siege pharmaceuticals

Targeting the root causes of metabolic disease

Obesity is killing us

Obesity is now the second leading cause of preventable death in the US

2/3 of US adults have obesity or are overweight and rates are increasing

Obesity is a *disease*

with treatable, biological causes – diet and exercise are not sufficient

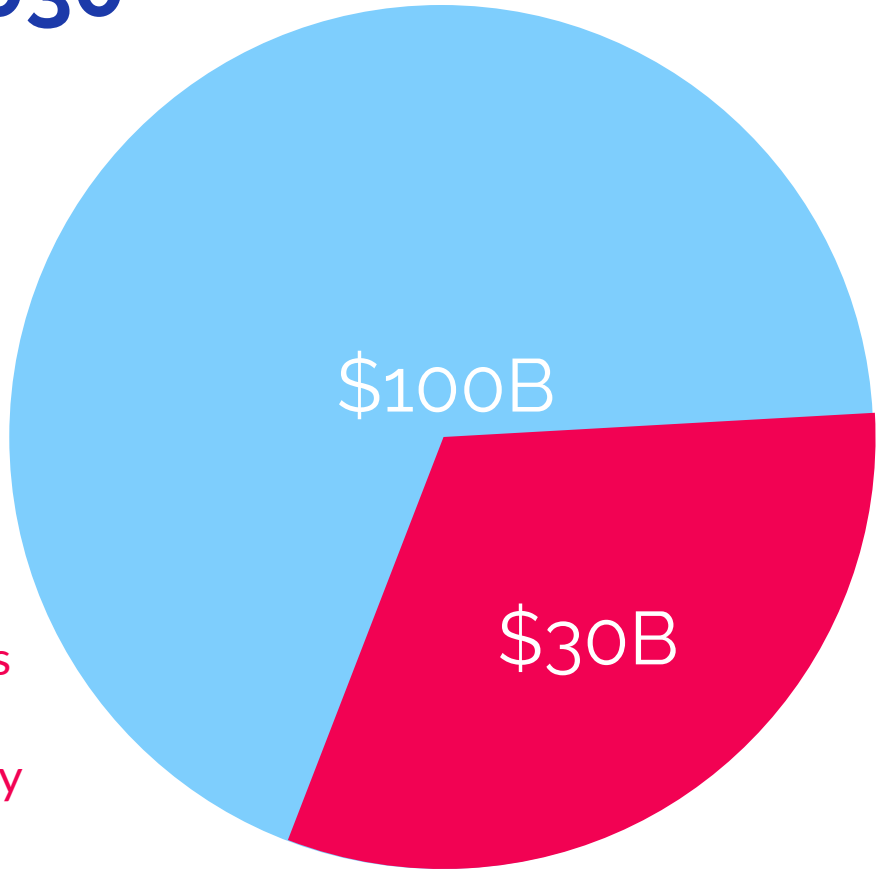
Hunger for treatments

High consumer demand

Hot marketplace ripe for innovations that broaden insurance coverage

Obesity Marketplace 2030

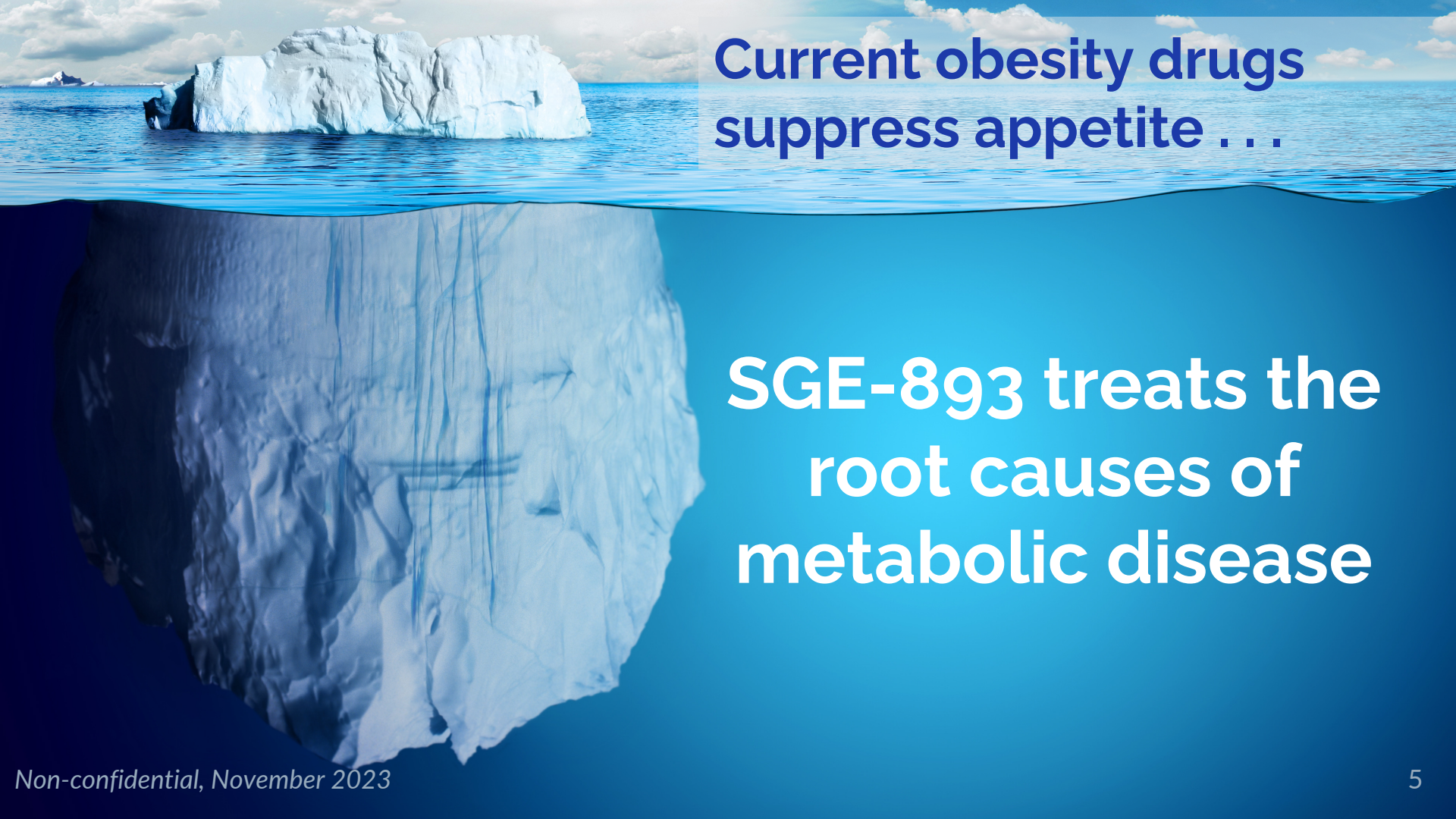
- **Total Addressable Market – $412B** annual US medical costs related to high BMI *World Obesity Atlas 2023*
- **Serviceable Available Market** – Projected market for obesity drugs *Goldman Sachs, October 2023*
- **Serviceable Obtainable Market** – Anticipate >30% market share for Obesity*PLUS* agent that directly addresses drivers of cardiovascular disease, type 2 diabetes, fatty liver disease, chronic kidney disease



The competition:

- Peptide GLP-1R and/or GIPR agonists Wegovy (Novo) & Mounjaro (Lilly) - 15% weight loss; gut issues and weight re-gain (above baseline) problematic
- Pfizer, Lilly, Novo have oral small molecule GLP-1 agonists in trials that match injectables for weight loss
- Triple agonists in development

Unmet need: *oral drugs that* ***directly address insured co-morbidities*** *or* ***improve weight loss*** *(best-in-class or in combination)*


Current obesity drugs suppress appetite . . .
SGE-893 treats the root causes of metabolic disease

The Siege Advantage

Targets the root causes of metabolic disease

- → Improves mitochondrial function, ↓ inflammation & fibrosis
- → Obesity*PLUS* ↑market share & insurance coverage

Multiple novel targets

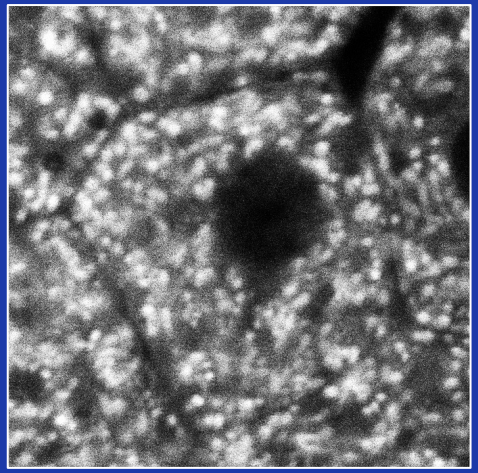
- → Robust single-agent activity beyond appetite control
- → Potential for synergy with other drugs

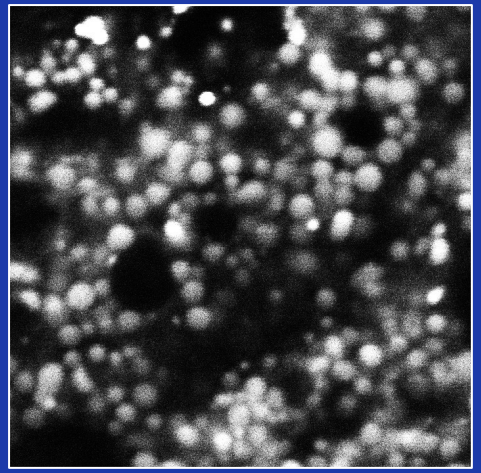
Mimics a natural regulator to minimize toxicity

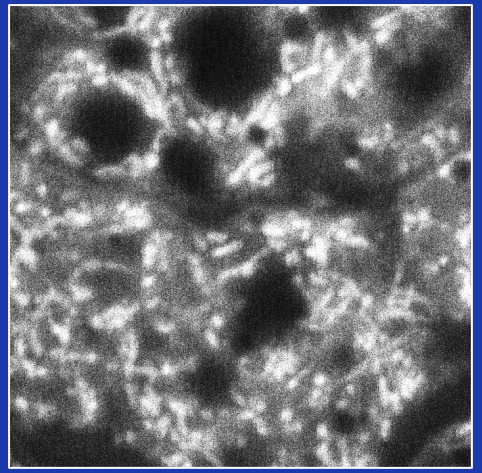
- → Targets selected by nature
- → Safe even with long-term dosing
- → IP protection
- → Additional indications
  (Cancer, ASO, neuro, addiction)

SGE-893 restores mitochondrial form and function

normal | High Fat Diet | HFD + SGE-893







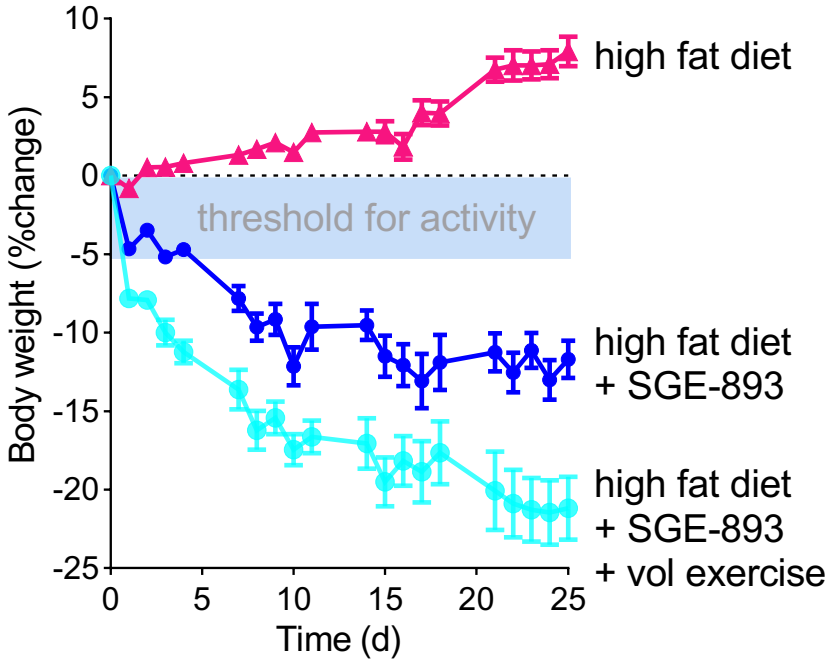
Live imaging of mitochondria in mouse livers

4 h after oral dosing

SGE-893 out-performs other agents targeting mitochondrial fission

Proof of concept established

Oral treatment 3 days/week



Jayashankar et al., (2021),
EMBO Mol Med 13:e13086

- Rapid weight loss in mice on a high fat diet without toxicity
- Weight loss in mice = Wegovy, externally replicated
- Funded SBIR will benchmark efficacy vs. semaglutide in obesity and NASH and evaluate in combination

The Siege Team

Alison McCracken, PhD

CEO

>10 years experience with Siege compounds, CLS FAST graduate

Aimee Edinger, VMD/PhD

Founder

Prof & UCI Chancellor's Fellow

>20 years' experience with sphingolipids and metabolism

Steve Hanessian, PhD

Founder

UCI Distinguished Prof of Chemistry and Pharm Sci

Consultant for >20 pharma companies

Advisors

John Bauman
Anthony Casarez
Vandana Date
Adam Galan
Dan Levy
Joe Markunas
Masoud Mokhtrani
Kay Olmstead
Roopa Rai
Peter Weinstein
Bo Zhou

$3 million

Needed to optimize lead compound into a clinical candidate over 1 year

- Additional $7.5M to IND plus $6M through Phase 1

Milestone Map

	Q3 2023	Q4 2023	Q1 2024	Q2 2024	Q3 2024	Q4 2024	Q1 2025	Q2 2025	Q3 2025	Q4 2025
PROJECT A: Establish competitiveness in obesity marketplace: SBIR FUNDED										
Milestone 1: Activity at weight loss-independent NASH endpoints (fibrosis, inflammation)	$150,000									
Milestone 2: Efficacy vs semaglutide & in combination for obesity/ NASH		$100,000								
PROJECT B: Generate IND-ready compound: SEEKING NEW FUNDING (Ph I SBIR submitted)										
Milestone 3: Optimized lead with therapeutic index >10, 5-fold lower dose			$3M							
Milestone 4: In vivo efficacy studies with optimized compound, non-GLP tox						$2.5M				
Milestone 5: GLP toxicity, IND filing, GMP scale-up								$5M		
Milestone 6: Phase I Clinical Trial									$6M	

EXIT STRATEGY: Partner pre/post-PhI with pharma with obesity/NASH pipelines

Siege compounds correct more than just obesity

- **Novel targets**
  - Polypharmacology distinct from GLP1/GCGR/GIPR agonists
  - High potential for synergy with competitors' drugs
- **Weight loss *PLUS* reduced fibrosis, inflammation**
  - Direct benefits for CVD, NASH, T2DM
  - Will enhance insurance coverage, expand market share

Siege MOA addresses other indications:

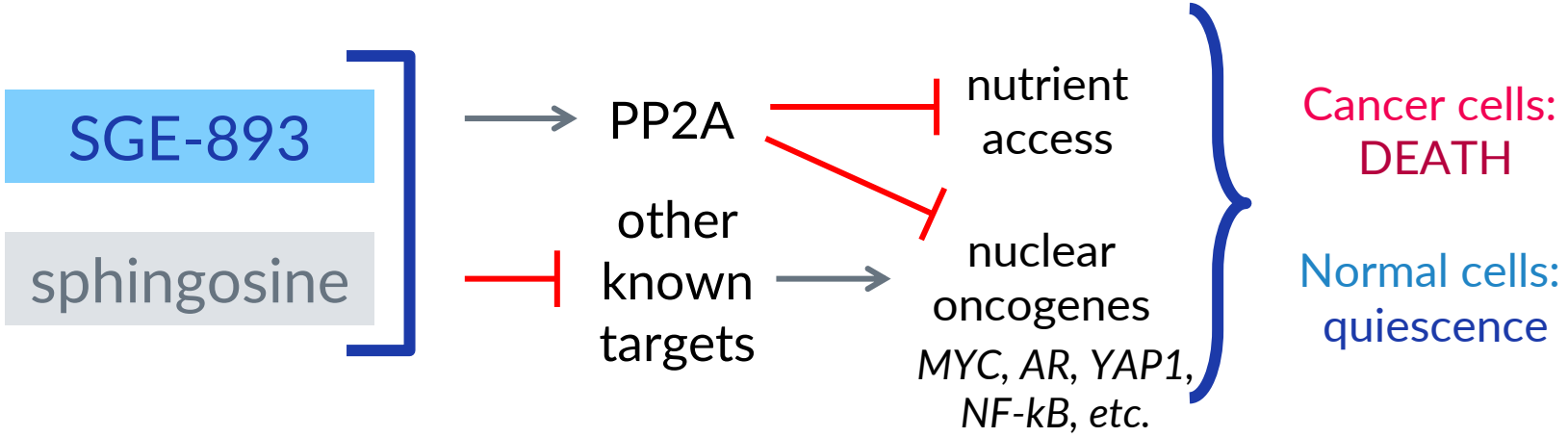
In vivo POC completed

- *Cancer*
- *Oligonucleotide therapeutic potentiator*
- *Anti-viral*

POC required

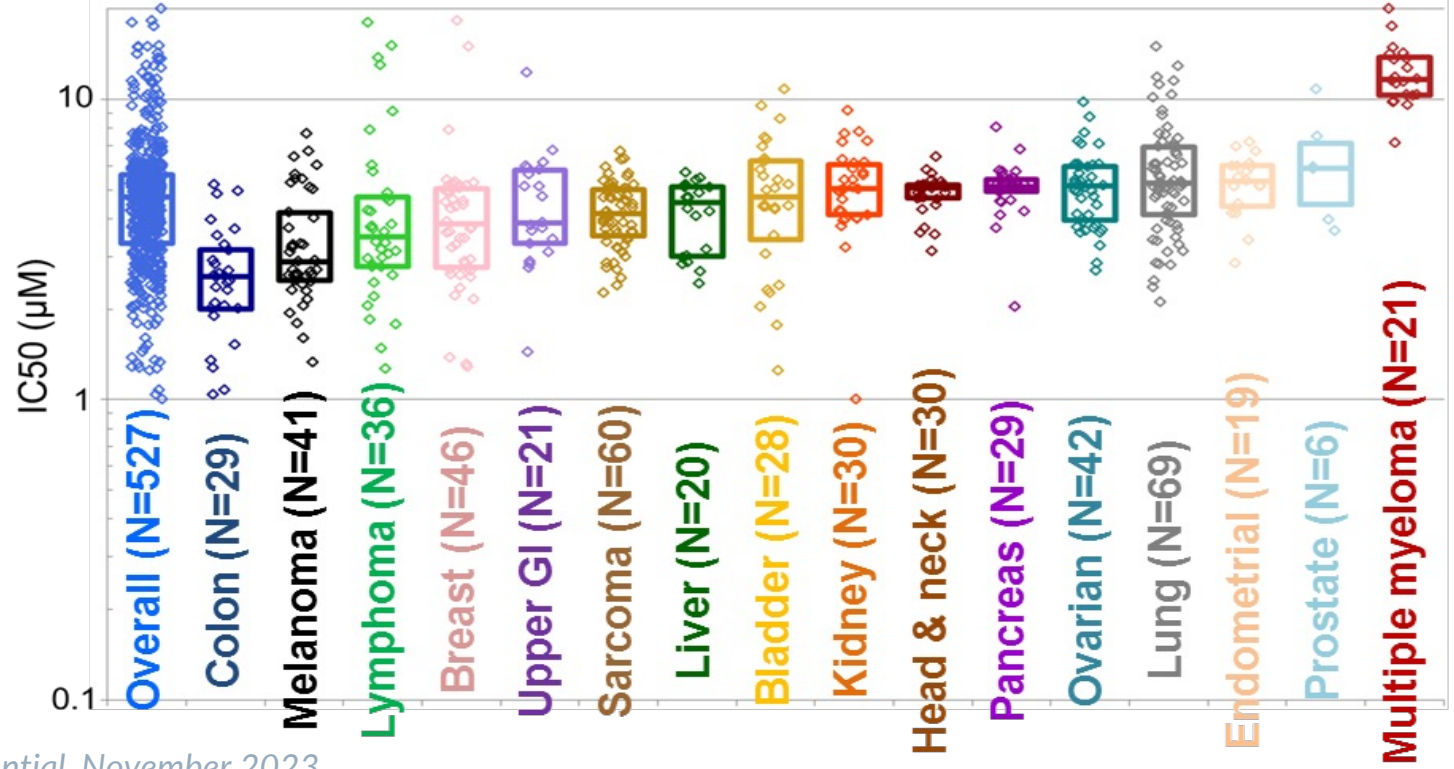
- *Neurodegenerative diseases*
- *Addiction*

SGE-893 engages multiple, complimentary oncology targets

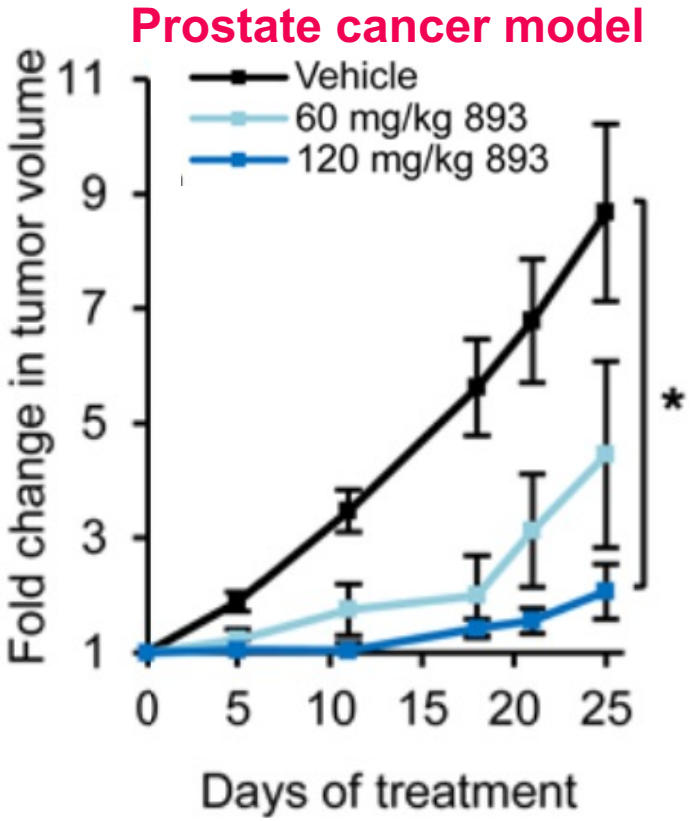


Siege compounds active across cancer type and driver mutation

IC50s in human cancer cell lines generated in collaboration w/Dennis Slamon's TORL group at UCLA



Proof of concept: oncology



- Kills enzalutamide-resistant, patient-derived PC tumor samples in vitro
- Autochthonous prostate tumor growth inhibited by 82%
- *Anti-cancer dose spares normal tissues*
- Raised $3.7M in VC and SBIR funding for cancer indication
- Non-GLP tox uncovered ADME liability addressable with med chem program

Development strategy: oncology

- SGE-893 has impressive pan-cancer activity in vitro consistent with known targets
- Failed in pre-IND oncology studies due to ADME limitations (poor accumulation in flank PDX tumors, solubility-limited in buffered solutions)
- **Plan:** use traditional and AI-assisted drug design to simultaneously optimize potency and pharmaceutical properties while maintaining target engagement (assay available) and synthetic accessibility

SGE-893: POC for sphingolipid analogs

By using a natural master regulator as the template, we have developed safe and effective oral drugs that redundantly target

- Novel, upstream mechanism of action
- High-value, "undruggable" oncology targets
- Oral drug – single agent or complementary therapy

while avoiding toxicities and side-effects

Contact: Alison McCracken, CEO
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siege pharmaceuticals

Supplementary slides

LEAD OPTIMIZATION:

Improve ADME to reduce efficacious dose and increase therapeutic index

state-of-the-art generative modeling solutions with built-in synthetic accessibility for successful drug discovery projects

- **Proven success - efficient optimization of 11 properties in parallel**
  - Iterative design-synthesis cycles guided by target engagement, biological, and ADME assays
  - Feasibility analysis already completed in partnership with Iktos

Projected R&D Expenses: Metabolism/NASH

	Optimized Lead	In Vivo Efficacy, Tox de-risk	GLP tox/IND
R&D			
AI-assisted lead optimization	$850,000		
Synthesis	$500,000		
Testing (ADME/PK)	$200,000		
Compound scale-up		$700,000	
Obesity/NASH study (2 mouse models)		$400,000	
non-GLP tox (rat and dog)		$350,000	
Genotoxicity			$10,000
GLP tox (rat and dog)			$800,000
Success Fees (AI partner)			$1,450,000
GMP scale-up			$1,250,000
	$1,550,000	**$1,250,000**	**$3,510,000**