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Development of RNAi-Based Therapeutics using Dynamic Polyconjugates™ (DPC™) Technology

11th Annual OTS Meeting

Bruce D. Given, MD

COO Arrowhead Research Corporation

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Presentation outline

- DPC™ for liver delivery
  - Example: ARC-520 for treatment of chronic hepatitis B virus (HBV) infection
- DPC™ for extra-hepatic delivery
  - Example: ARC-HIF2 for treatment of clear renal cell carcinoma (ccRCC)
- New subcutaneous format
  - Example: ARC-LPA for treatment of cardiovascular disease

DPC™ for liver delivery

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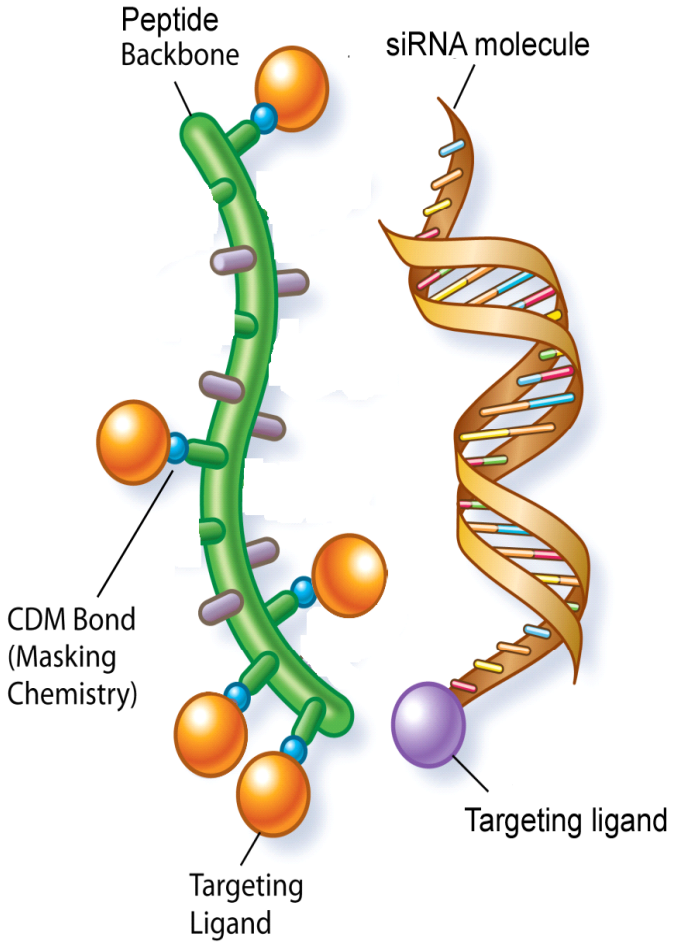
DPC

- Amphipathic peptide for endosomal escape
- Peptide amines “masked” with pH-labile moiety, unmasked in endosome
- Targeted to liver with NAG
- Co-injected with RNAi trigger



RNAi Trigger

- Canonical siRNA or other format
- Liver-tropic targeting ligand (eg. cholesterol)

DPC and RNAi trigger do *NOT* form a complex, they are separately targeted to the liver

ARC-520 targets the HBV transcriptome

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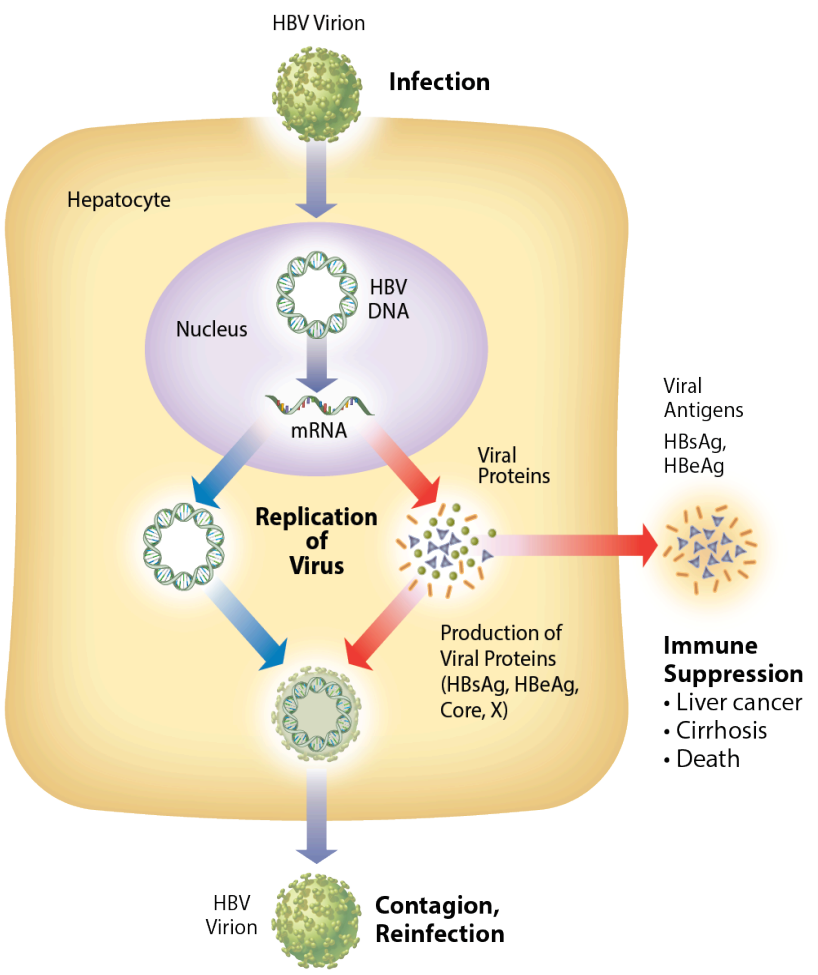
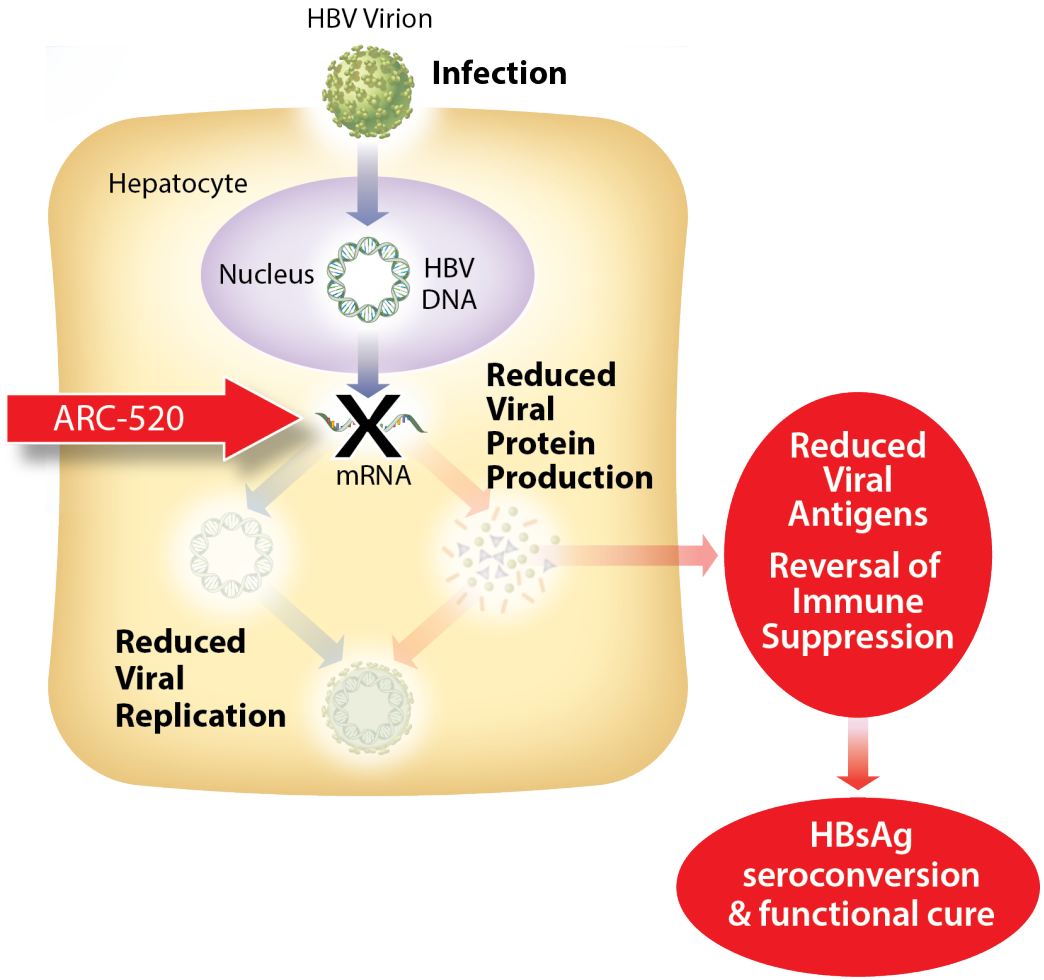
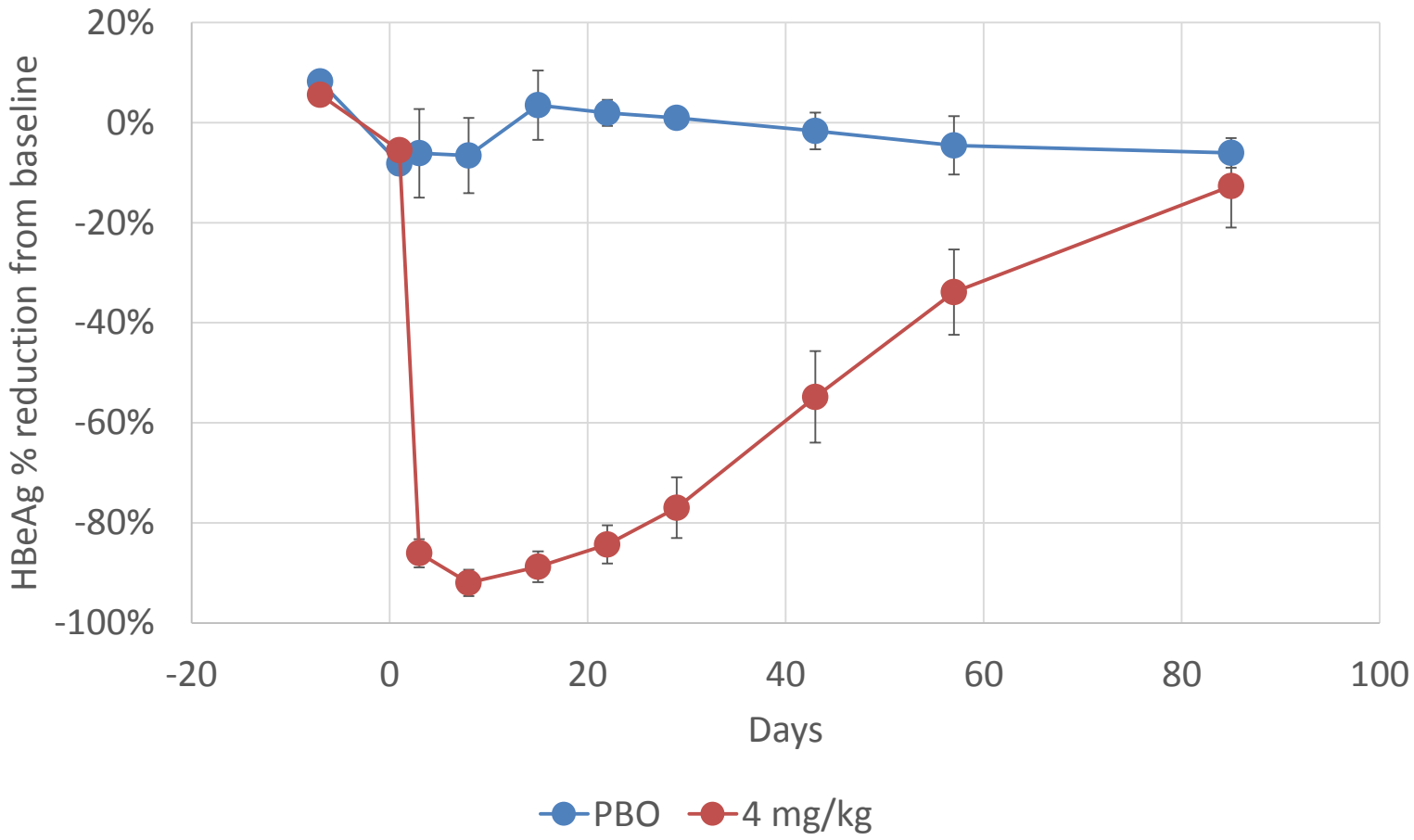
Untreated



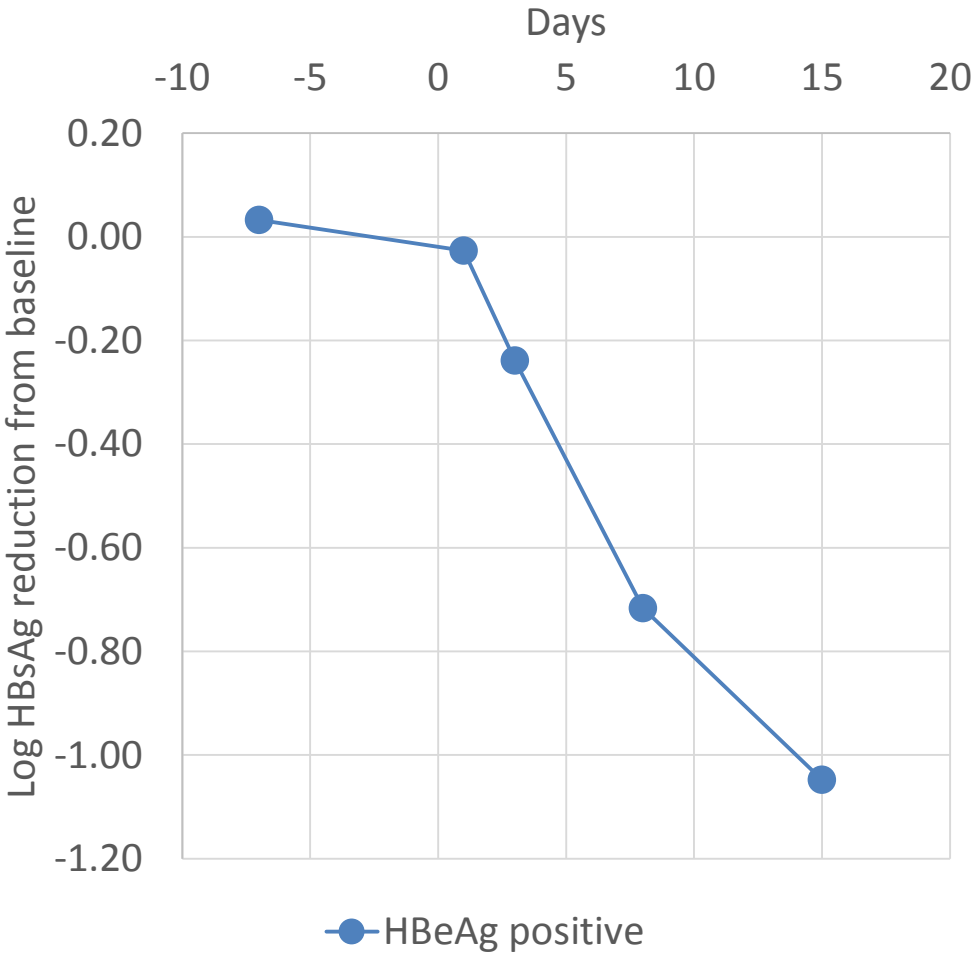
ARC-520



HBeAg drops deeply in patients treated with ARC-520



Naïve HBeAg positive patients show deep HBsAg reduction



- Single dose of 4 mg/kg results in a mean HBsAg reduction of >1 log at Day 15
- Peak KD likely not yet achieved
- Data are still maturing
- Maximum KD to date is 1.9 log (99%)

What the ARC-520 clinical data has told us

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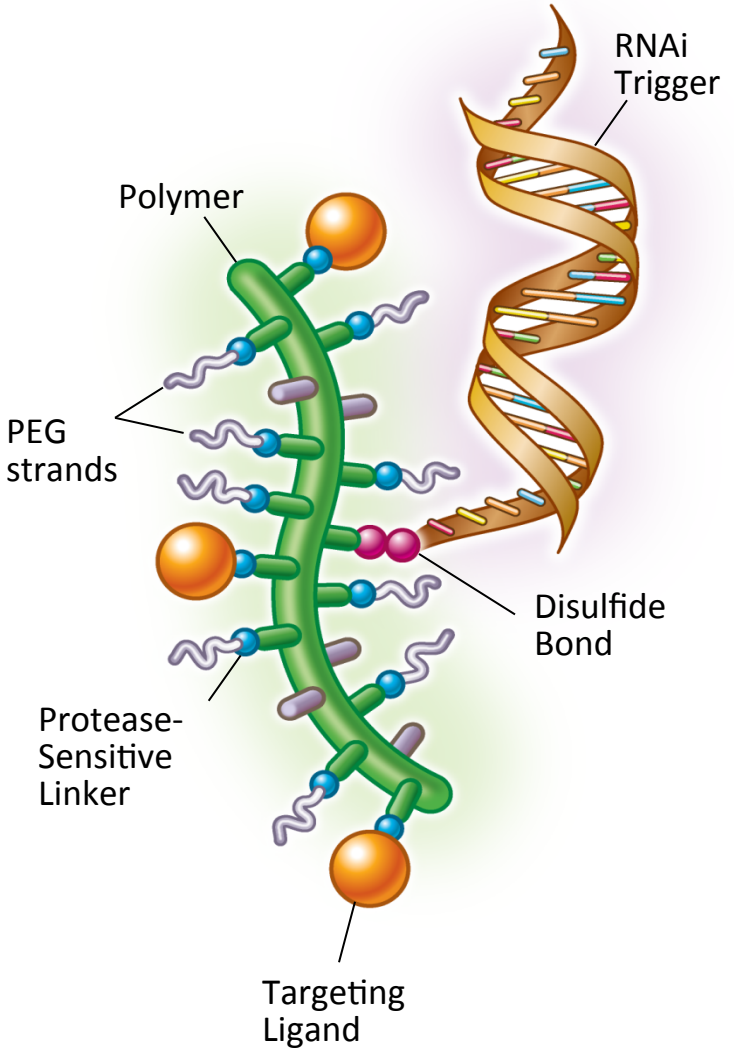
- ARC-520 has shown good single dose tolerability in 84 humans and good multi-dose tolerability in 9 chimps
  - No serious or severe AEs or dropouts due to AEs
  - No suspected signs of end-organ toxicity on labs
- ARC-520 can produce deep and sustained KD of cccDNA-derived mRNA/proteins
  - HBeAg, core-related antigen, HBsAg
- *The technology works! Highest reported single dose KD in humans with RNAi therapeutic*

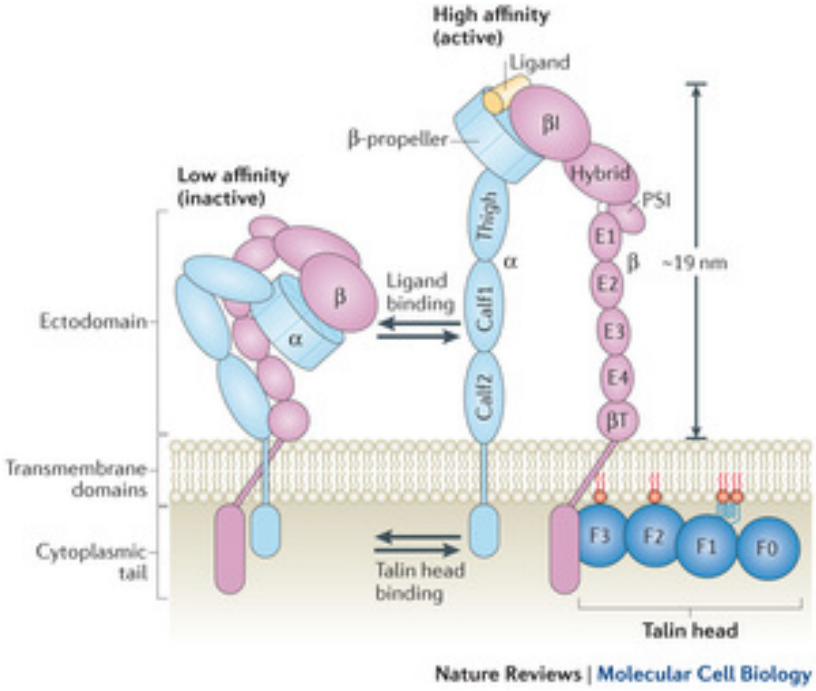
DPC™ for extra-hepatic delivery

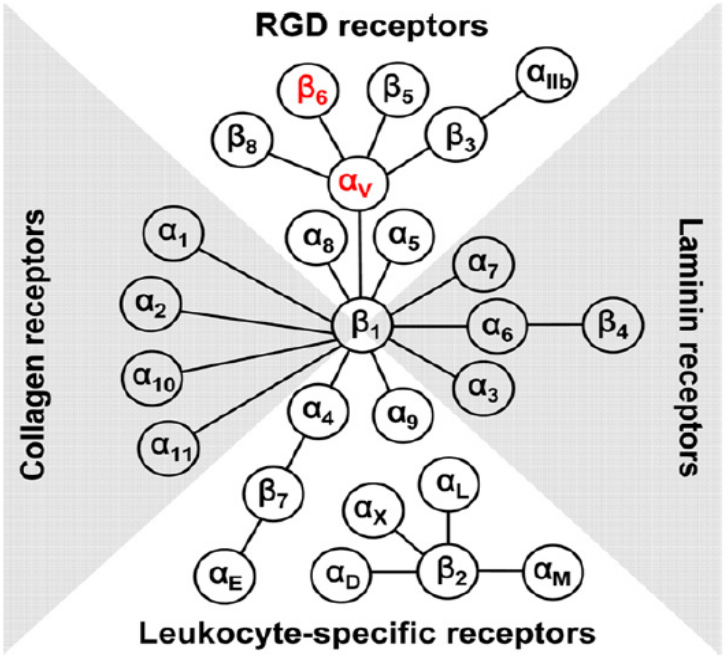
- Employs endosomolytic polymer
- Polymeric amines “masked” with hydrophilic PEG or targeting ligand
- RNAi trigger attached to polymer
- Cellular uptake ligand driven
- Proteases in endosomes drive polymer unmasking
- Unmasked polymer disrupts endosomal membrane
- siRNA released to cytoplasm



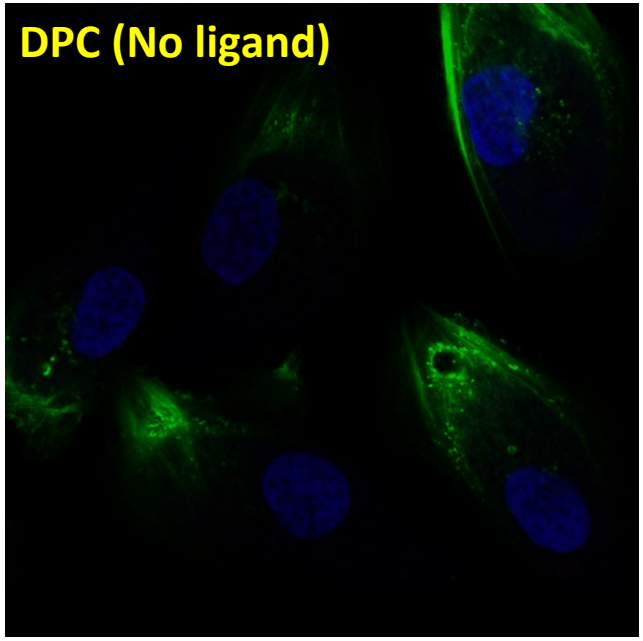
Extra-hepatic Targeting with integrin ligand

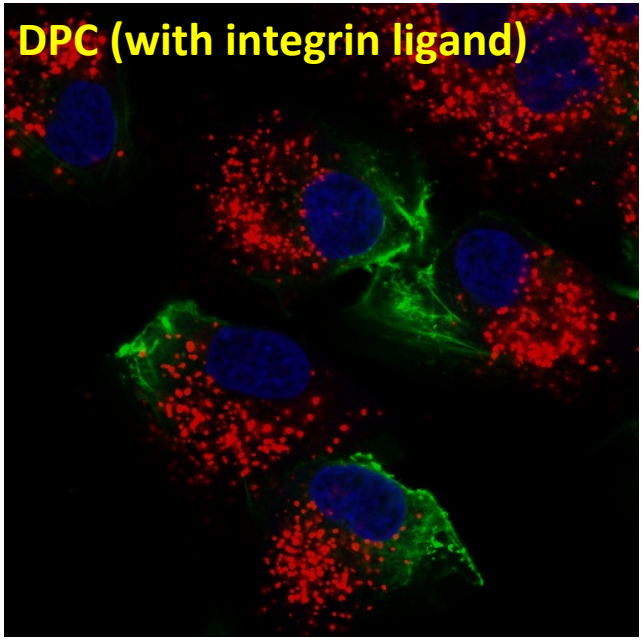
- Integrins involved in cell adhesion and signaling
  - Heterodimers: 18 α and 8 β subunits
  - Diverse ligands: ECM, growth factors, etc.
  - Exploited by tumor cells
  - Proprietary ligand binds $\alpha V\beta 3$ in ccRCC





Ligand-dependent DPC™ uptake in ccRCC tumor cell line



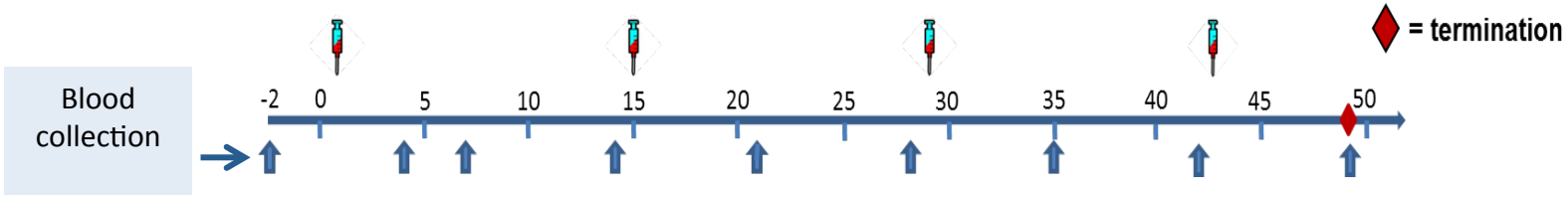


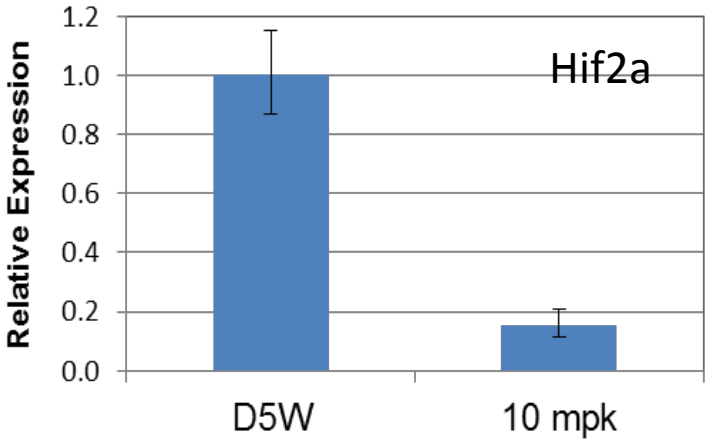
Green: Actin
Blue: Nuclei
Red: RGD-DPC

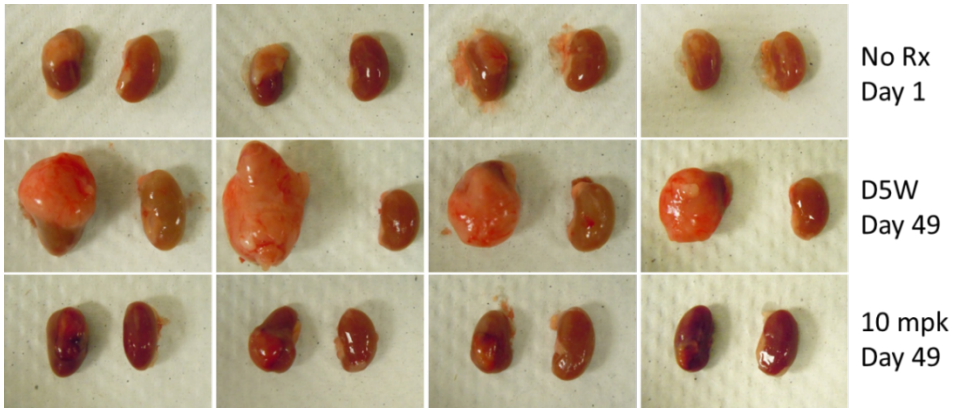
HIF2α is an important driver in ccRCC

- HIF2α as gene target for clear cell renal cell carcinoma (ccRCC)
  - Normally expressed in response to low oxygen conditions
  - Overexpression of HiF2α in tumors drives tumor growth and metastasis
  - Overexpression of HIF2a is due to mutations in Von Hippel-Lindau protein which normally promotes degradation of HIF2a
  - 90% of ccRCC have Von Hippel-Lindau mutations

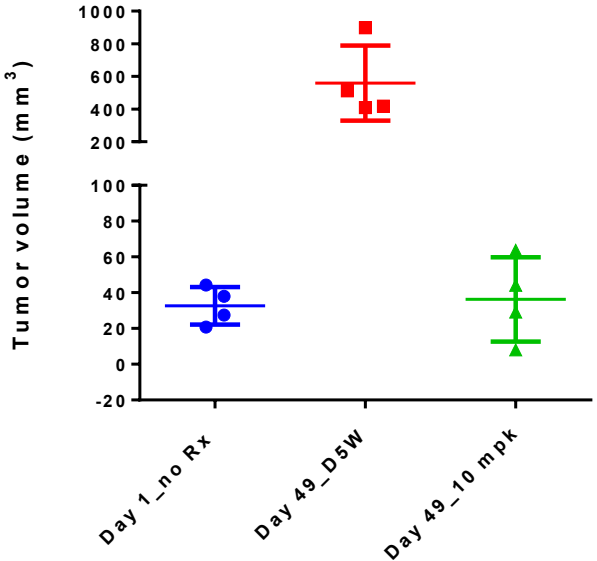
Tumor growth inhibited after 4 bi-weekly doses in orthotopic ccRCC mice







- Tumor volumes unchanged in the treatment group, suggesting tumor stasis
- Histological examination revealed extensive tumor destruction
- Treatment was well tolerated

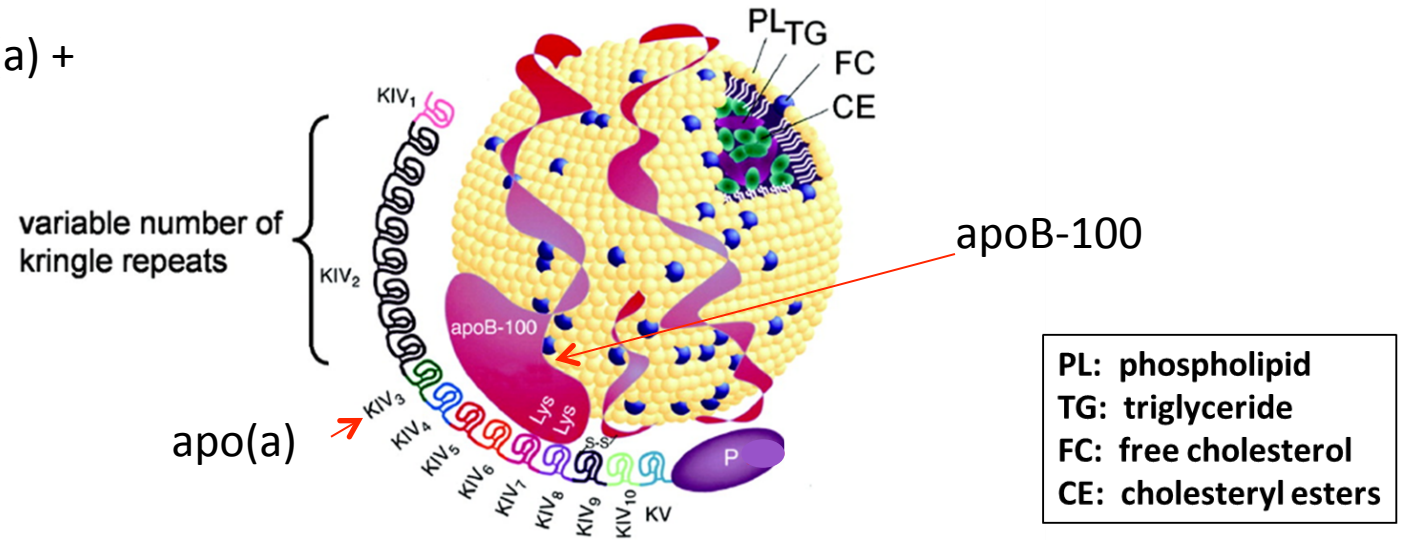


New subcutaneous format developed for hepatic delivery

- Current construct does not employ active endosomal escape
- Employs N-acetyl galactosamine for hepatic targeting
- Lead compound in place, optimization ongoing

Lp(a) as a Cardiovascular Disease Target

LP(a) particle = apo(a) + apoB-100 LDL-like particle

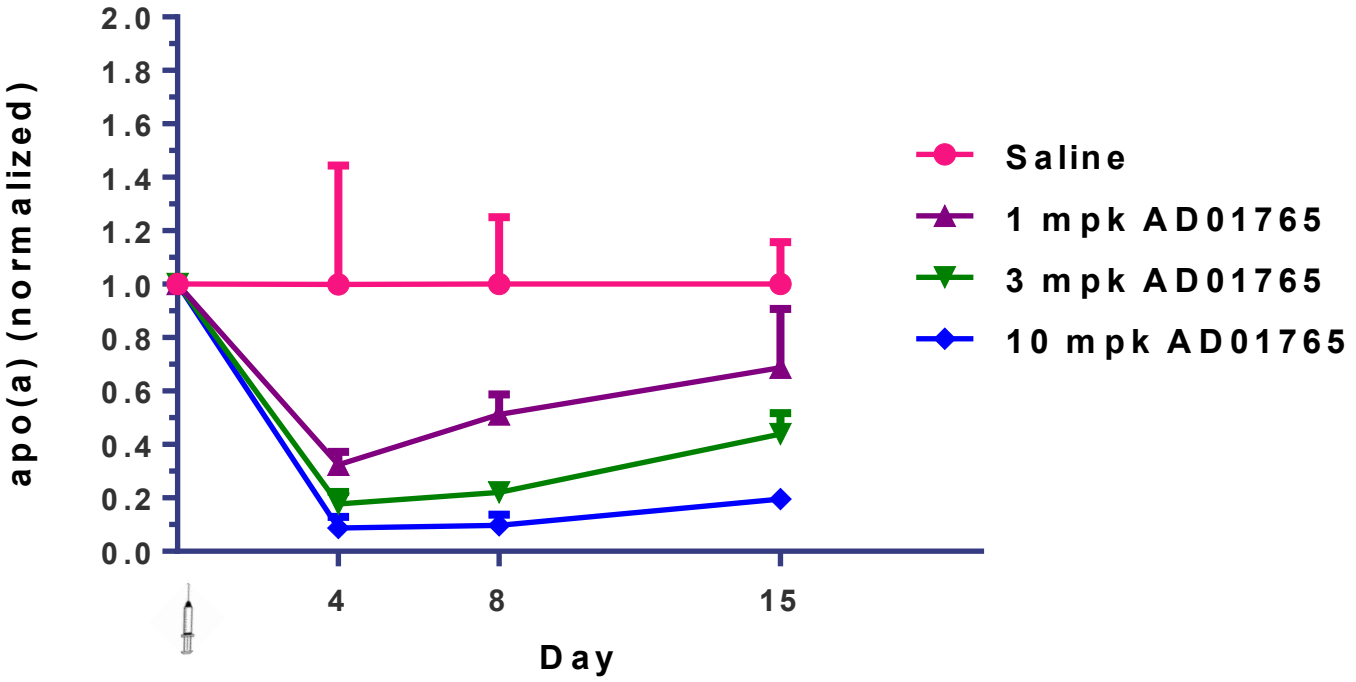


- apo(a) produced predominantly in liver and restricted to humans and non-human primates
- Expression of apo(a) inversely correlated with the number of Kringle (KIV-2) domains present

<u>Target Indication: Cardiovascular Disease</u>

- Lp(a) levels reported to be independent risk factor for cardiovascular diseases (myocardial infarction, stroke, thrombosis, and aortic stenosis)

Subcutaneous platform gives potent knockdown in apo(a) Tg mice after a single dose



AD01765 shows dose response with good duration of effect – study ongoing

Conclusions – Arrowhead delivery platform diversifying in program number and formats

- Arrowhead is in the clinic with two hepatic products using DPC delivery systems with two additional announced
- Recently announced Hif-2α program employs a new DPC delivery system for extra-hepatic delivery with a novel targeting ligand
- Today we have disclosed initial data for a new, proprietary SQ format with preclinical studies underway targeting the apo(A) gene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