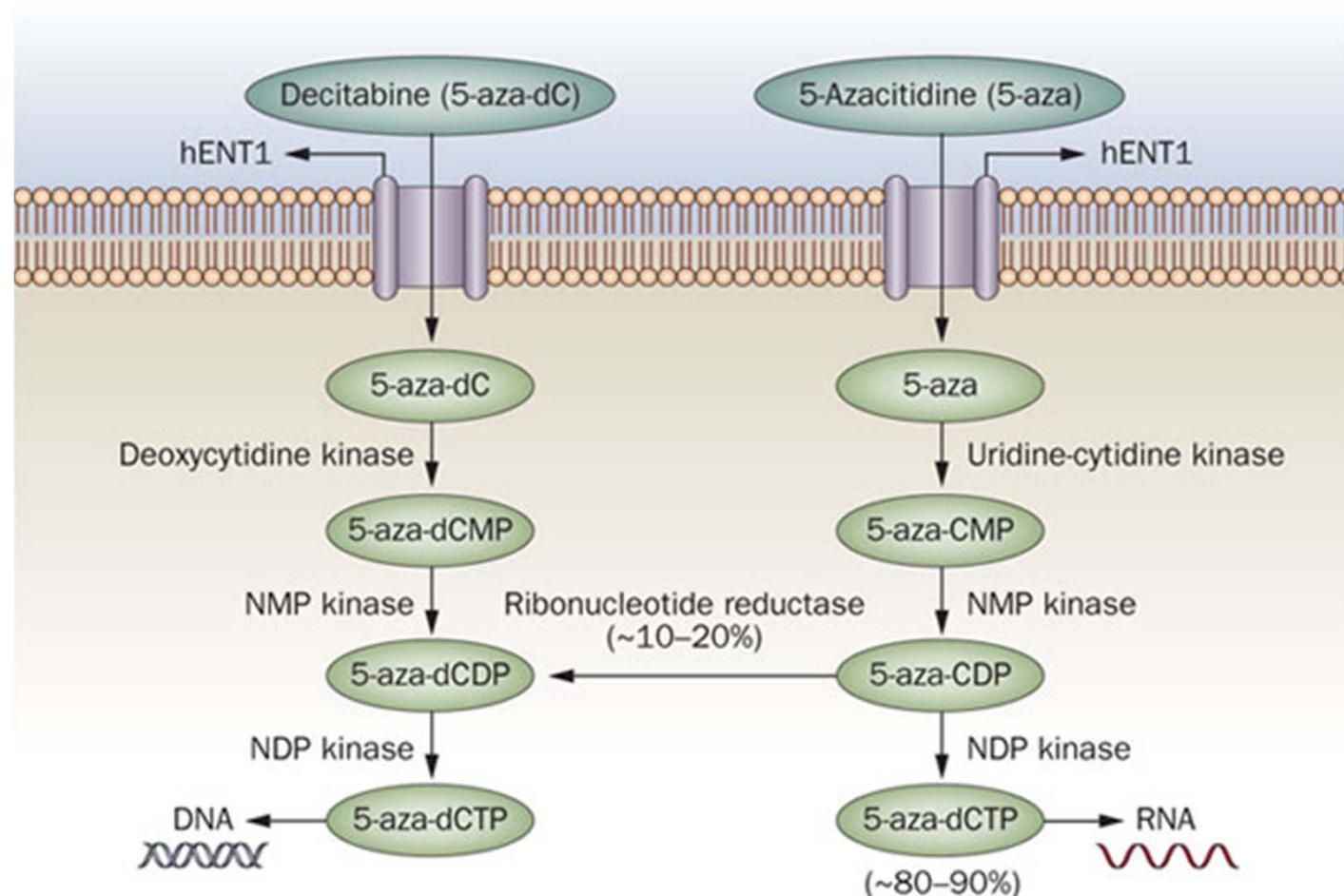
Decitabine challenges

- Decitabine is a potent, well-characterized hypomethylating agent



DNMT1 with decitabine
Target for decitabine activity

DAC & AZA metabolism and transport



Quintás-Cardama, A. et al. (2010) Therapy with azanucleosides for myelodysplastic syndromes. *Nat. Rev. Clin. Oncol.* 2010

SGI-110 Improves Stability of Decitabine

Stability of S110 vs. Decitabine

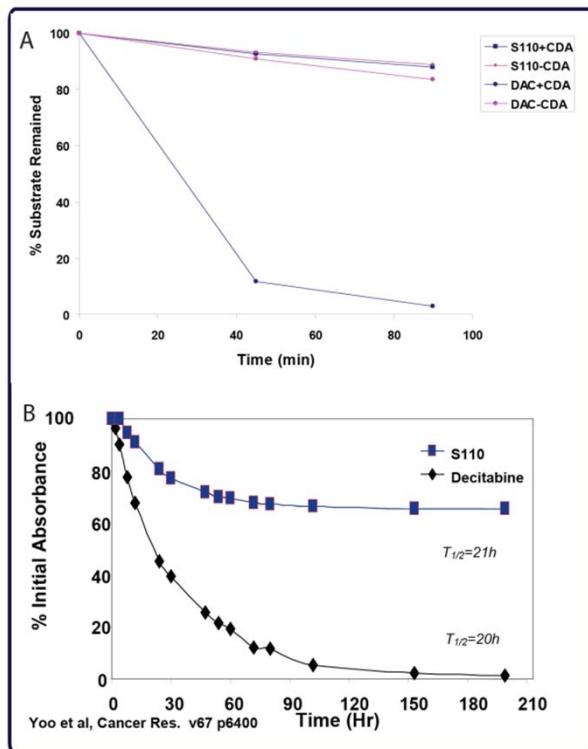


Fig 2: (A) Recombinant CDA (0.1 unit) incubated with decitabine or S110 (0.2 mmol/L) at 38°C, and percent substrate remaining determined by HPLC. (B) Compounds incubated at 37°C in PBS, and absorbance of each measured over time.

- Increases half-life
- Improves metabolic stability
- Lowers C_{max}

Plasma stability

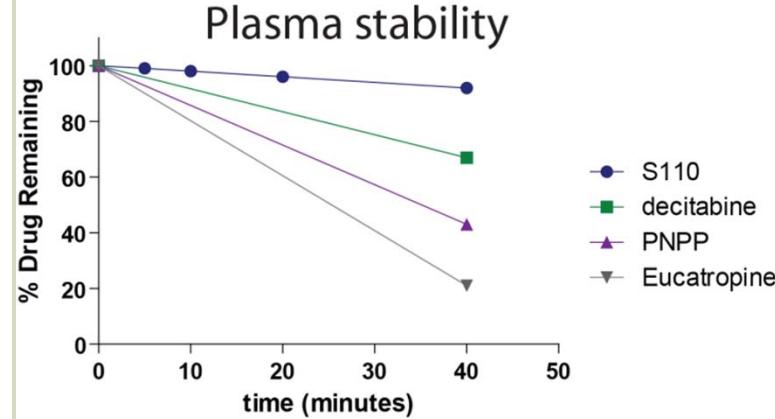
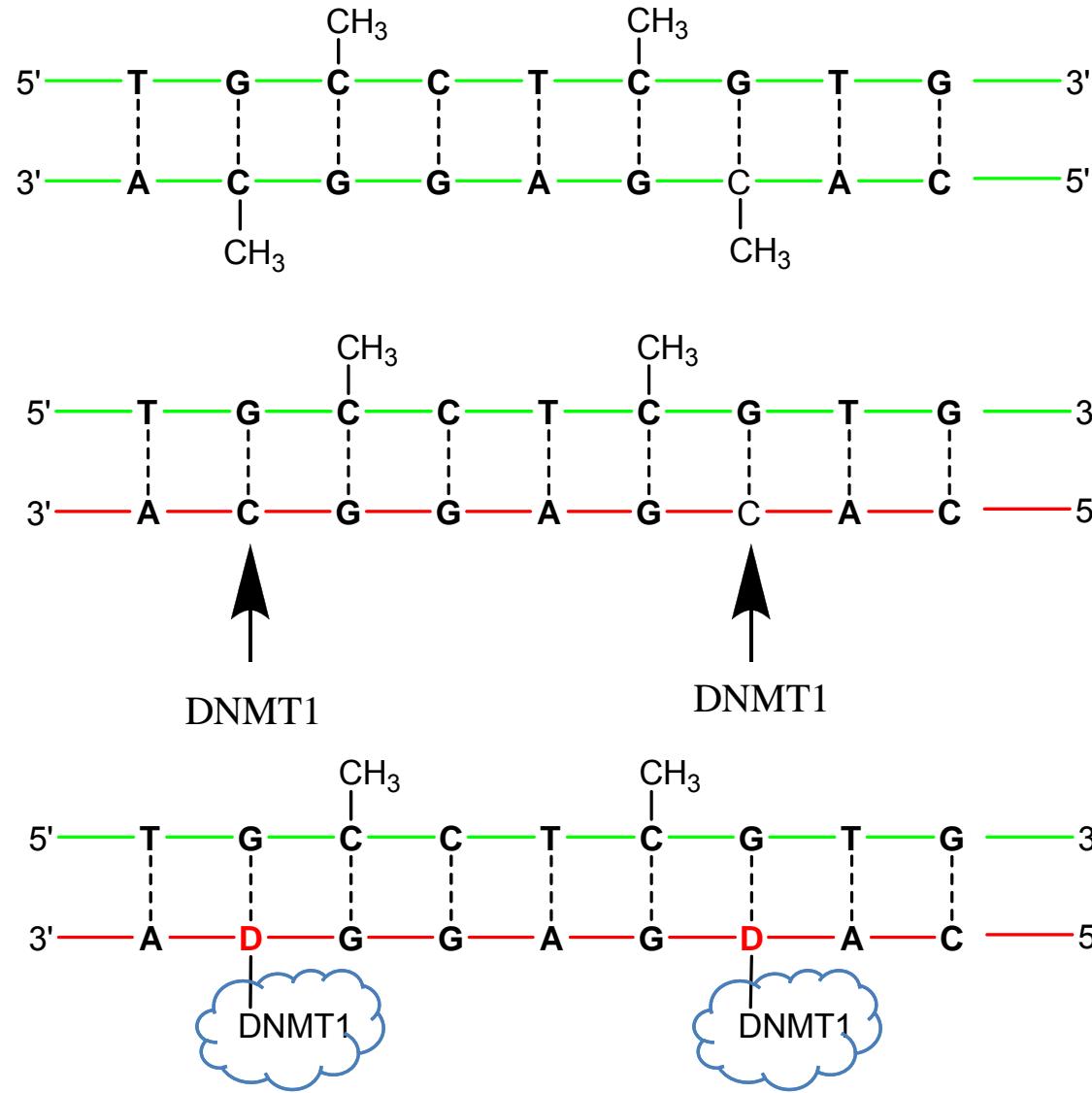


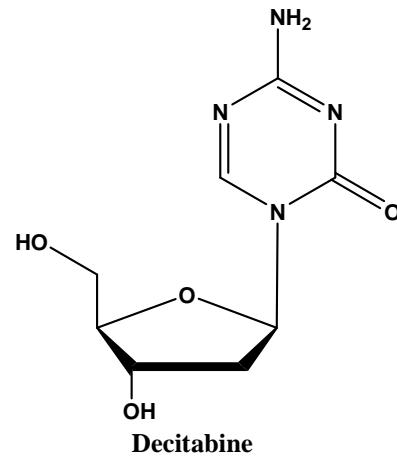
Fig 5: Stability of S110 and decitabine over time in human serum. PNPP and Eucatropine are assay controls.

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

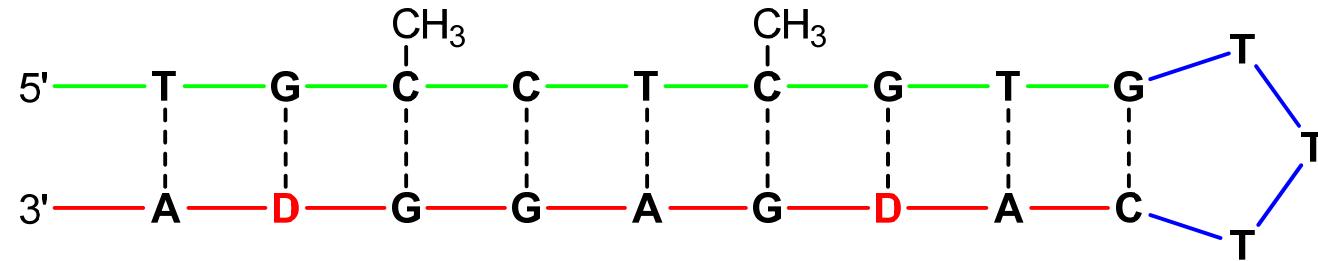
DNA Methylation on CpG Islands



How to overcome challenges



- Improve stability
- Eliminate DNA incorporation



Hairpin oligos with DAC

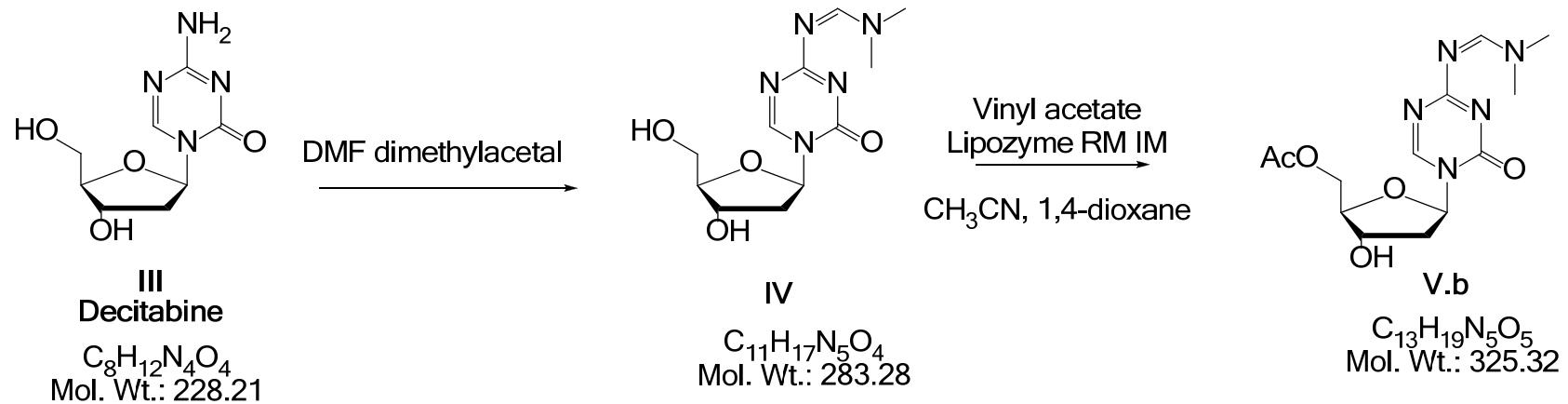
Early results on Oligos

Compound	Structure	p16 Induction
Decitabine (D)	5-Aza-CdR	+++
S110	D↓pG	+++
S112	*HEG↓pD↓pG	++
S53	G↓pD	+++
S52R	D↓psG	+

- Cleavage was essential for activity – acting as a prodrug

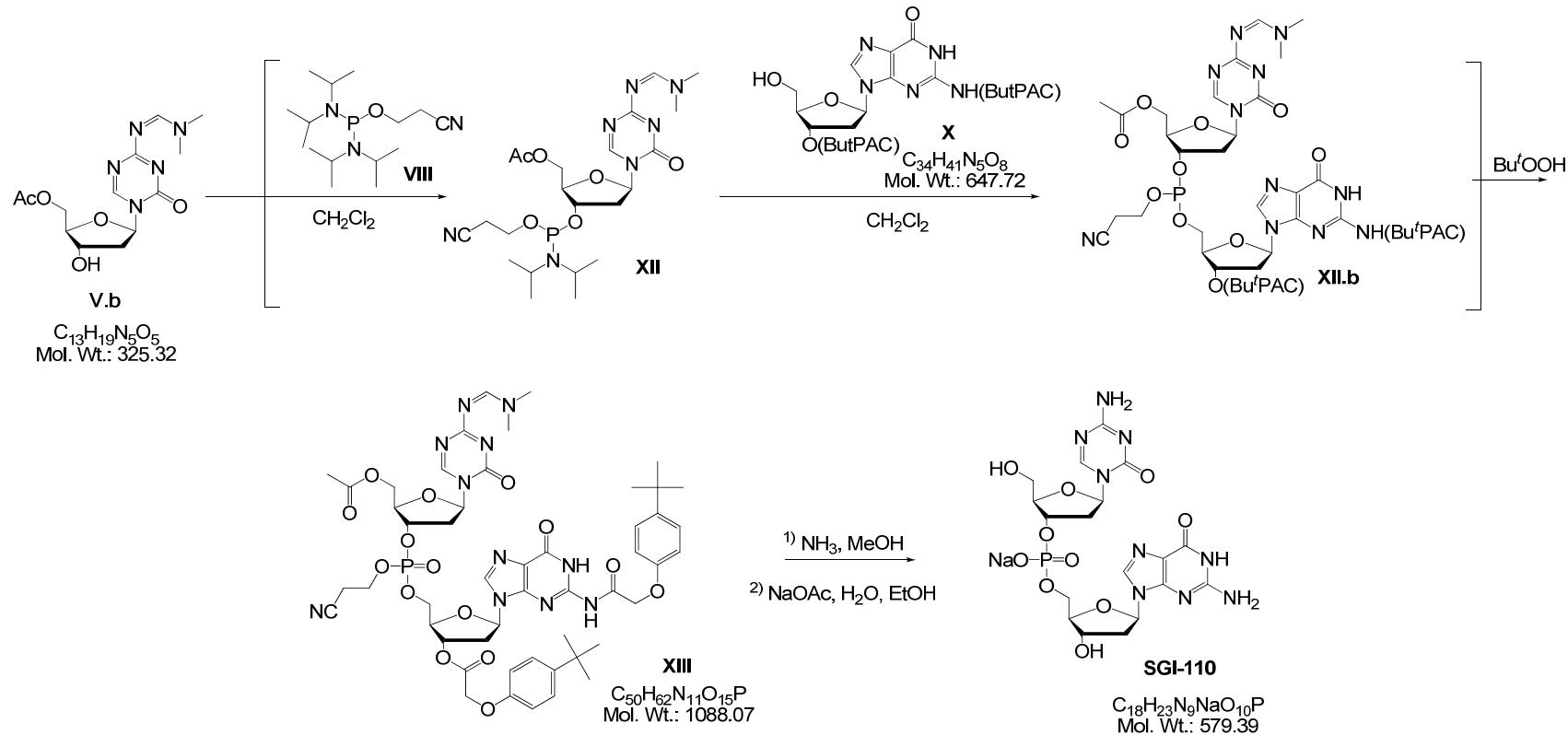
SGI-110 synthesis

- Decitabine's inherent aqueous instability



SGI-110 synthesis

- Solution phase versus solid phase synthesis
- Chromatography for impurity removal
- Sodium salt precipitates as an amorphous powder
- Scaled up from 500 mg to 1 kg scale



SGI-110 API Tests

- **Identity**
 - IR and HPLC
- **Purity**
 - Assay by HPLC
 - Related substances by HPLC (multiple degradation products)
 - % Purity by HPLC
 - Residual Solvents
 - Heavy Metals
 - Water
 - Residue on Ignition
- **Microbiological**
 - Microbial Limits
 - Endotoxins

SGI-110 Product formulation

- SGI-110 has limited stability in aqueous solution at all pHs

Reconstituted SGI-110 Lyophile		
Diluent	Water For Injection	Non-aqueous Formulation
SGI-110 solubility	~20 mg/mL	~130 mg/mL
Injection volume	> 1 mL	< 1 mL
Solution stability	Unstable at 2-8°C	Stable for a month in the refrigerator

Stable subcutaneous formulation

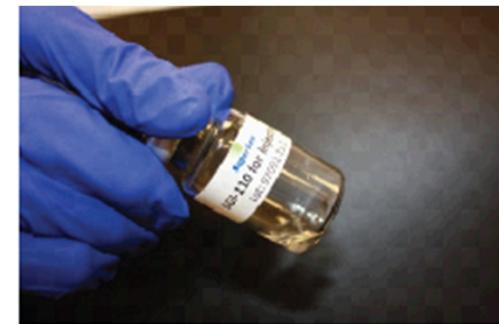
- A two vial kit - “Ready to reconstitute” product.
- Non-aqueous diluent using GRAS (generally recognized as safe) excipients
- High concentration (100 mg/mL) allows for low volumes of injection.
- Reconstituted solution stable for over 1 month under refrigerated conditions



Two vial kit - SGI-110 powder and diluent



Diluent added to SGI-110 powder

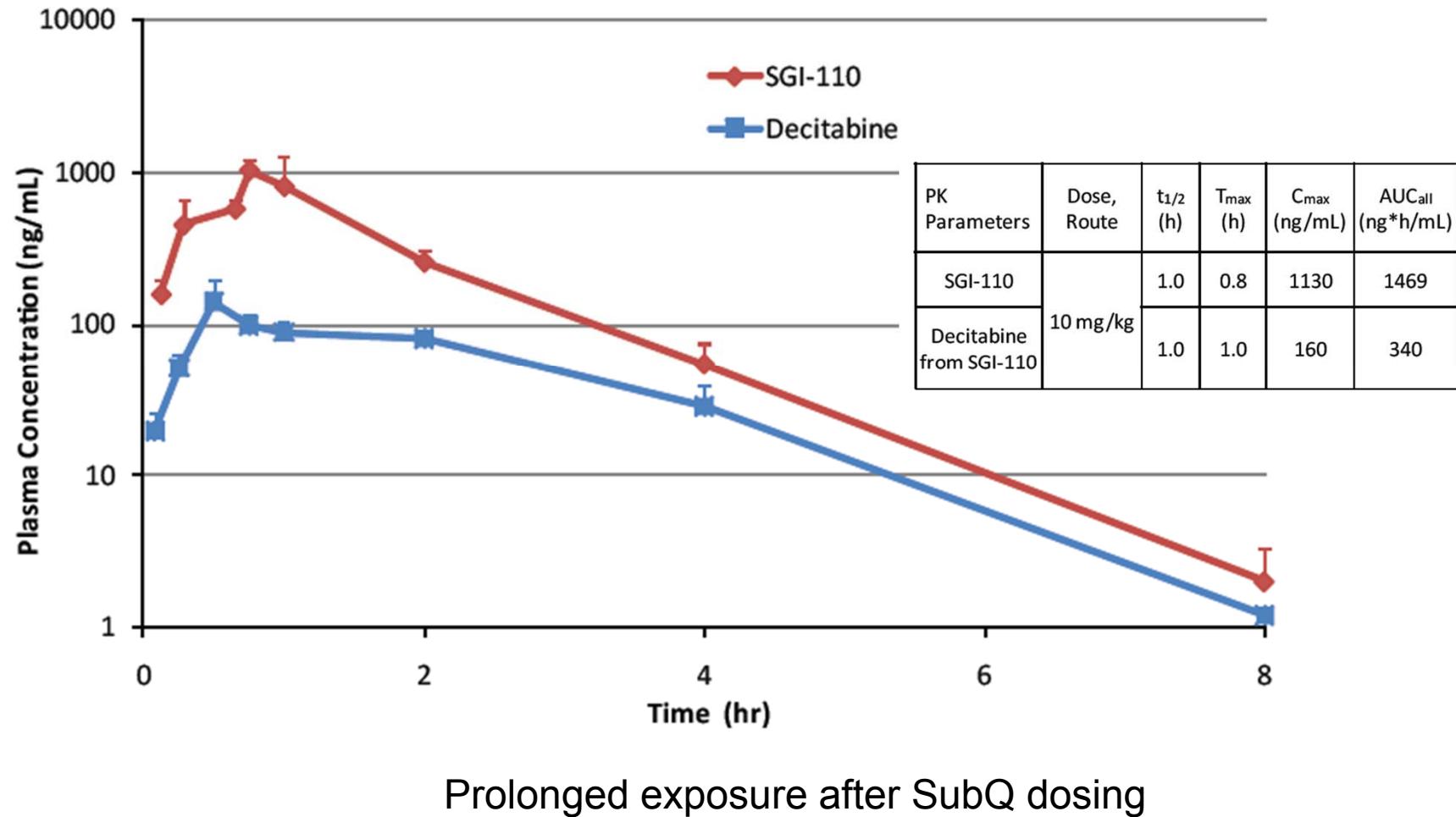


Stable solution formed

SGI-110 Product Scale up

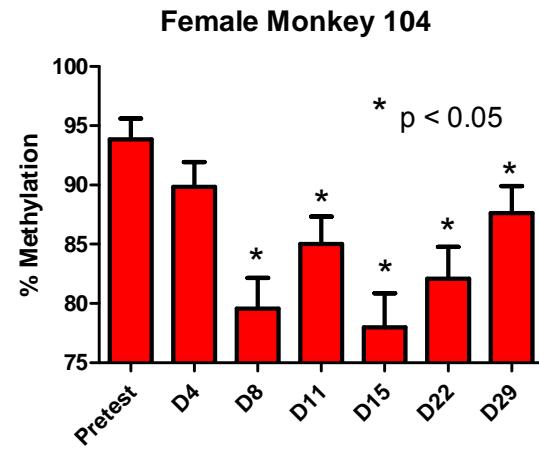
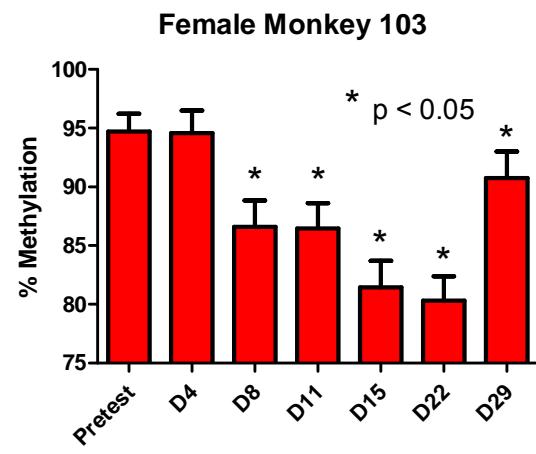
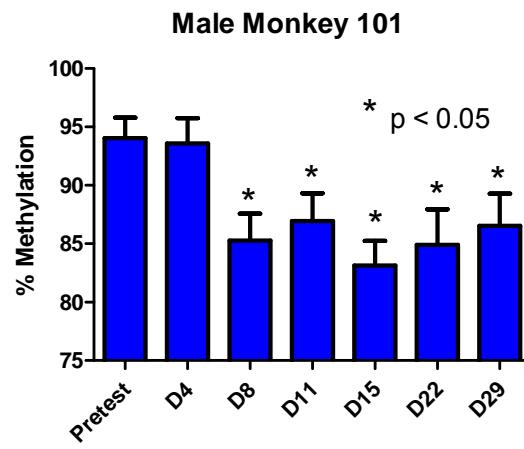
- **Bulk solution in aqueous versus solvent based lyophilization**
 - If aqueous bulk, then limited compounding and filling times
 - Use of solvents for bulk compounding allows longer time window
 - Class 3 solvents acceptable
- **Residual solvent in Lyophilized product**
- **Reconstitution time and procedure**
- **Process scaled to 3500 vials/lot for clinical needs**

PK in Monkey post SubQ dosing



Sustained hypometh. with weekly dosing

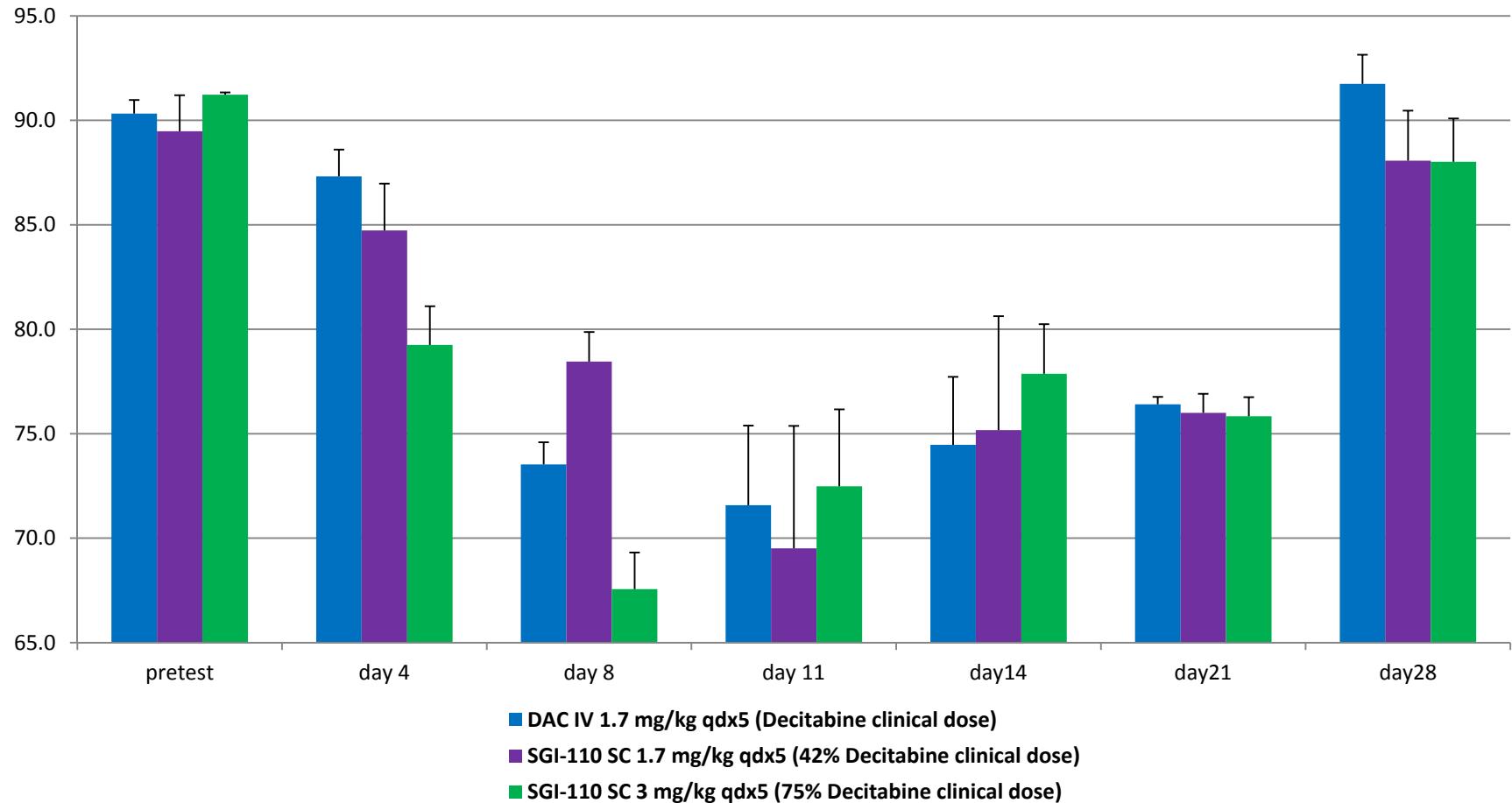
Methylation Results in Monkeys
(Weekly SQ Regimen 3 mg/kg on D1, D8, D15)



Significant decrease (p<0.05) in global methylation

Scholl et al, *Blood* (ASH Annual Meeting Abstracts) 2010 116: Abstract 1872

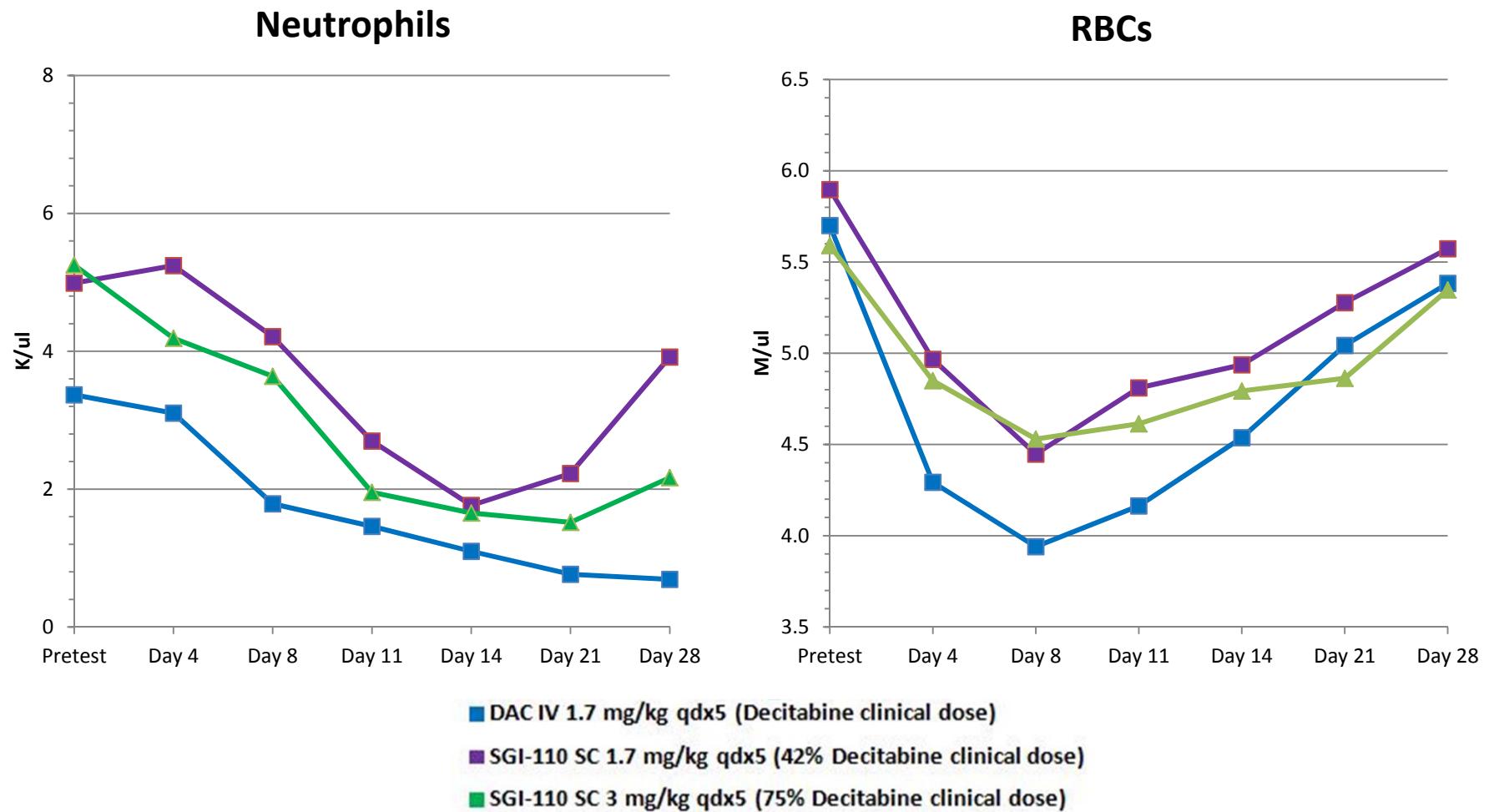
Comparison to Dacogen



Similar or better hypomethylation with SGI-110 at lower doses

Taverna et al, AACR 2012, Abstract 4076, Tuesday, Apr 03, 1:00 PM - 5:00 PM

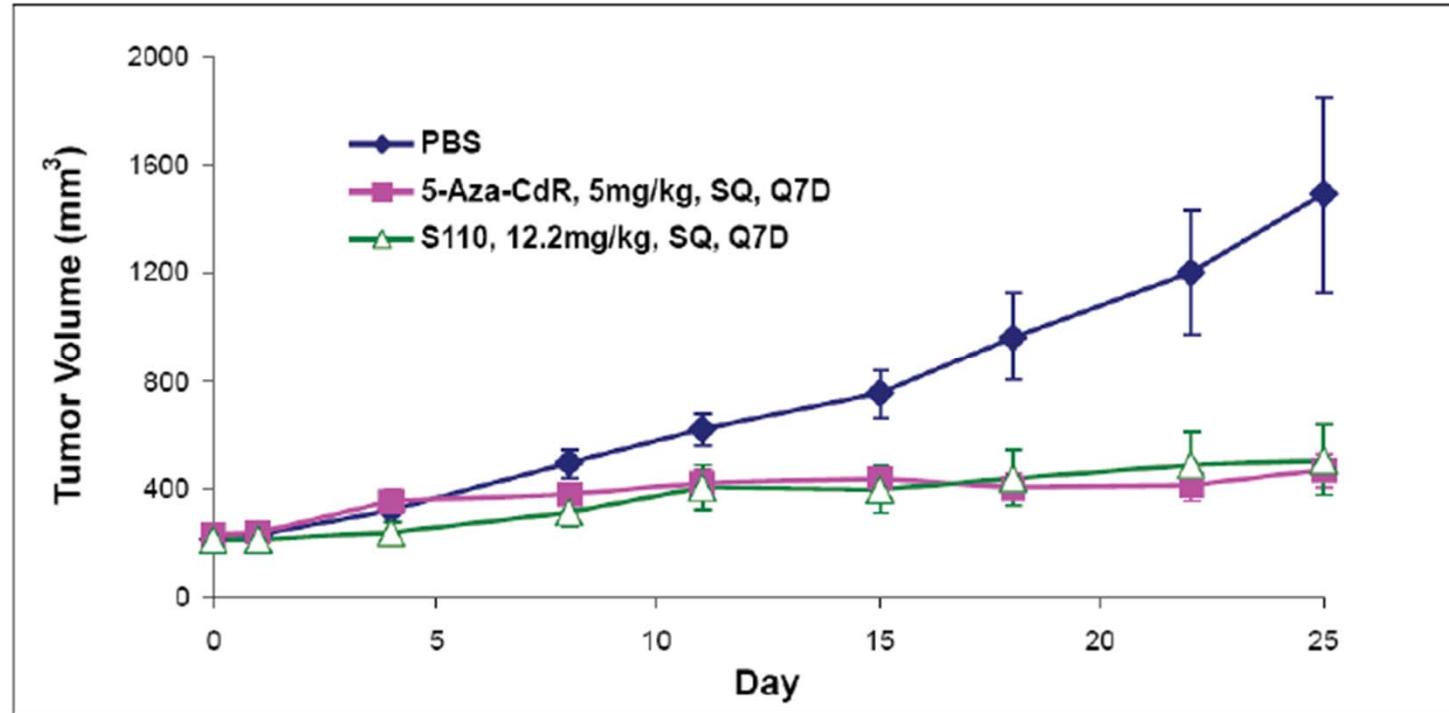
Improved tolerability



Less hematological suppression with SGI-110 at lower doses

Taverna et al, AACR 2012, Abstract 4076, Tuesday, Apr 03, 1:00 PM - 5:00 PM

Efficacy SQ dosing



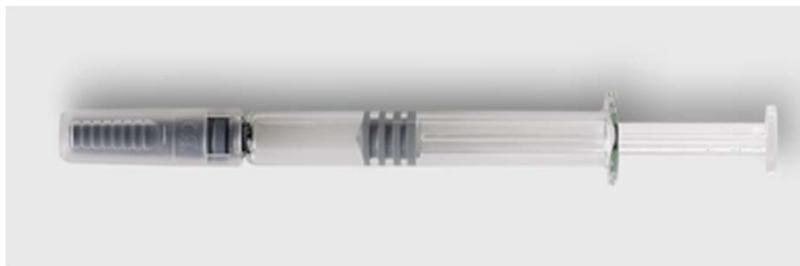
SGI-110 is effective at slowing EJ6 tumor growth *in vivo*

↓ in p16 promoter methylation as well as ↑ in p16 expression in tumors

Chuang et al. Mol. Can. Ther. 2010; 5: 1443-50.

Ongoing Product Development

- “Ready to use” SC injection, 100 mg/mL
 - Stable for ≥ 2 years refrigerated
 - Will make pharmacy compounding easier
 - Possible self-administration



OR



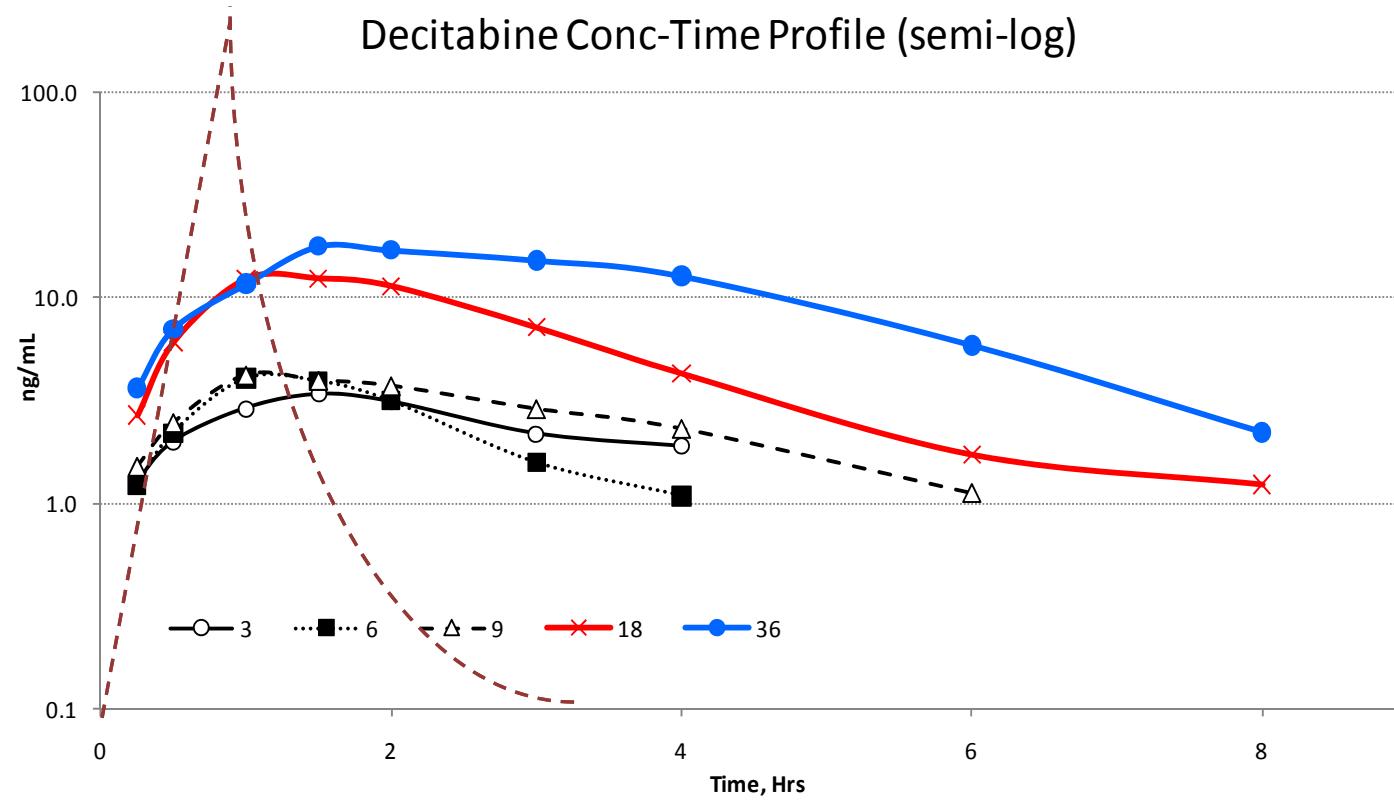


A Phase I, Dose Escalation, Multicenter Study of Two Subcutaneous Regimens of SGI-110, a DNA Hypomethylating Agent, in Subjects with Intermediate or High-Risk Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML)

**Oral presentation Monday, April 2, 2012, 3:00 p.m. - 5:10 p.m.,
Room W183, McCormick Place West**

Jean Pierre Issa, Fels Institute, Temple University, Philadelphia, PA

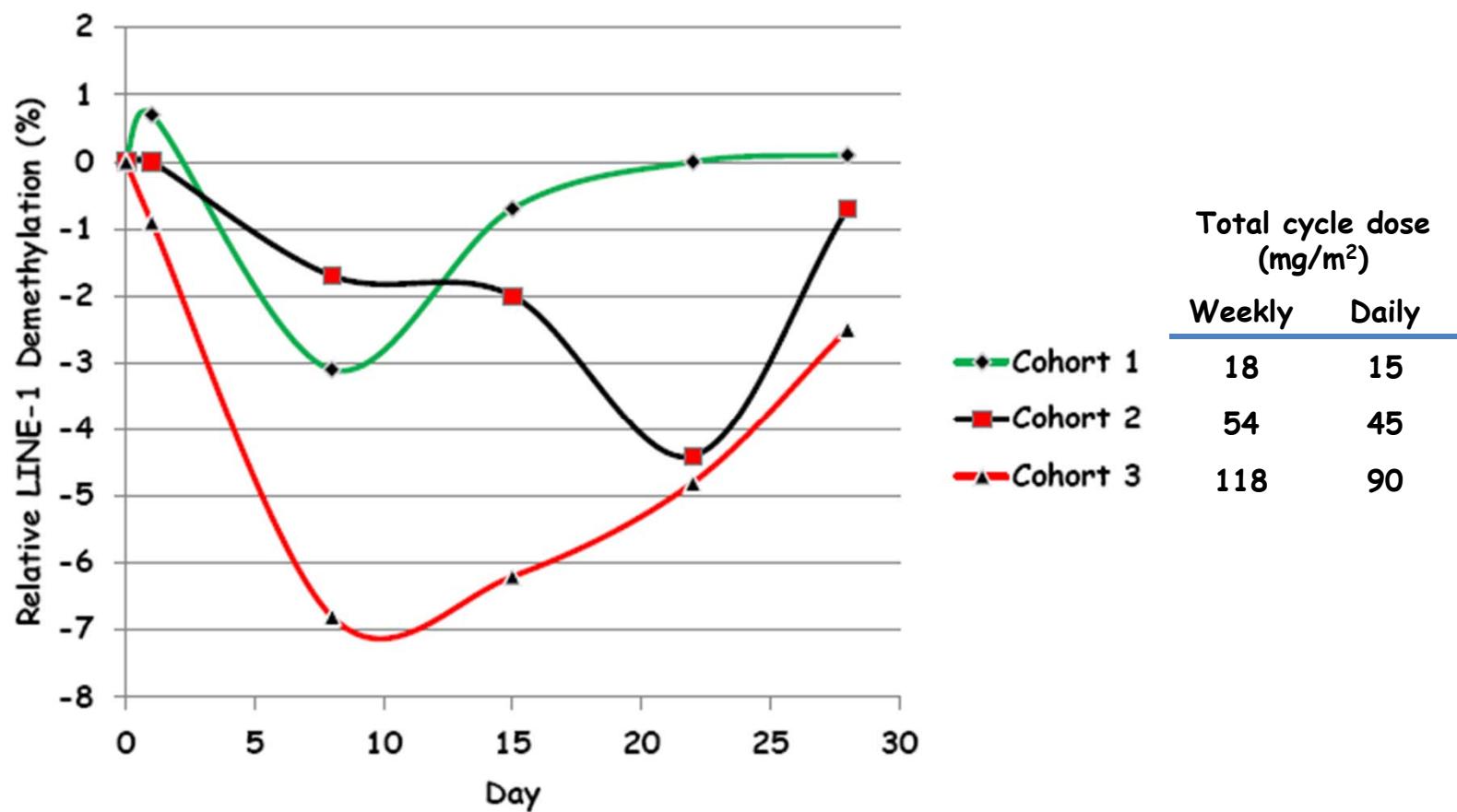
Decitabine PK Profile After SGI-110 Injection



- Lower C_{max} and more prolonged plasma decitabine exposures compared to IV decitabine.

EORTC 2011, J.P. Issa

Relative LINE-1 Demethylation



EORTC 2011, J.P. Issa

Conclusion

- **SGI-110 is a dinucleotide delivering decitabine**
- **Developed a 1 kg chemical synthesis and a nonaqueous subcutaneous formulation for clinical trials**
- **SGI-110 is expected to improve tolerability with a longer PK profile than IV Dacogen**
- **SGI-110 showed sustained hypomethylation with daily and weekly dosing in monkeys**
- **Encouraging PK and biomarker data from early Phase I study**

Acknowledgements

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- Clinical Development
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- Ellen Ritchie, Cornell
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- Karen Yee, Princess Margaret Hosp.
- Elizabeth Griffiths, Roswell Park
- William Blum, Ohio State

Stand Up to Cancer

- Peter Jones, USC
- Steve Baylin, JHU
- Jean Pierre Issa, Temple

