Development of a HIF2a-Targeted RNAi Therapeutic for the Treatment of ccRCC

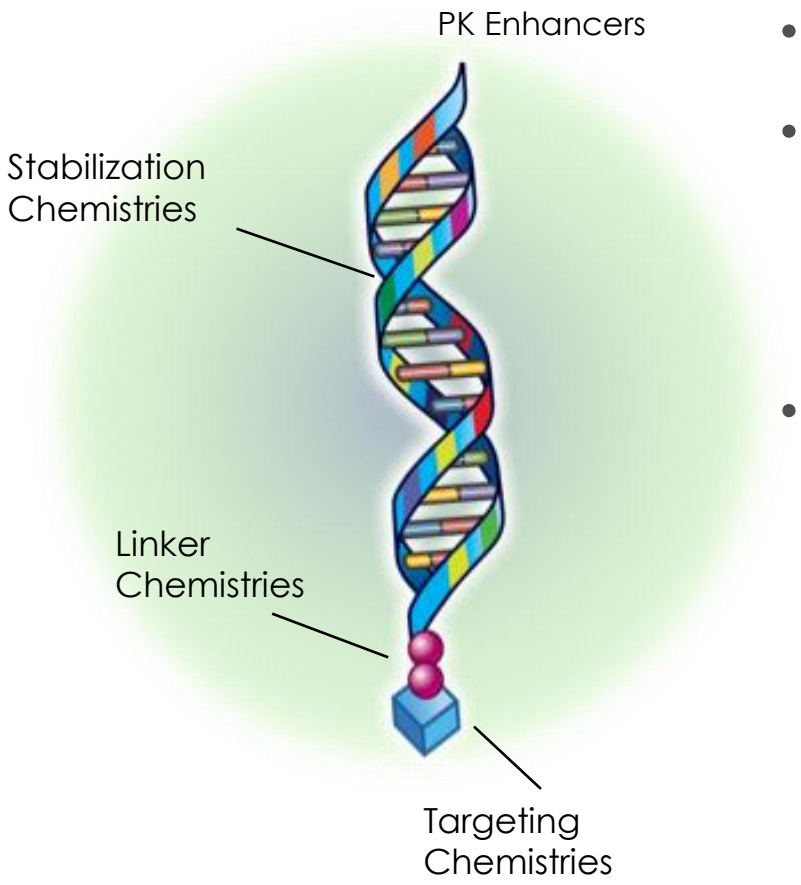
So C. Wong, Ph.D.

Arrowhead Pharmaceuticals

Outline

- Development of ARO-HIF2
- Key pre-clinical proof-of-concept results
- ARO-HIF2 clinical study

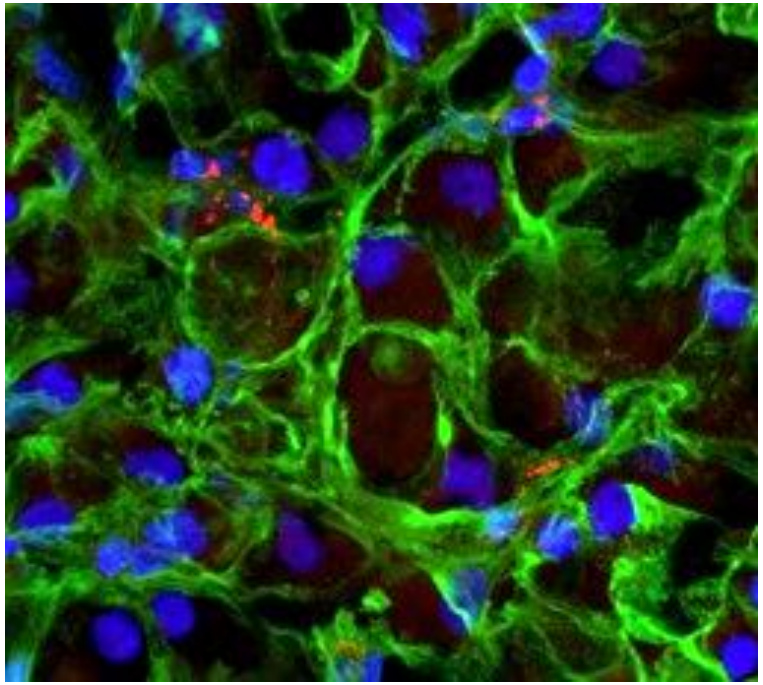
Arrowhead's ARO-HIF2 Program



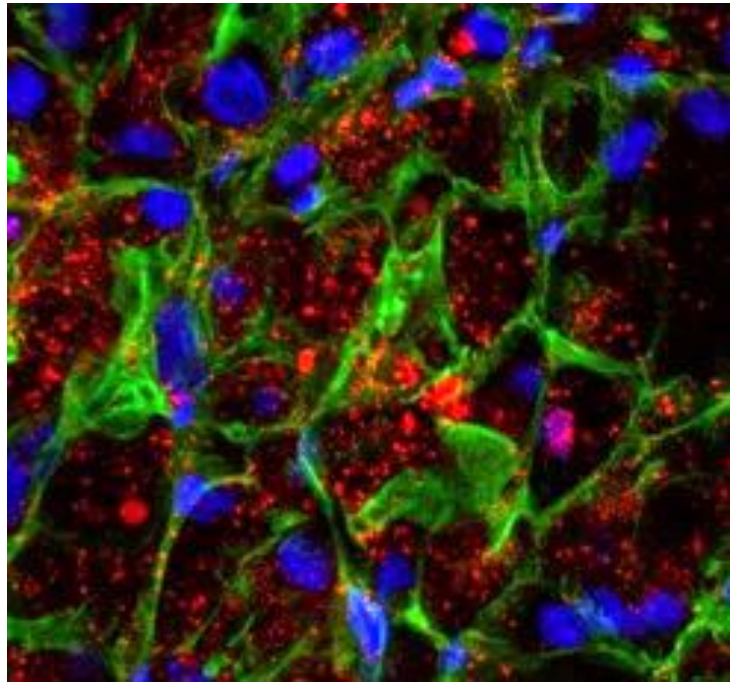
- Second Gen Platform: **T**argeted **R**NA**i** **M**olecules (TRiM™)
- Enhanced delivery via an integrin receptor (avβ3) that is over-expressed in many cancers
  - Tumor tissue microarrays confirmed receptor expression in ccRCC at high frequency
- RNAi trigger specifically targets HIF2α mRNA
  - Over-expression in ccRCC especially with VHL mutations
    - HIF2α is regarded as a key tumorigenic driver of ccRCC
  - Limited restrictive expression in normal tissues
  - Chemically modified to enhance potency and prevent immune activation
  - Minimal off-target risks

Tumor Delivery is Ligand Dependent

No ligand



With Ligand



A498 ccRCC orthotopic tumor mouse model

- Efficient delivery to all tumor cells
- Weak delivery without ligand

2 mg/kg Cy3-labled ARO-HIF
4 h after injection

Red = ARO-HIF2
Blue = nuclei
Green = actin (cell membrane)

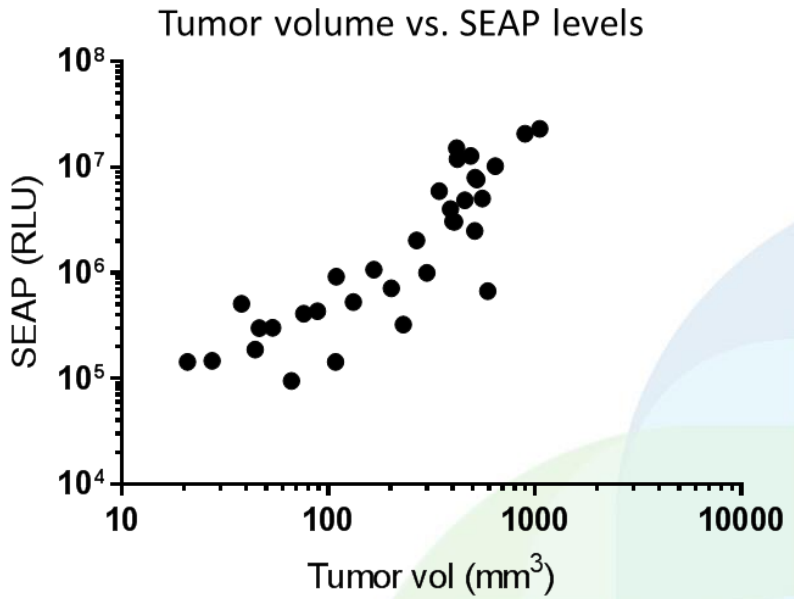
ARO-HIF2 in Xenograft Mouse Model

A498 orthotopic kidney xenograft mouse model

- A498 is an established ccRCC cancer cell line
  - VHL mutated, HIF2a over-expressed
  - Integrin avβ3 positive

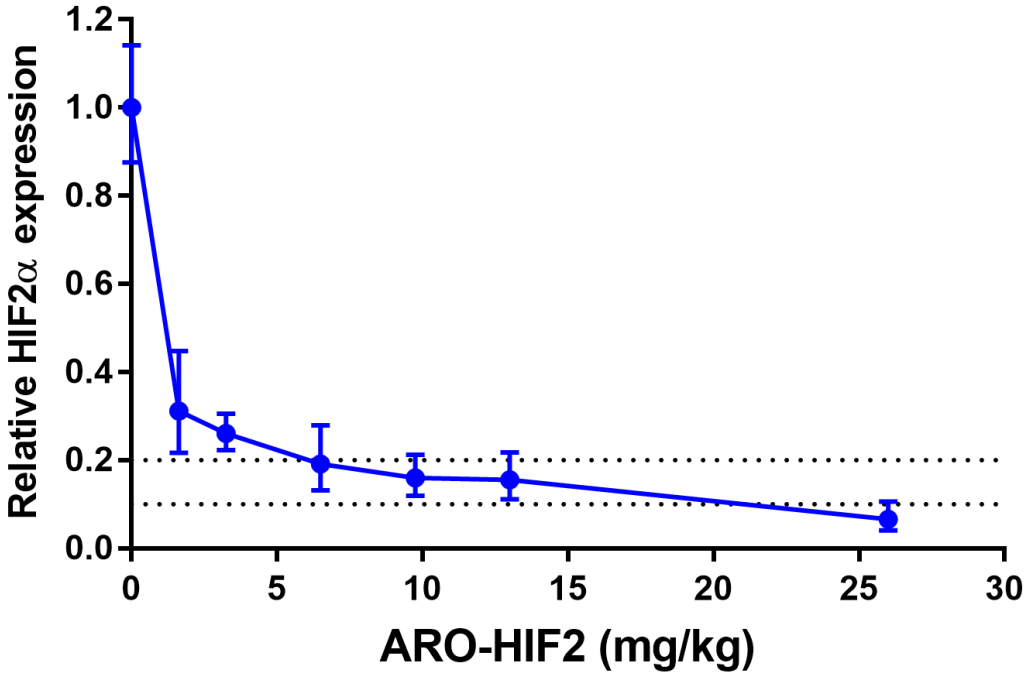
- SEAP-A498 model
  - Stably expresses SEAP (secreted embryonic alkaline phosphatase)
  - Good correlation between SEAP levels and tumor volumes

- Sensitive serum biomarker to monitor tumor growth



ARO-HIF2 Dose Response in A498 Mouse Model

ARO-HIF2 Dose Response (single injection)

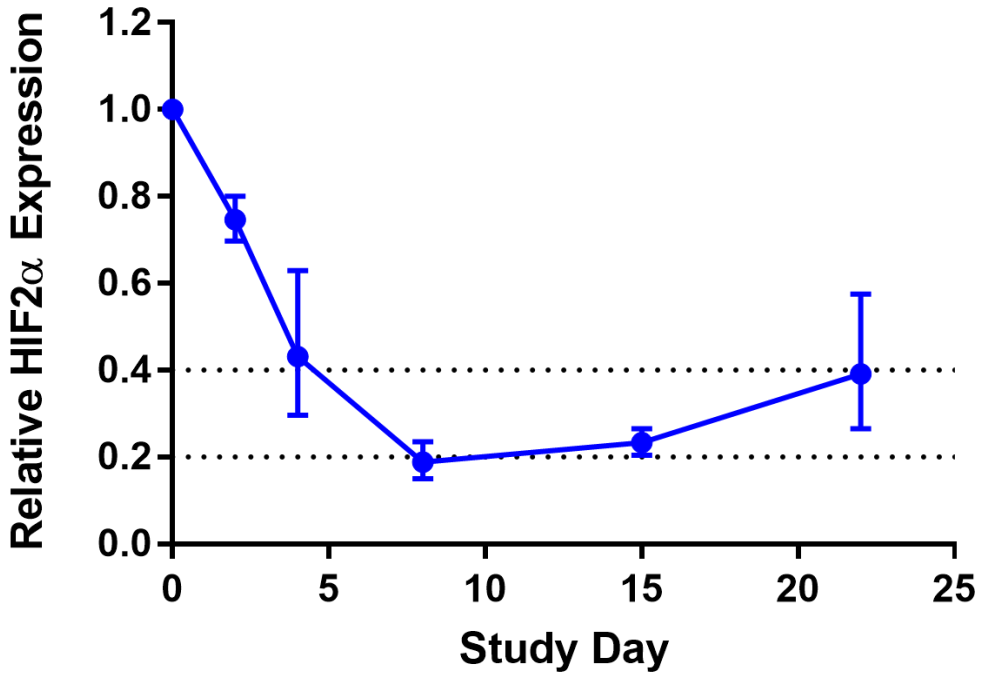


- Single dose on study Day 1
- Gene expression (KD) on Day 8

- Shallow dose response above 6 mg/kg

ARO-HIF2 Response Duration in A498 Mouse Model

HIF2α KD duration after a single 13 mg/kg injection

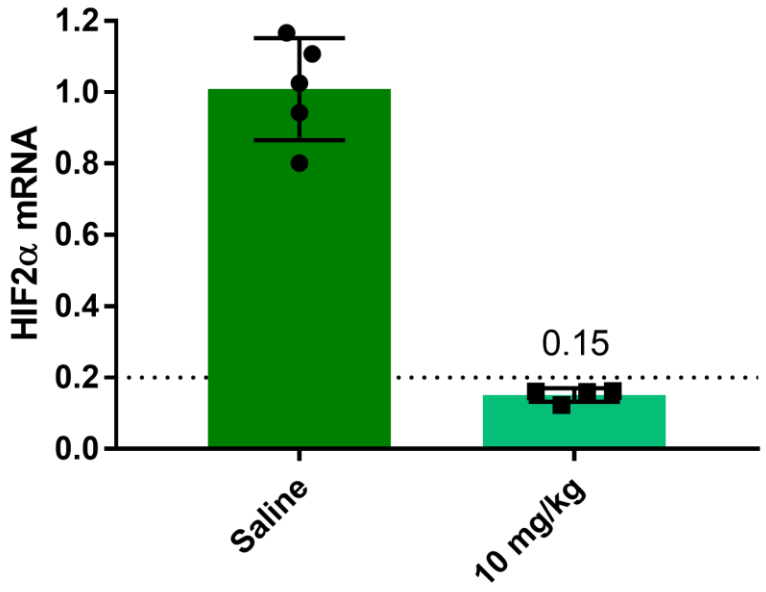


- Single dose on study Day 1
- Nadir Day 8, HIF2α 82.2 % KD
- Max KD last for about 1 week

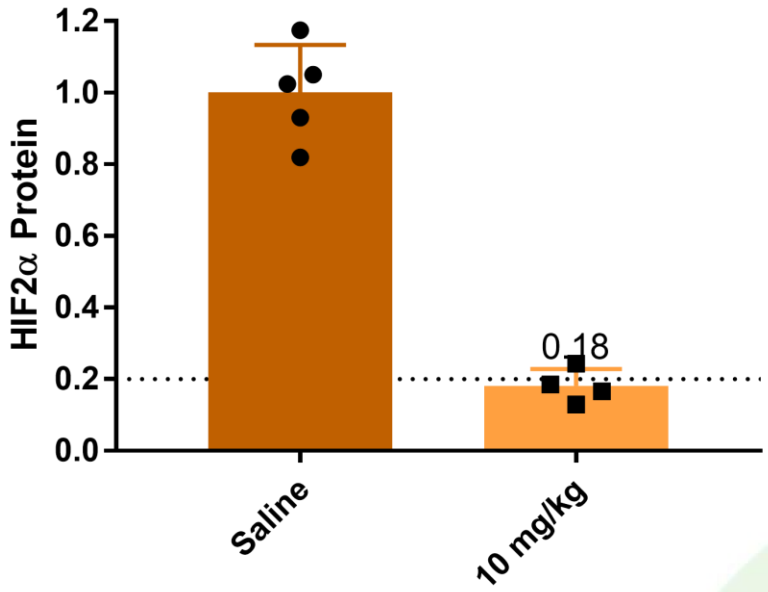
Reduction in HIF2a mRNA and Protein

Single 10 mg/kg iv dose (n= 4 to 5)
Tumor HIF2a mRNA and protein levels one week after dosing

mRNA



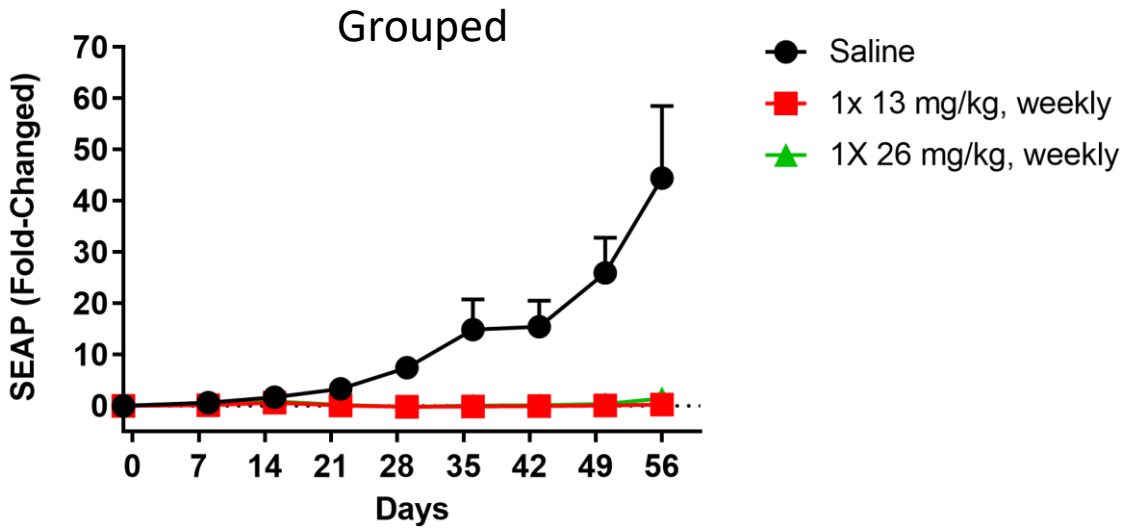
Protein



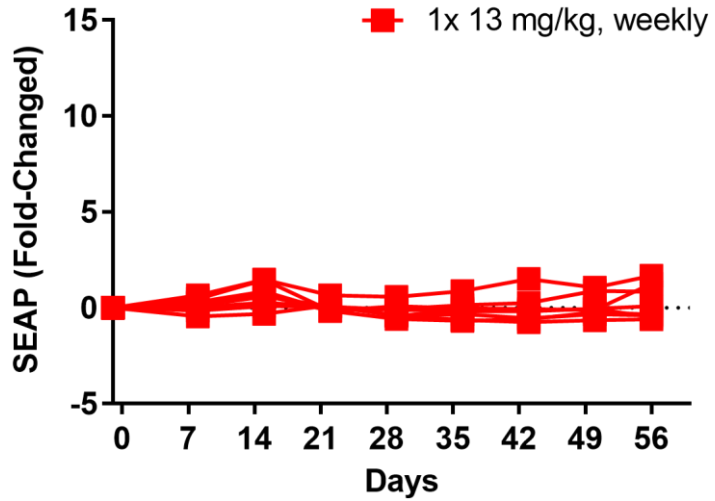
Multi-Dose Tumor Growth Inhibition (TGI) Study

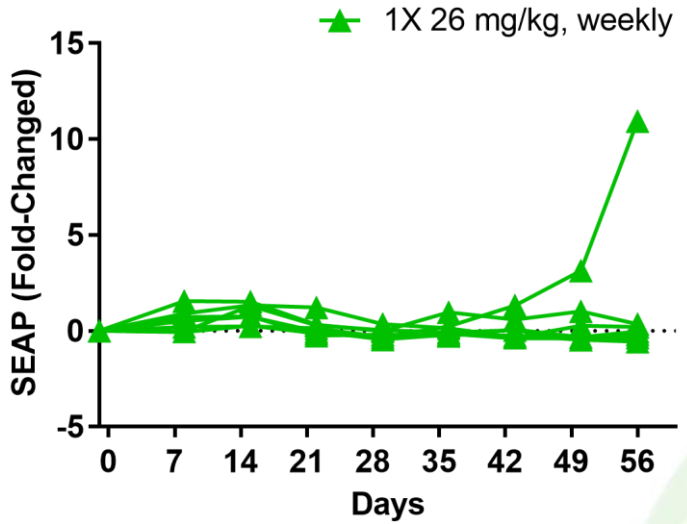
- Eight weekly doses of 13 mg/kg or 26 mg/kg of ARO-HIF2
- Weekly SEAP monitoring for TGI
- End of study tumor HIF2a gene silencing, sizes and histology

ARO-HIF2 TGI Study: Response by SEAP



- A498 orthotopic SEAP mouse model
- Similar TGI response based on SEAP readout
- Both treatment groups had mice showed regression by SEAP
- One mouse in 26 mg/kg treatment group showed sign of treatment escape by SEAP readout

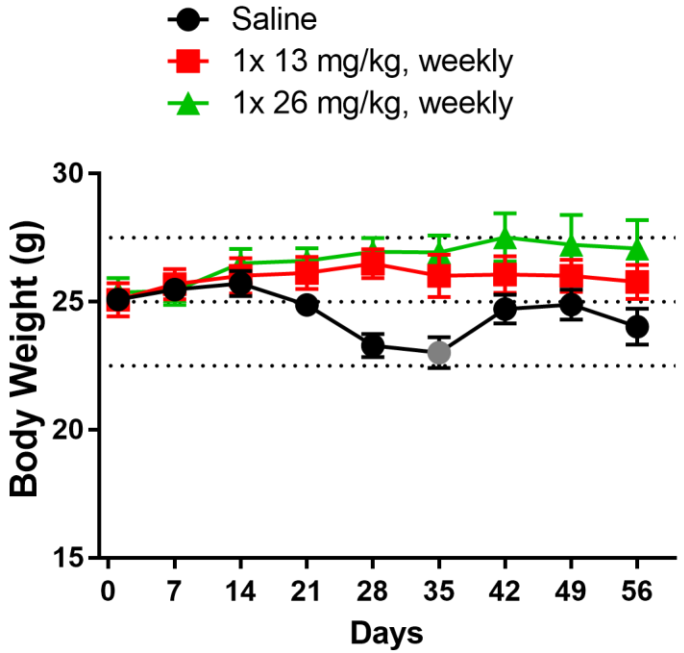




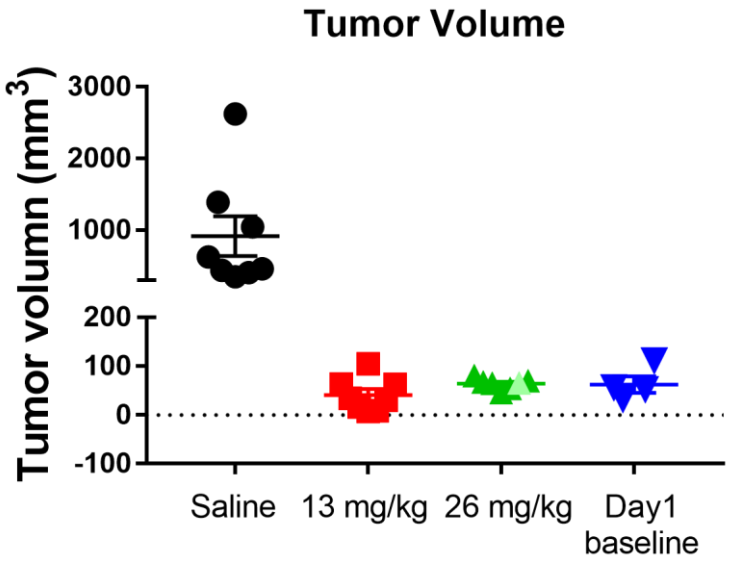
arrowhead pharmaceuticals

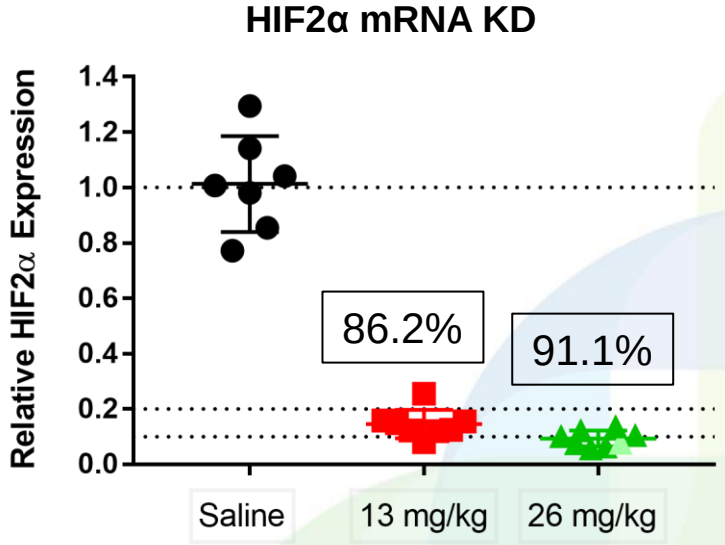
A498 TGI Study: Response by Tumor Volume and Gene Silencing

- Treatment groups shows better BW maintenance
- Both dose levels showed strong tumor growth inhibition (TGI) and deep HIF2a mRNA KD



D37 euthanized 1 mouse

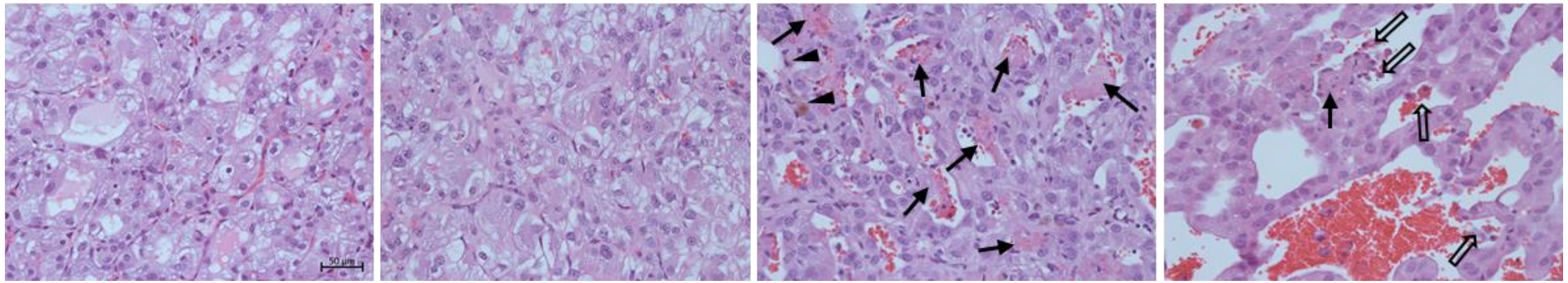




- Symbols with lighter tone: escapee by SEAP
- All graphs shows mean (SEM)

Tumor Histology

Day 1 baseline | Day 57 Saline | Day 57 13 mg/kg | Day 57 26 mg/kg



- ARO-HIF2 treated group showed wide-spread tumor destruction
- Loss of clear cell characteristic
- Areas of apoptosis and necrosis

→ Necrosis
► Macrophage infiltration
⇨ Apoptosis

Summary of ARO-HIF2 Pre-Clinical Studies

- Efficient ligand enhanced tumor delivery of ARO-HIF2
  - Demonstrated deep HIF2α mRNA knockdown with corresponding reduction in HIF2a protein in tumor cells
  - Inhibition of tumor growth and improved overall survival in tumor models
- Single and multiple doses up to 26 mg/kg tested
- Exploratory toxicity studies in rats and NHPs up to 120 mg/kg
  - No drug-related observations or effect on body weight
  - Minimal LFT increase at top dose
  - No decrease in EPO level
  - No significant HIF2a mRNA KD in NHP liver, kidney, spleen and adrenal at 80 mg/kg

ARO-HIF2 Phase 1 Clinical Program

- Phase 1 dose range finding study
  - To be conducted in I/O and/or anti-VEGF refractory ccRCC patients
- Initiated 08/2020, dose escalation on-going
- Primary objectives:
  - Safety & determination of phase 2 dose
- Secondary objectives
  - PK, efficacy based on RECIST
- Key exploratory objective
  - Tumor biopsy HIF2a expression

Thank You