



Recombinant DNA Advisory Committee Meeting

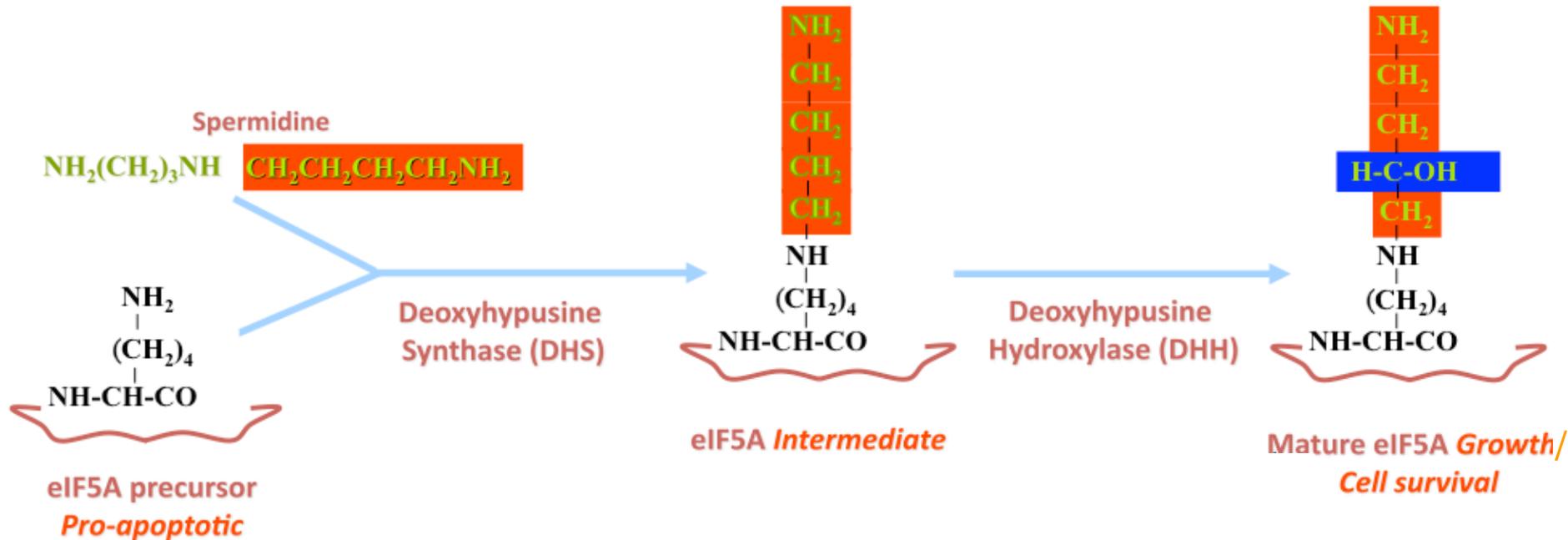
September 16, 2010

SNS01-T: eIF5A-based therapy for multiple myeloma

Why Multiple Myeloma?

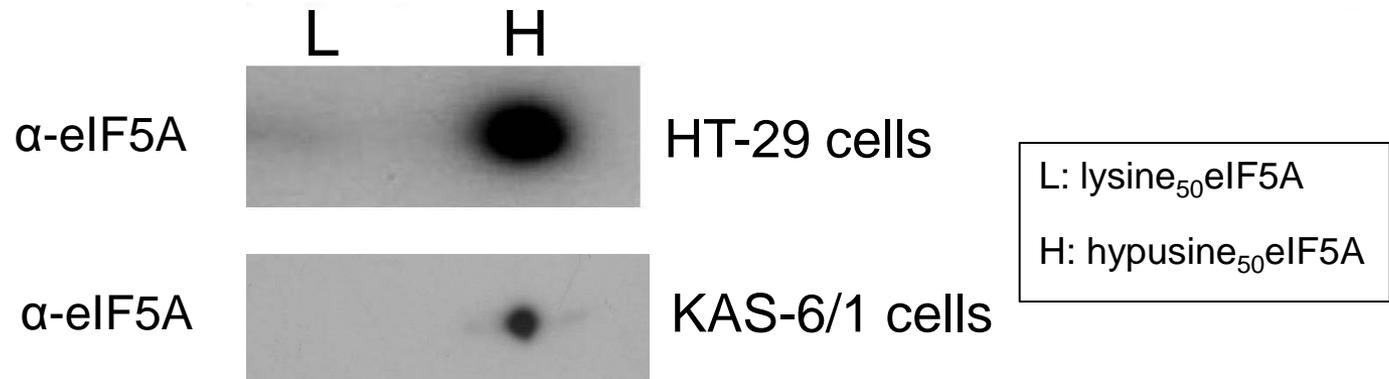
- **Characterized by proliferation of malignant plasma cells in the bone marrow**
 - Attributable in part to constitutive activation of NF-κB
- **Well established predictive markers for assessment of efficacy**
 - e.g., M-protein
- **Almost all patients experience drug-resistant relapse and succumb to the disease**
- **SNS01-T:**
 - Induces apoptosis in myeloma cells
 - Inhibits activation of NF-κB
 - NF-κB is a transcription factor that regulates cell survival and inhibits apoptosis
 - NF-κB promotes cytokine formation, including IL-6, an important growth factor for myeloma
 - Has shown efficacy in animal models of multiple myeloma

Unique Post-Translational Modification of eIF5A at Lysine₅₀



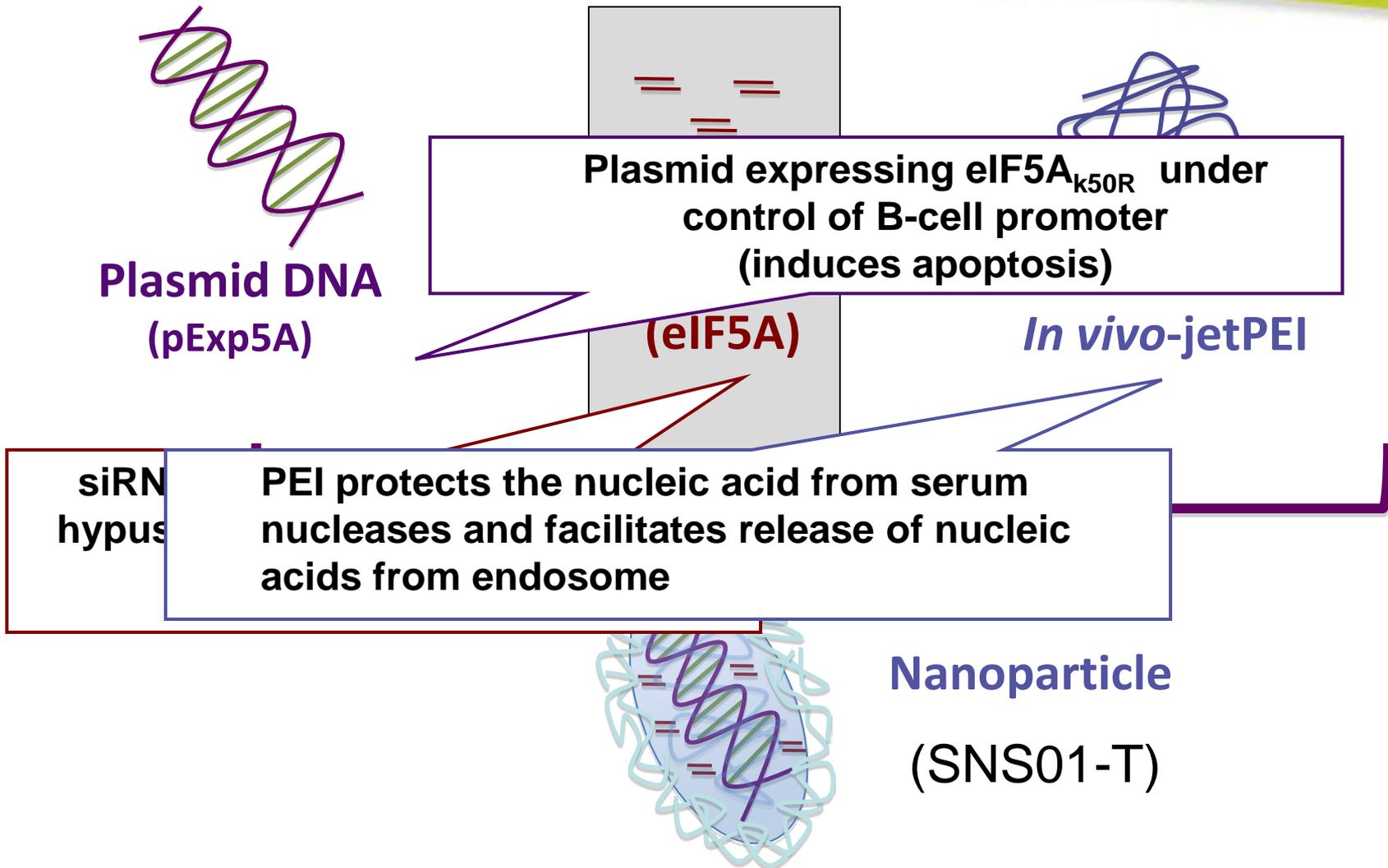
- eIF5A precursor (or eIF5A_{K50R}) induces apoptosis in myeloma cells
- Mature eIF5A (hypusine₅₀ eIF5A) promotes survival and cytokine production via NF-κB

SNS01-T: Therapeutic Strategy



- SNS01-T has been designed to have two therapeutic functions

SNS01-T has 3 Components





Toxicity of SNS01-T

- Currently being assessed in GLP pivotal toxicology studies in mice and dogs



SNS01-T: 6-Week Toxicity Study in Mice

➤ GLP study performed by BioReliance

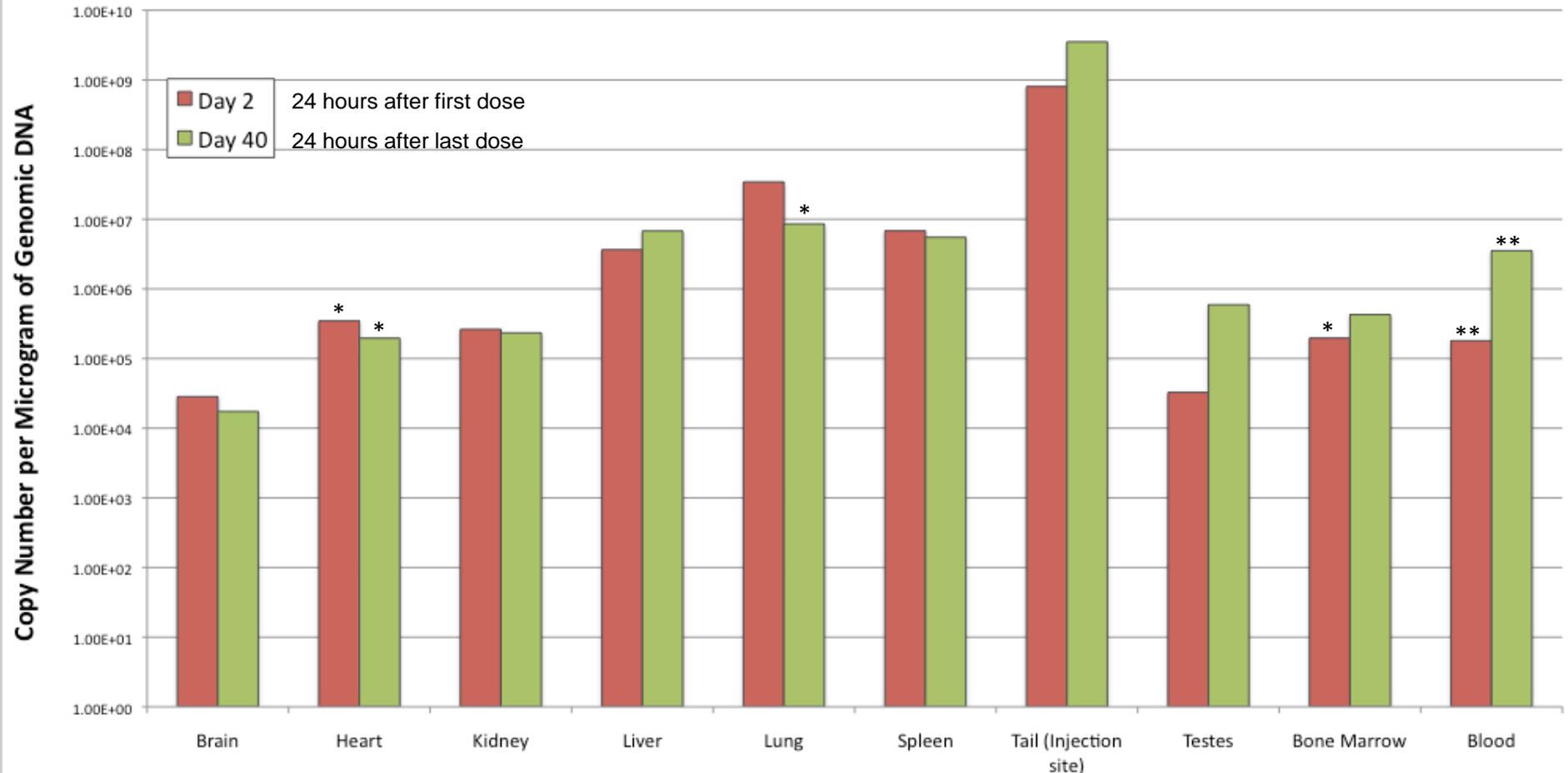
- SNS01-T dose groups
 - 0.25 mg/kg/d
 - 0.5 mg/kg/d
- Control groups
 - 5% glucose/Tris (no PEI)
 - 0.5 mg/kg/d empty plasmid
 - Human siRNA only (with empty plasmid) – 0.25 mg/kg/d
 - Mouse siRNA only (with empty plasmid) – 0.25 mg/kg/d
 - Plasmid and mouse siRNA – 0.25 mg/kg/d
 - Plasmid only – 0.25 mg/kg/d
- Intravenous injection, twice per week + 14 day recovery

➤ Study Design

- Observations include:
 - clinical signs
 - clinical pathology
 - ✓ hematology, coagulation, clinical chemistry, urinalysis
 - gross pathology and histopathology
 - cytokine response
 - ✓ serum: IFN- γ , IL-1 β , IL-10, IL-12p70, IL-6, GRO, TNF- α
 - T-cell response
 - ✓ splenocytes: IFN- γ , IL-1 β , IL-10, IL-12p70, IL-6, GRO, TNF- α
- Biodistribution (qPCR)

Preliminary Biodistribution Data in Mice

Biodistribution of Plasmid in Male Mice (Days 2 and 40)



* Values represent n < 3; ** copy number per 10 microliters of blood

B Cell-Specific Promoter

- Potential off-target toxicity minimized by using a B cell-specific promoter / enhancer to regulate eIF5A_{K50R} expression

* Copy number of eIF5A_{K50R} mRNA per ng total RNA

	Tumor	Liver	Kidney
Control	153 ± 81	18.78 ± 9.6	16.3 ± 1.4
SNS01-T	5694 ± 2772	81.70 ± 89.8	31.2 ± 47.9

*SCID mice bearing subcutaneous MM tumors (RPMI 8226) treated twice weekly with SNS01-T for 30 days

SNS01-T: 6-Week Toxicity Study in Dogs

- GLP study performed by Charles River Laboratories
 - Study Design
 - Dose groups: 0, 0.375, 0.75 mg/kg/day
 - Intravenous infusion, twice per week + 14 day recovery period
 - 3 dogs/sex/group (main study) + 2 dogs/sex/group (recovery study)
 - Observations include:
 - Clinical signs & ECGs
 - Clinical pathology (hematology, coagulation, clinical chemistry, urinalysis)
 - Gross pathology
 - Histopathology
 - Cytokine measurements



SNS01-T Efficacy Assessment

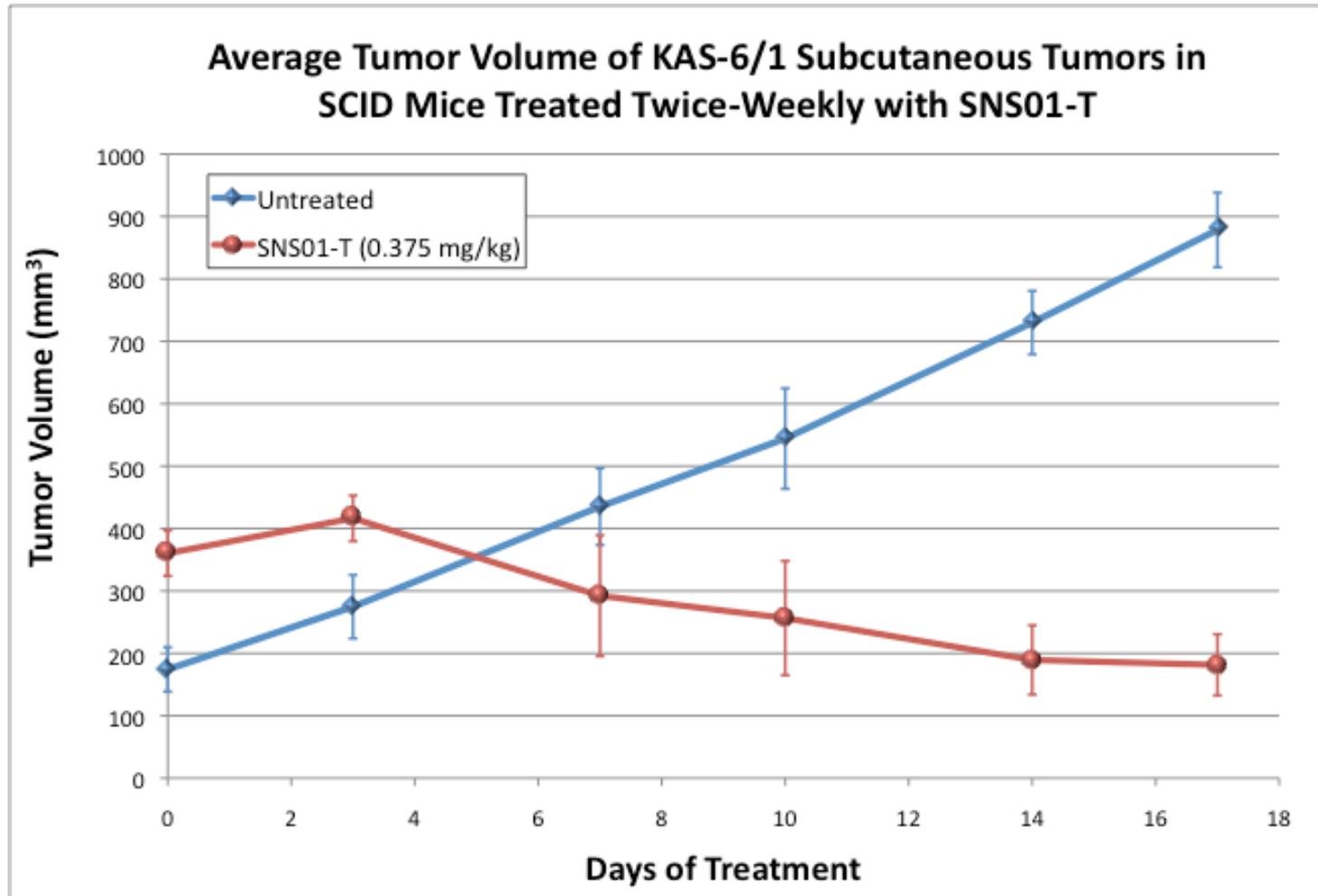
➤ Multiple approaches:

- Studies with human myeloma cell lines demonstrating:
 - *eIF5A1_{k50R} induces apoptosis*
 - *eIF5A1 siRNA suppresss pro-survival hypusine-eIF5A and inhibits activation of NF-κB*

- Studies with human MM mouse xenograft models, demonstrating :
 - *Co-localization of pExp –GFP and eIF5A1-siRNA in tumor cells*
 - *Apoptosis in tumor cells*
 - *Inhibition of tumor growth; tumor shrinkage*
 - *Minimal effects in non target tissues (e.g., liver)*

- Biodistribution studies of IV administered SNS01-T showing:
 - *Localization in bone marrow based on qPCR of the plasmid*

Efficacy in Mouse Xenograft Model



Orthotopic Models

- Orthotopic models have limitations; not clearly shown to be more predictive of efficacy than xenograft model
- Plan to evaluate localization of plasmid and siRNA to bone marrow in sorted myeloma cells from patients



Clinical Protocol SNS01-T-001

- Single clinical site
 - Mayo Clinic, Rochester, MN

- Principal investigator
 - John Lust, M.D., Ph.D.

Clinical Protocol Design

- Patients with relapsed/refractory multiple myeloma (previously failed two standard regimens)
- Dose escalation
 - 3 cohorts, 4 patients per cohort
 - Proposed dose levels (dependent on nonclinical studies)
 - 0.094 mg/kg
 - 0.188 mg/kg
 - 0.375 mg/kg
- 6-week therapy
- 2 intravenous infusions per week
 - Approximately 3 hours per infusion

Clinical Protocol Design (2)

- Single cohort dosed at a time
- After completion of 6-week dosing period, each patient followed up for 4-week safety period
- Independent data and safety monitoring board to review data after completion of each cohort and approve escalation to next dose level



Inclusion Criteria

- Have measurable disease as defined by M-protein
- Have acceptable liver function and creatinine levels
- Have acceptable WBC and platelet levels
- Have relapsed or refractory disease after two or more prior multiple myeloma regimens
- Be at least 4 weeks beyond the last multiple myeloma therapy and have recovered from acute toxicities of prior regimens
- Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- Have life expectancy of at least 3 months
- Be ≥ 18 years of age and willing to sign the informed consent

Exclusion Criteria

- Presence of nonsecretory myeloma
- Presence of an active infection or serious co-morbid medical condition
- Be receiving other concurrent anticancer agents or therapies
- Be receiving other concurrent investigational therapies or have received investigational therapies within 4 weeks of screening
- Be pregnant or nursing

Clinical Endpoints

- **Safety** - frequency, severity, and duration of treatment-emergent AEs and changes in laboratory parameters
- **PK** – serum (and possibly bone marrow) concentration of plasmid and siRNA components
- **Immunogenicity** – antibodies against SNS01-T and inflammatory cytokines
- **Preliminary efficacy** - time to progression as determined by changes in biomarkers (M-protein, hemoglobin, C- reactive protein, free light chain, bone marrow plasma cell %, plasma cell labeling index)

Group Discussion