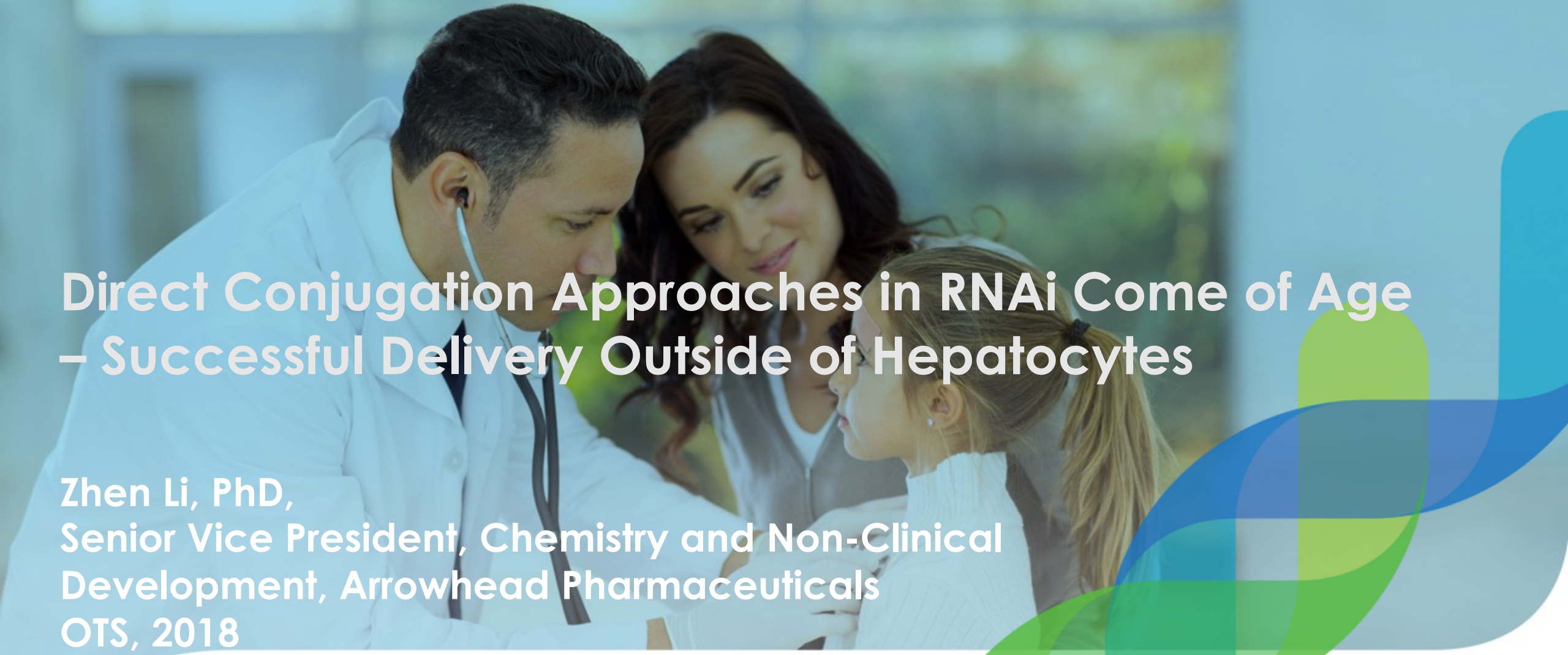


Direct Conjugation Approaches in RNAi Come of Age – Successful Delivery Outside of Hepatocytes

Zhen Li, PhD,
Senior Vice President, Chemistry and Non-Clinical Development, Arrowhead Pharmaceuticals
OTS, 2018

arrowhead pharmaceuticals

Disclosures

- I am an employee and shareholder of Arrowhead Pharmaceuticals, Inc.

Forward-looking Statements

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, the safety and efficacy of our product candidates, the duration and impact of regulatory delays in our clinical programs, our ability to finance operations, the timing for starting and completing clinical trials, rapid technological change in our markets, and the enforcement of our intellectual property rights. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Outline

- Hif2a - a validated target gene for ccRCC
- Discovery and development of Arrowhead's drug candidate for the treatment of ccRCC
- Survival data
- Latest TGI data

Renal Cell Carcinoma (RCC) and ccRCC

- RCC
  - The most common type of kidney cancer in adults, responsible for ~90-95% of all cases
  - Cancer arising from the lining of proximal renal tubules
  - The most lethal of all the genitourinary tumors
  - Accounts for ~200K new cases per year worldwide and ~100K deaths

- ccRCC - (clear cell renal cell carcinoma)
  - Most common form of hereditary and sporadic RCC in adults (70%–85%)
  - Characterized by malignant epithelial cells with clear cytoplasm

Hif2a – A Genetically Validated Target Gene for ccRCC

- ccRCC - distinctive genetics
  - The majority of ccRCC have either somatic or germline inactivation in the Von Hippel-Lindau (VHL) gene
- Loss of VHL leads to over-expression of HiF2a
  - Evidence from literature and our experimental results support HIF2a as an oncogenic driver

RNAi for ccRCC: Challenges and Opportunities

Challenges:

- Delivery
  - Extrahepatic delivery of RNAi sequences to the tissue of interest and cell of interest is hard
  - **Extrahepatic, systemic delivery is harder**
- Safety concerns
  - Toxicities associated with delivery components or vehicles (polymer)

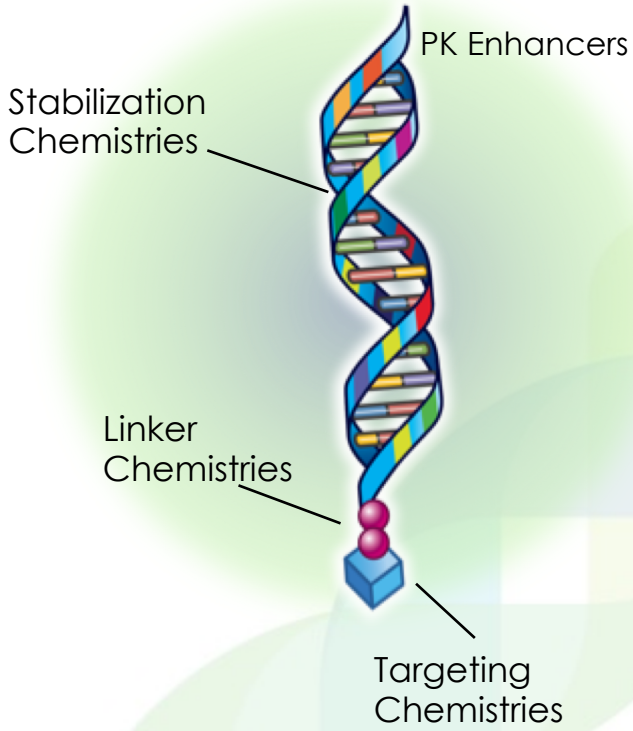
Opportunities for RNAi

- Highly specific
  - Gene specific
    - Limit off-target effect through in-depth bioinformatics studies
  - Cell specific – receptor/ligand interaction
- TRiM™ platform based conjugate?

TRiM™ Platform for Extrahepatic Tumor Delivery

Requires all components of TRiM™ working synergistically together

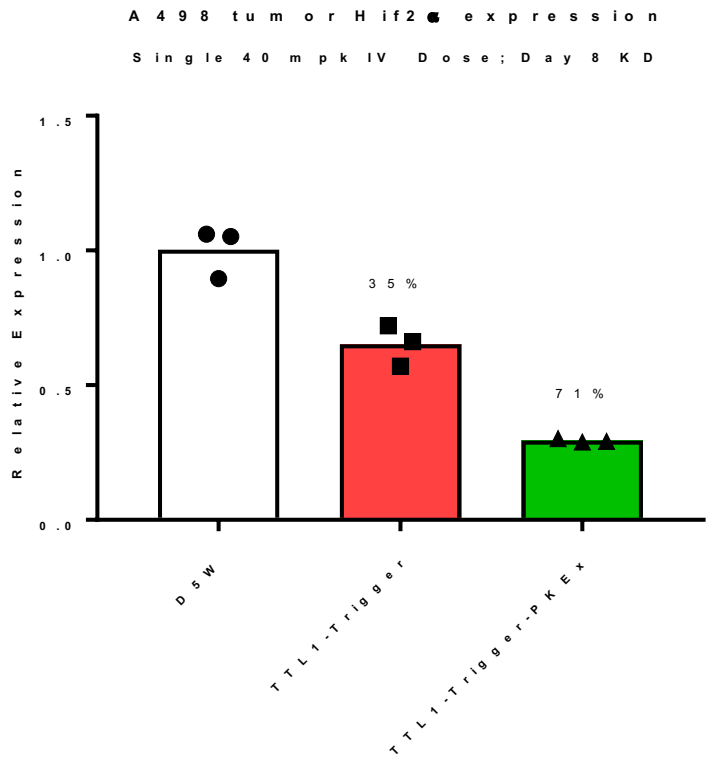
- RNAi sequence selection and optimization
  - Paramount importance
  - Determines potency, selectivity and stability of the conjugate
- Ligand/receptor pairs discovery and development
  - Critical for RNAi delivery
    - Enables tissue specific, cell specific delivery and uptake through endocytosis
- PK enhancers
  - RNAi sequences are highly hydrophilic
- Linker study
  - Cleavability/stability

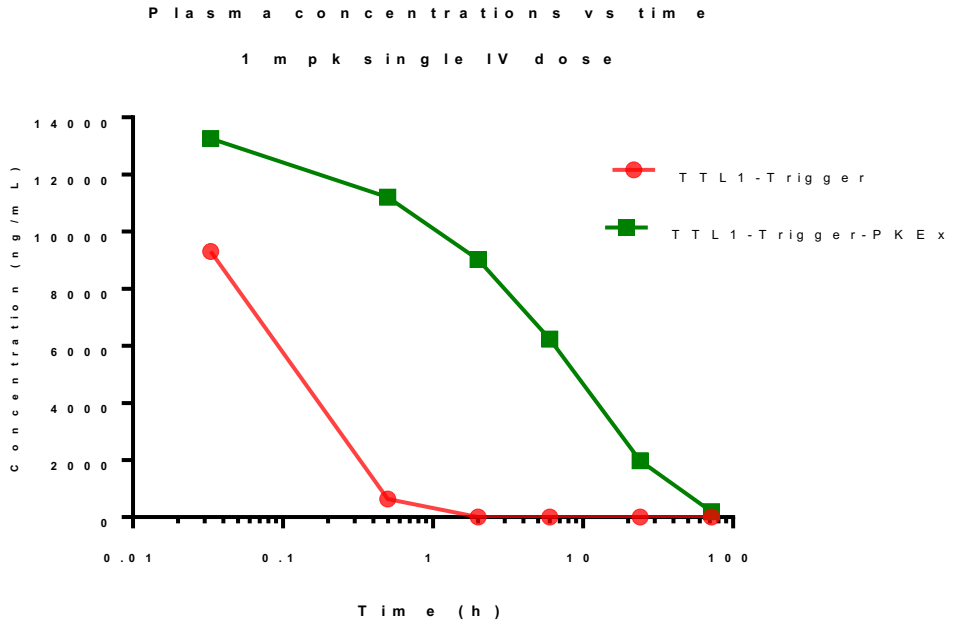


TRiM™ Platform for Extrahepatic Tumor Delivery: Key Design Elements

- IV or subcutaneous dosing, weekly or less frequent
- No need for active endosomal escape agent
- No need for "delivery vehicle" – no need for polymer or nanoparticles
- Powerful target gene knockdown
- Statistically significant survival data
- Wide therapeutic index
- Efficacy and safety in patients

Direct Conjugate? Not an Easy Start



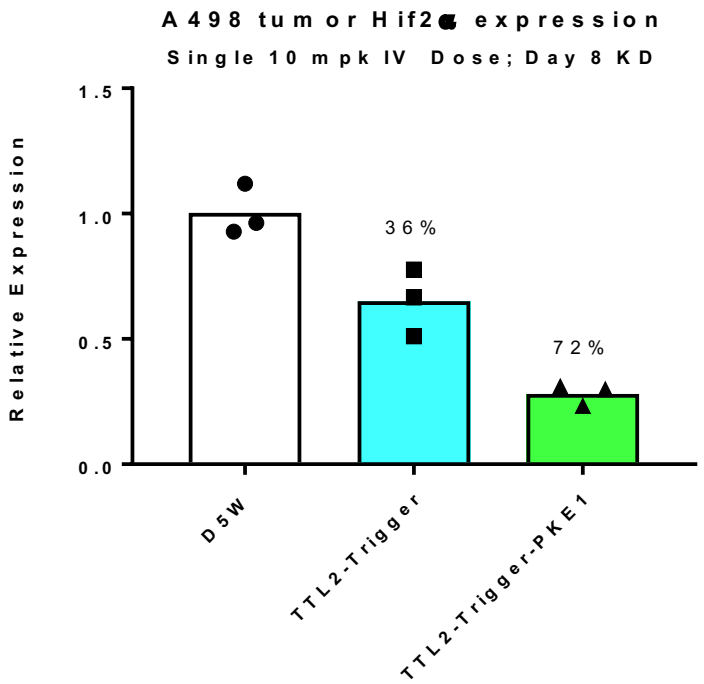


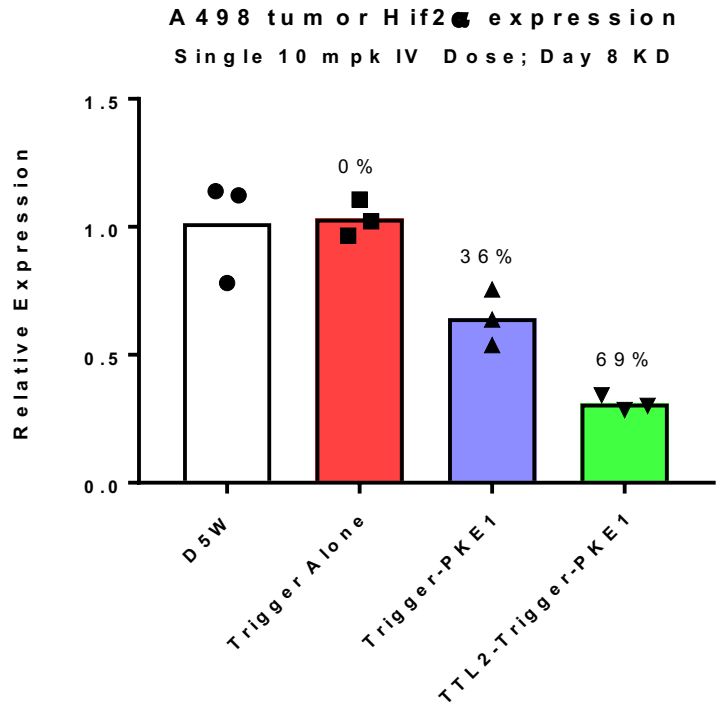
- Limited Hif2a mRNA reduction even at **40 mpk** without PK enhancer
- PK enhancer critical for extrahepatic delivery
  - KD increased to 71% at the same dose with TTL1 and PKEx
- KD activity appears to correlate with rat PK AUC

Ligand/Receptor and PK Enhancers

A498 Tumor Model: Hif2a Expression

- Trigger alone – no delivery
- Clear ligand effect observed

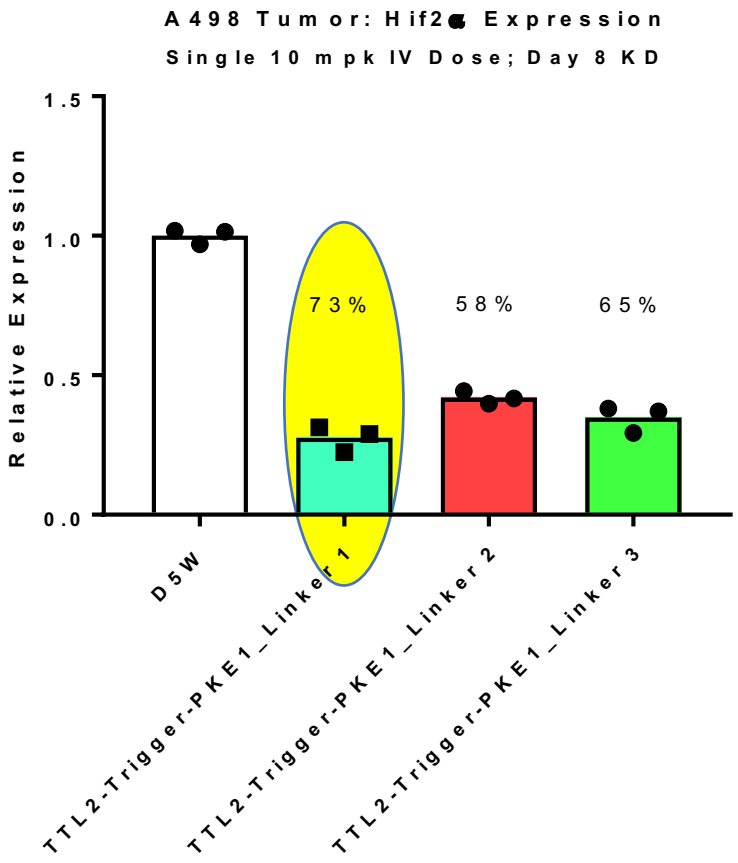




- PK enhancer plays critical role

Synergetic effects of ligand and PK enhancer observed

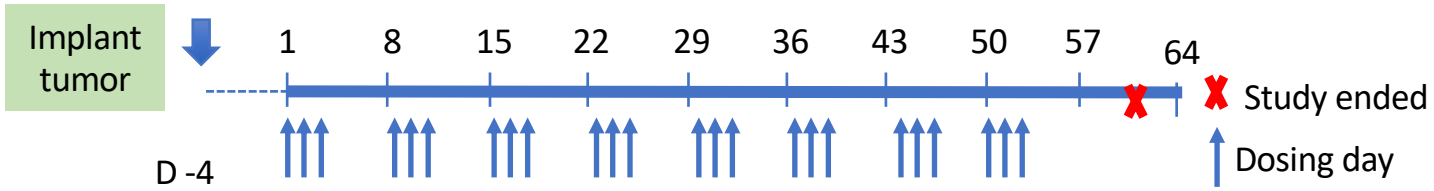
Linker Study – Nomination of Gen2-HIF2



- Chemically and enzymatically cleavable linkers studied
- Linker stability plays a role in potency of the conjugate
- TTR2-Trigger-PKE1nominated as the lead - **Gen2-HIF2**

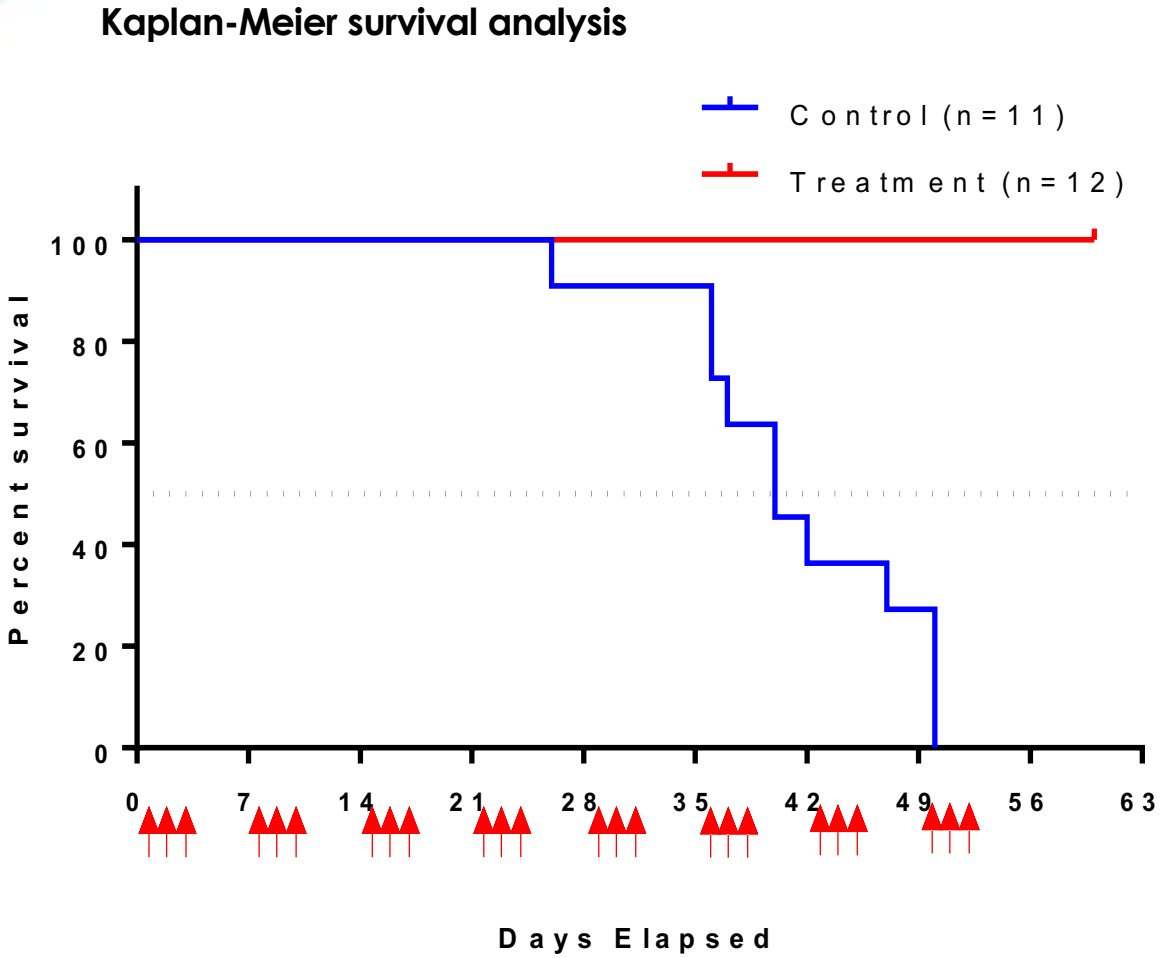
- Next steps for **Gen2-HIF2**
  - Survival study
  - Continued investigation
- Moving the frontier of extrahepatic, systematic delivery for RNAi

Survival Study: PDX Mouse Model with Gen2-HIF2



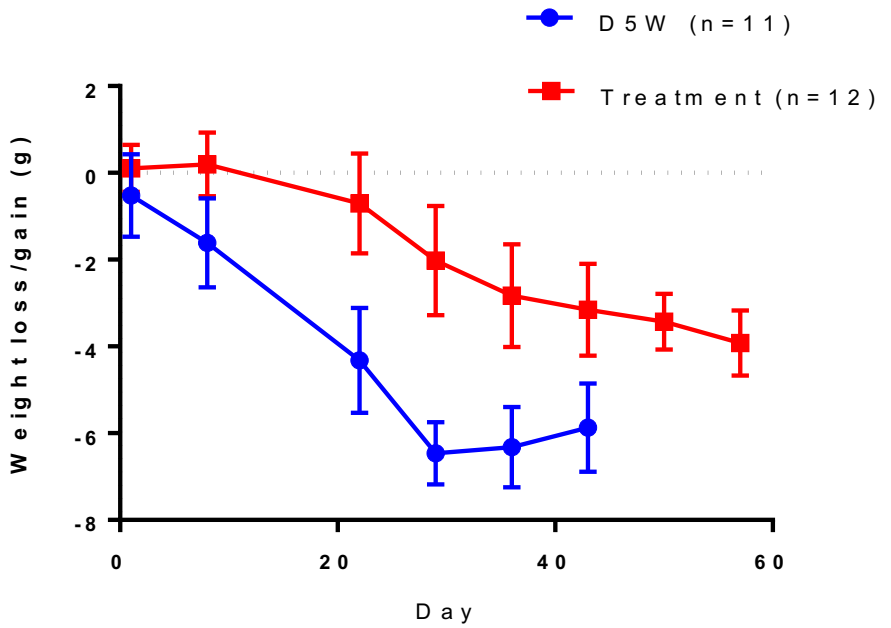
- Dosing began 4 days after tumor implant, 3 daily doses/week (15 mpk/dose) with a Gen2-Hif2 conjugate for 8 weeks
- Monitor body weight weekly and health check daily
- Palpate tumor weekly to estimate growth rate
- End-point is overall survival

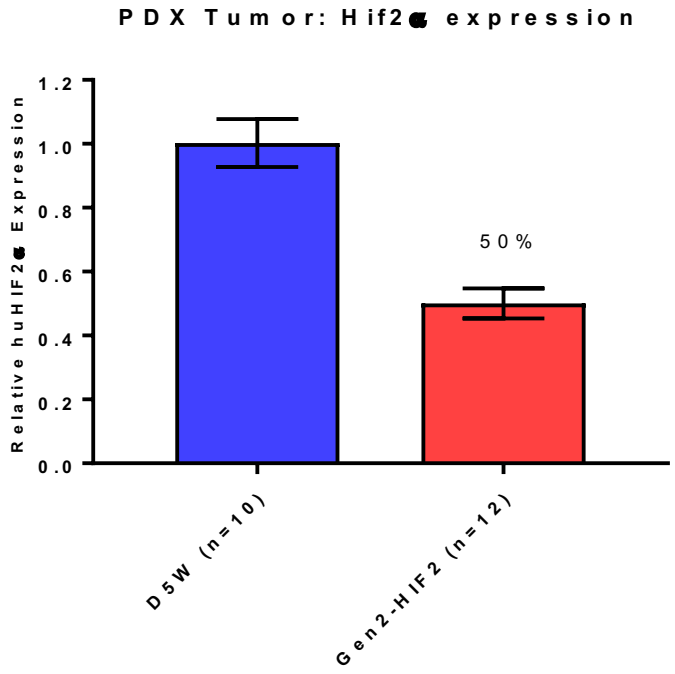
PDX Model Study Outcome With Gen2- HIF2



- All mice in the control group (untreated) died by day 50
  - First death observed at Day 26
- **All mice in treatment group survived** and study taken down on day 60

PDX Model Study With Gen2- HIF2: Body Weight and Target mRNA Knockdown

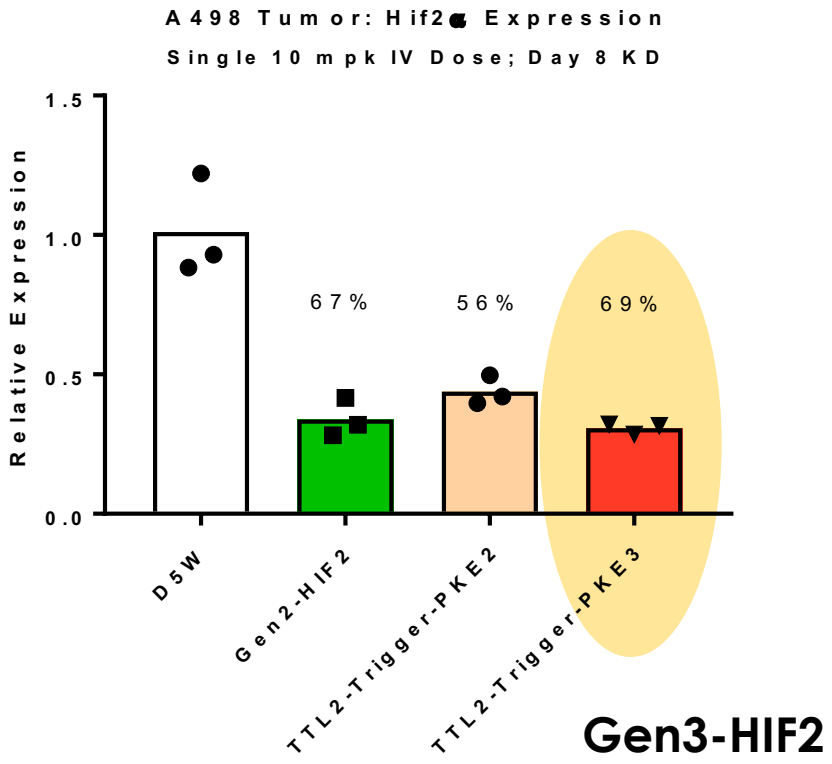




Day 60

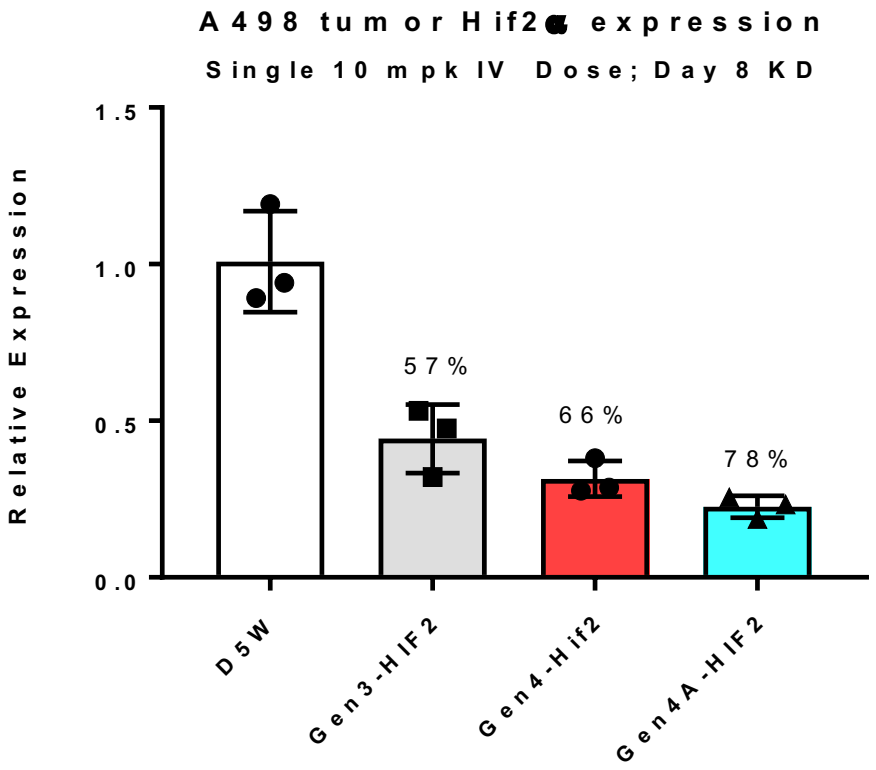
- Body weight loss much less significant in the treatment group

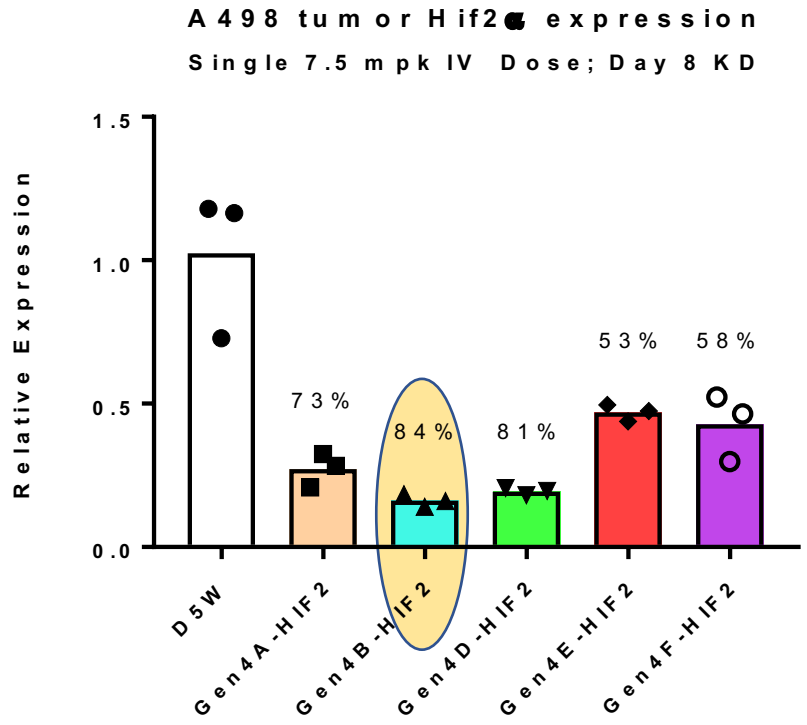
Gen3-HIF2 – Study on PK Enhancers



- Uncovered PKE3 - a new PK modifier
- Comparable Hif2 KD between Gen2-HIF2 and TTL2-trigger PKE3
- Reduced potential side effects
- TTL2-Trigger-PKE3 nominated as the lead – **Gen3-HIF2**

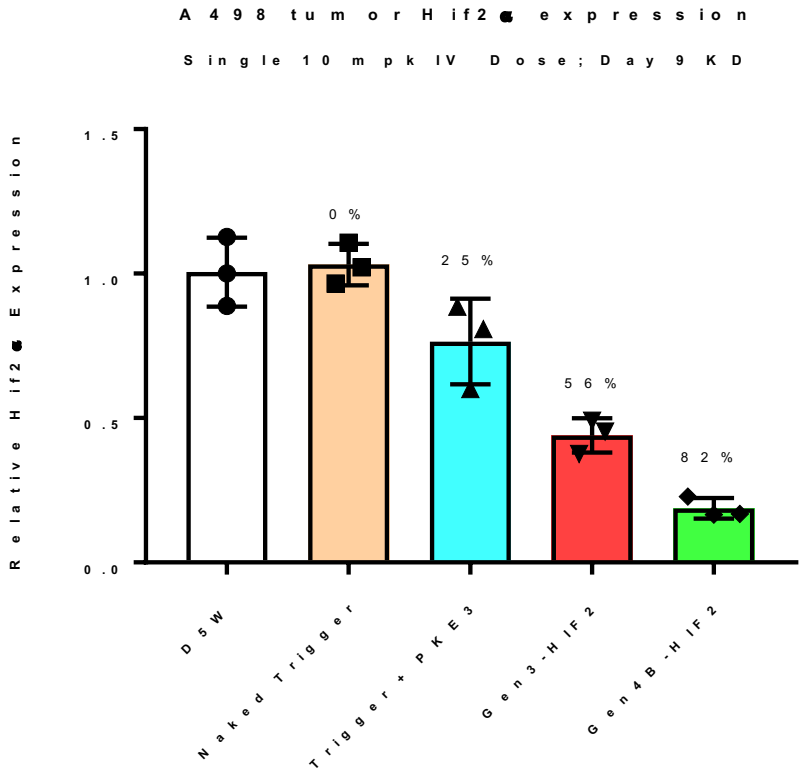
“Global” Optimization of Gen3-Hif2

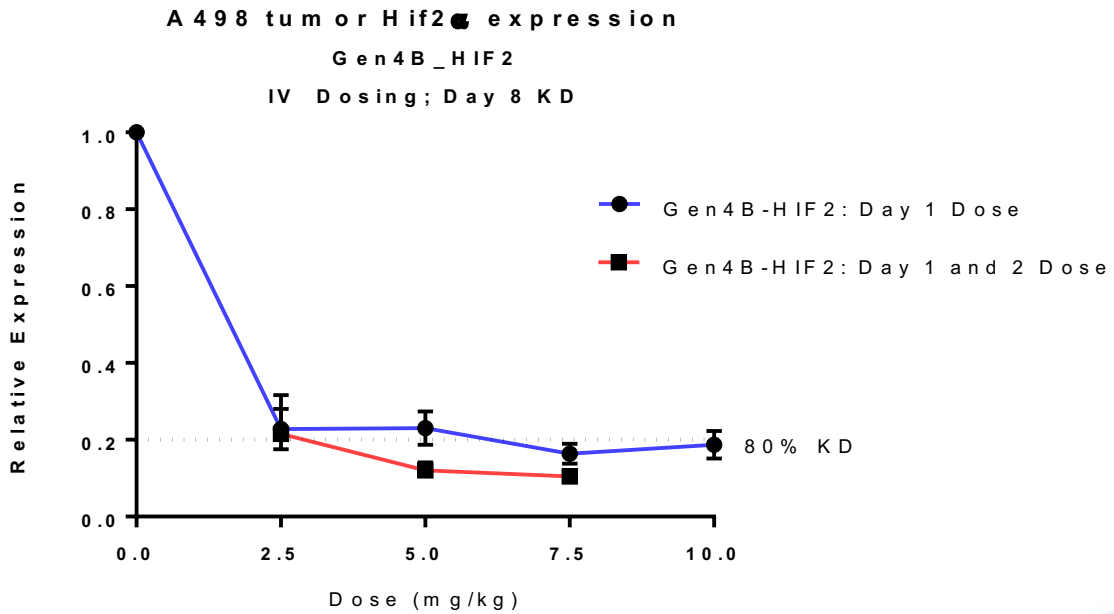




- Ligand optimization proven critical
- PK enhancers important for TRiM™ platform
- **Gen4B-HIF2** nominated as the lead TRiM™ construct

Gen4B-HIF2: Comparison with Earlier Generations

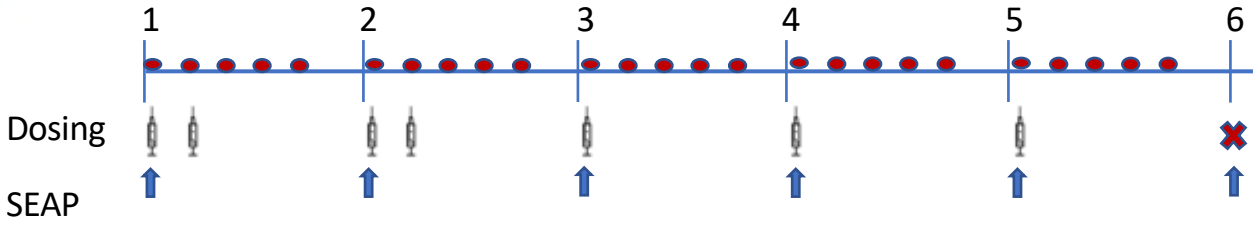




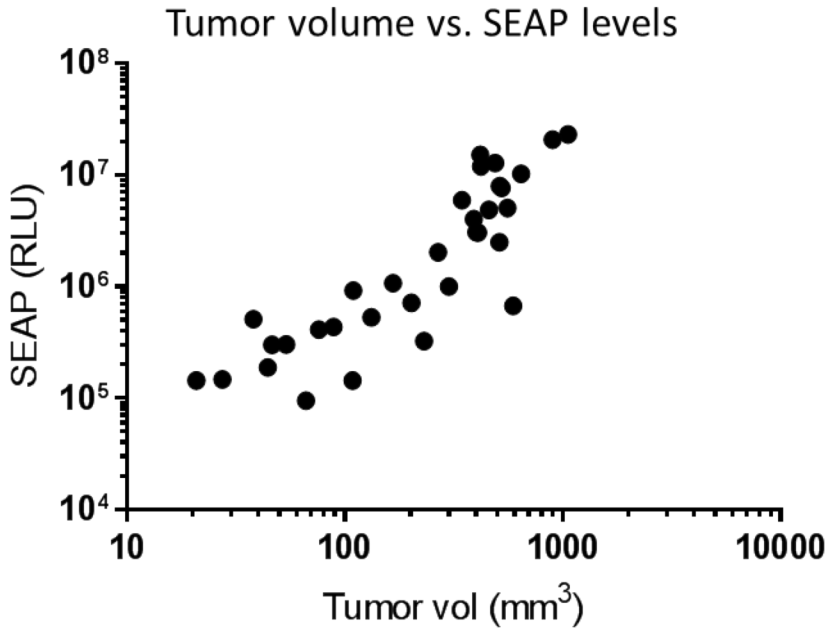
- All modules of TRiM™ platform optimized for extrahepatic delivery
- Gen4B-HIF2 demonstrate deep knockdown of Hif2a transcripts

- Single 2.5 mpk dose = 78% KD
  - Gen2-HIF2 = 46% KD @ 3.5 mpk
- Single 10 mpk dose = 81% KD
- Day 1 and Day 2 doses of 5 mpk = 88% KD
  - Gen2/Gen3: 3 x 14 mpk doses = 87% KD

Tumor Growth Inhibition Study Gen4B-HIF2

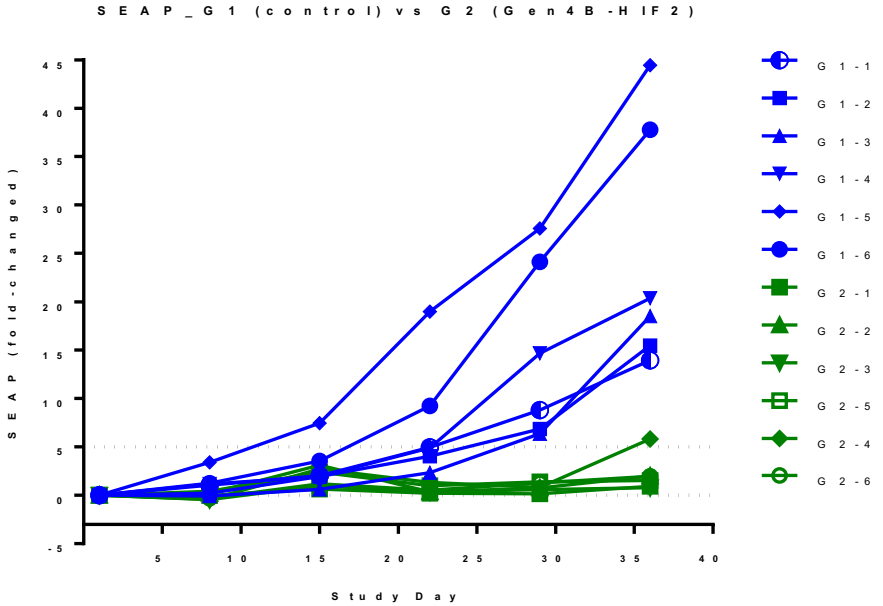


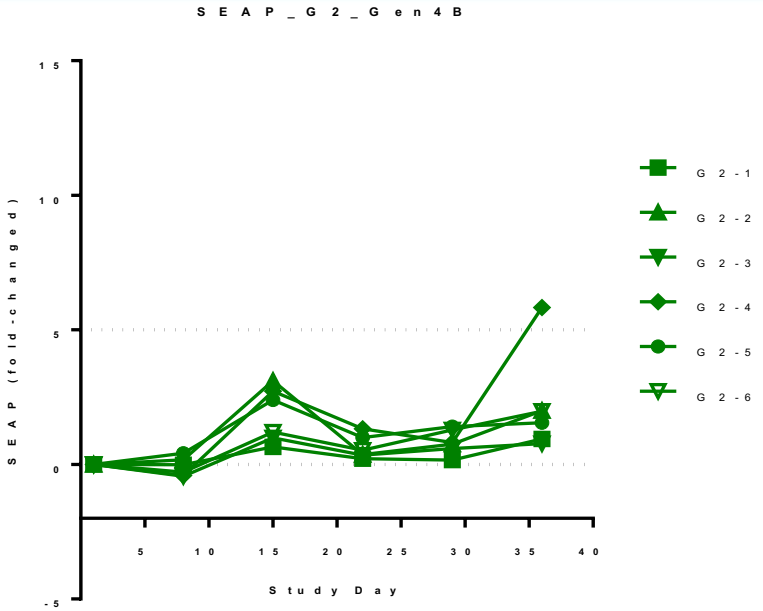
- 5 mpk for two days for the first two weeks, followed by once a week dosing at 5 mpk for 3 weeks

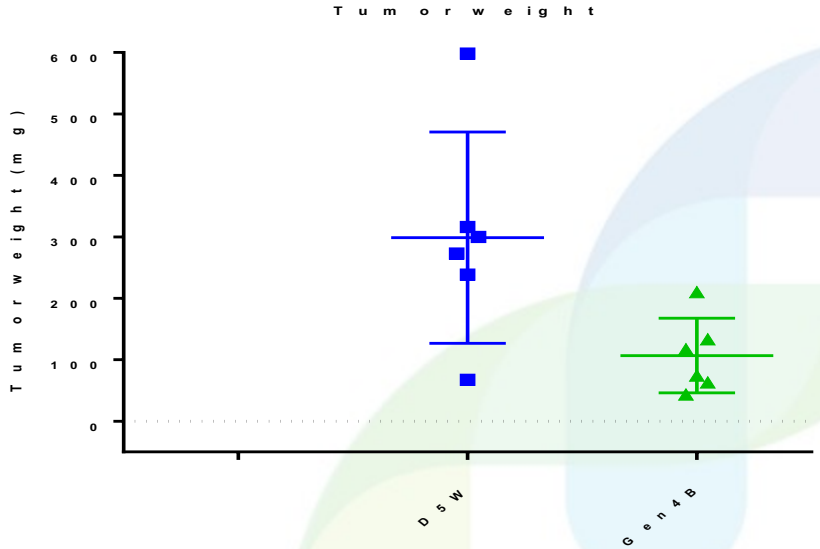


- Follow tumor growth by SEAP expression
  - Stably expresses SEAP (secreted embryonic alkaline phosphatase)
  - Sensitive serum biomarker to monitor tumor growth
- Observed good correlation between SEAP levels and tumor volumes

Tumor Growth by SEAP expression

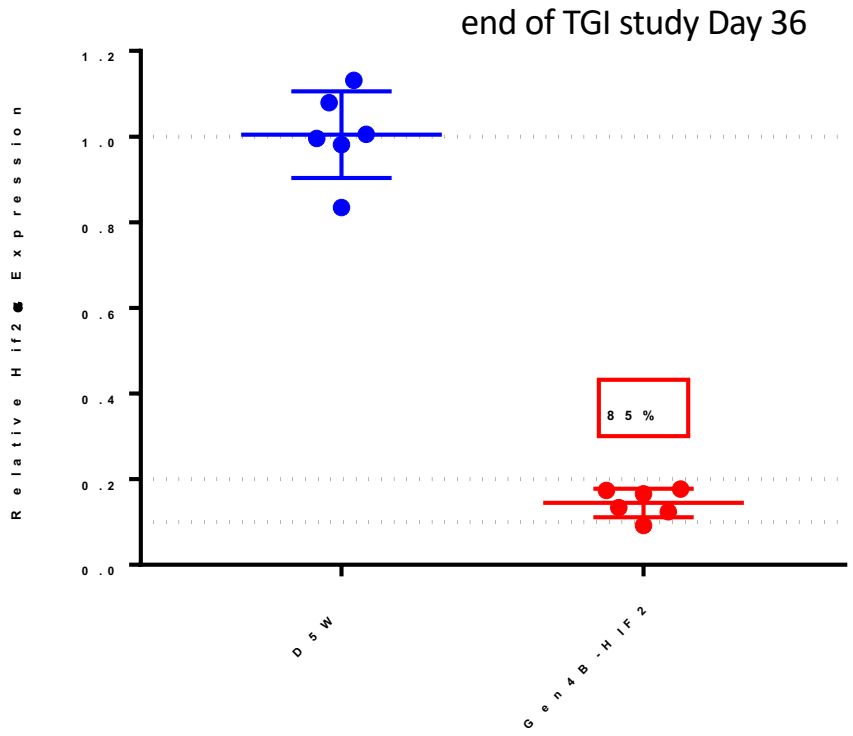






- The treatment groups showed tumor growth inhibition (TGI)
- SEAP expressions suggest **tumor regression** around day 22
- Longer study needed to determine if regression continues
- Reduction in tumor weight observed

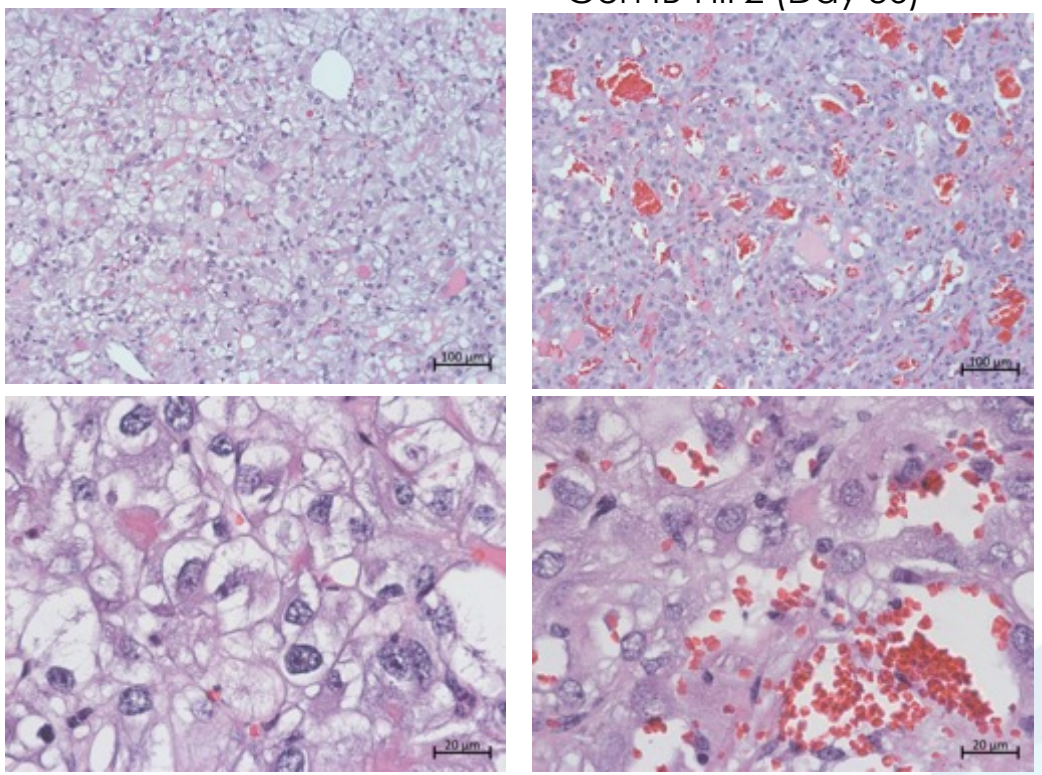
TGI Study - Gen4B-HIF2



- Gen4-HIF2 demonstrated deep Hif2a mRNA knockdown in the dosing regimen at Day 36

D5W (Day 36)

Gen4B-HIF2 (Day 36)



Normal tumor

Wide-spread tumor destruction

- Gen4B-HIF2 treated group showed wide-spread tumor damage
- Apoptosis and necrosis

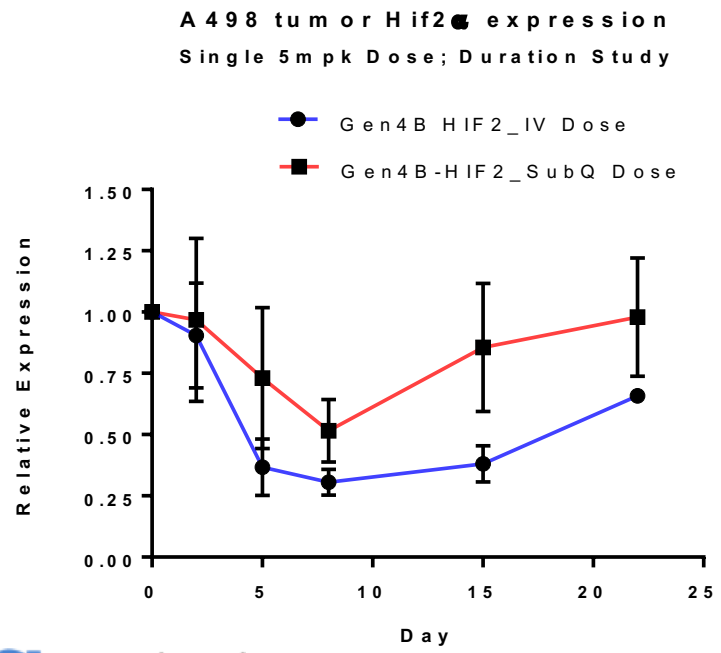
Gen4B-HIF2 in Exploratory Toxicology Study

- Exploratory toxicity study in rats (non-GLP)
  - 3 daily doses given over 5 weeks (total of 15 doses) by IV injection
  - Dose level: 30 mg/kg
    - Compared with dosing in TGI study – 5 mpk, twice a week for 2 weeks, followed by weekly doing of 5 mpk for 3 weeks
  - Evaluations: Clinical signs, body weight, clinical pathology and limited histopathology
- No significant findings or indications of toxicity
- Wide therapeutic index achieved

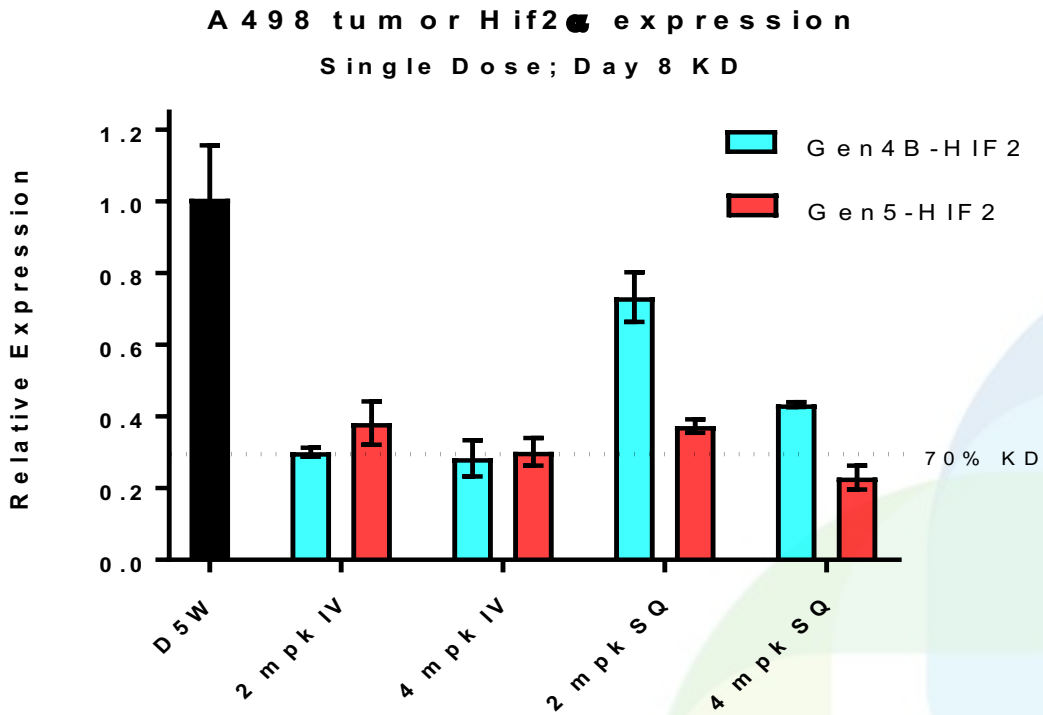
Next Generation: Pushing the Limit of Extrahepatic Delivery

Is subcutaneous administration a possibility for extrahepatic targets???

- Gen4B-HIF2: loss of potency via subcutaneous administration



- SubQ vs IV ROA
- **Gen5-HIF2 demonstrates equal or better potency via subQ**

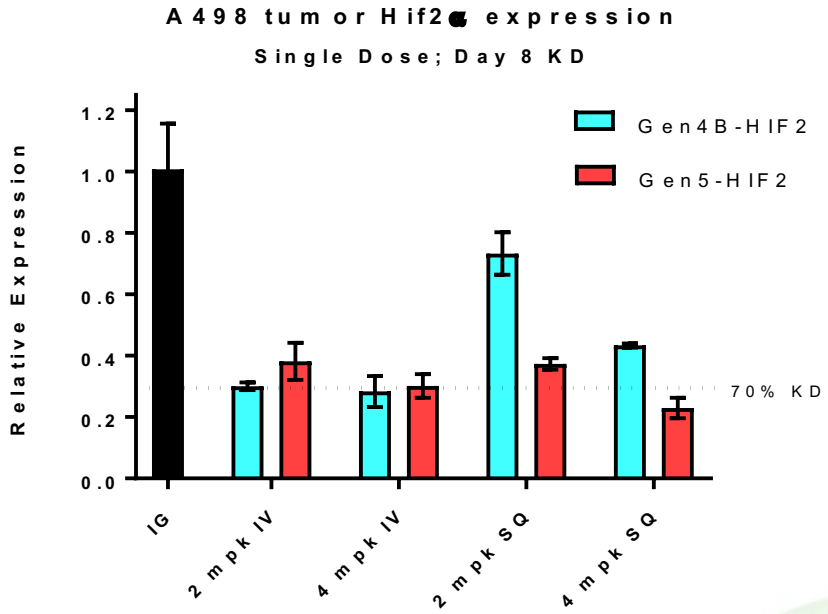


Next Generation: Pushing the Limit of Extrahepatic Delivery

- Is subcutaneous administration a possibility for extrahepatic targets???
- **YES**

- Achieved efficient silencing of an extrahepatic target gene via subcutaneous administration
- Demonstrates the power of TRiM™ platform

- SubQ vs IV ROA
- Gen5-HIF2 demonstrates equal or better potency via subQ



Summary for Extra-hepatocyte Work

- Extra hepatocyte delivery requires all of the modules of the TRiM™ platform to be fully optimized
- 100% survival achieved with earlier generation – Gen2-HIF2
- ARWR leading candidate, Gen4B-HIF2, effectively silences the target gene - Hif2a
  - Wide spread tumor cell killing and tumor structure damage in TGI study
  - Survival study using Gen4B-HIF2 on-going
- Wide therapeutic index achieved with Gen4B-HIF2
- Development candidate nomination in progress
- Achieved efficient extrahepatic gene silencing via subcutaneous administration
  - Other extrahepatic programs in progress using the platform

Acknowledgement

- Anthony Nicholas, Jeff Carlson, Rui Zhu, Dongxu Shu, Xiaokai Li, Bo Chen, Amanda Frankiewicz, Casi Schienebeck, Gary Christensen, Lucas Trilling, Zach Trilling, Jeff Casper, Collin Hagen, Matthew Fowler-Watters, Patrick Au, Audra Winter

- So Wong, Holly Hamilton, Aaron Andersen, Meredith Hinkes, Qili Chu, Stephanie Bertin, Che Liu

- Julia Hegge, Sheryl Ferger, Linda Goth, Tracie Milarch, Rachael Schmidt, Leah Staley

- Mark Seefeld, Beth Mock, Josh Schumacher, Vladimir Subbotin

- Robert Teigen

- Bruce Given


arrowhead
pharmaceuticals