

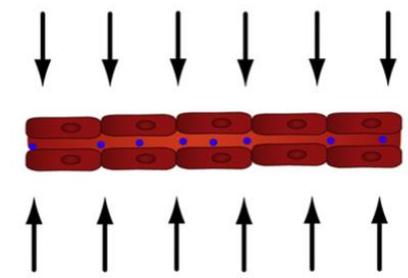
# How the choice of PK model and AIF affect DCE-MRI detection of pancreatic cancer responses to stroma-directed drug

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## Background & Rationale

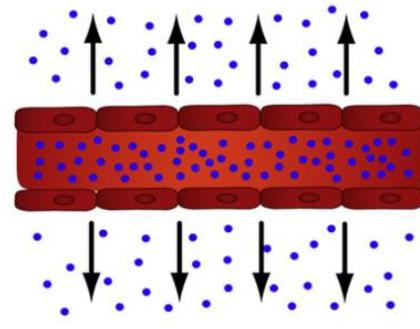
1. The dense extracellular matrix in **pancreatic ductal adenocarcinoma (PDA)** is a mechanism for treatment failure [1]. PEGPH20 degrades hyaluronan (HA) from ECM.
2. Test the utility of DCE-MRI to detect responses to stroma-directed interventions
  - DCE-metrics ( $K^{trans}$ ,  $k_{ep}$  and  $V_p$ ) and PK models
  - Individual arterial input function (AIF) vs. group-AIF
3. Corroborate imaging and immunostaining data.

### Vehicle followed by CA injection



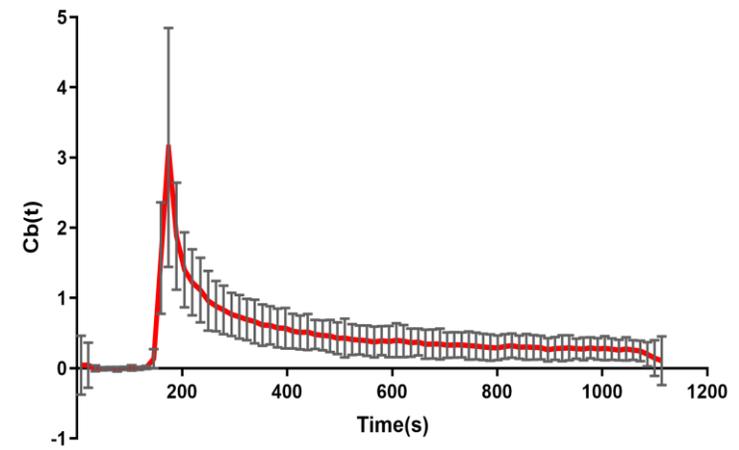
$P_{out} > P_{in}$ ; Limited permeability and perfusion

### PEGPH20 followed by CA injection

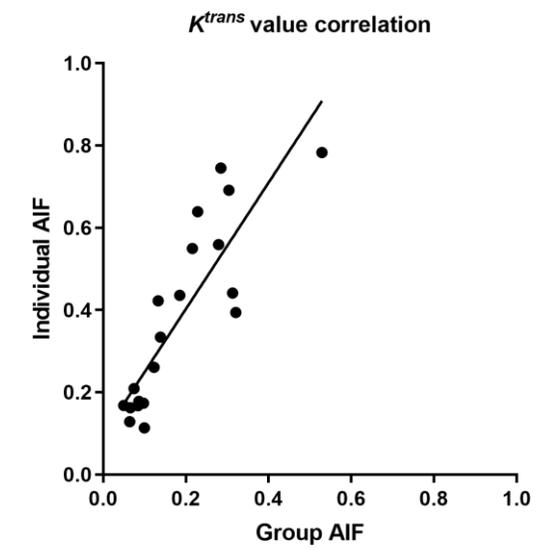


$P_{out} < P_{in}$ ; Permeability and perfusion increased

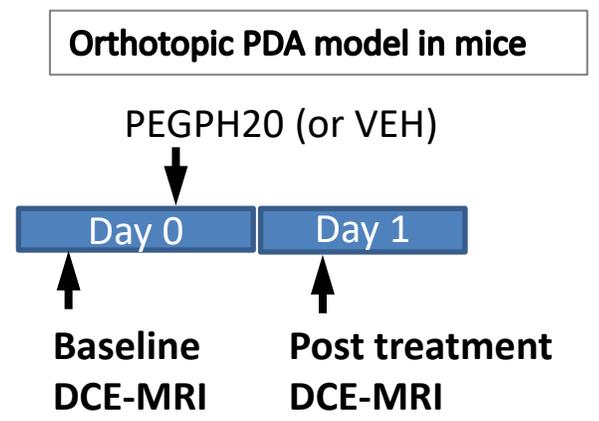
## Group AIF (n=20)



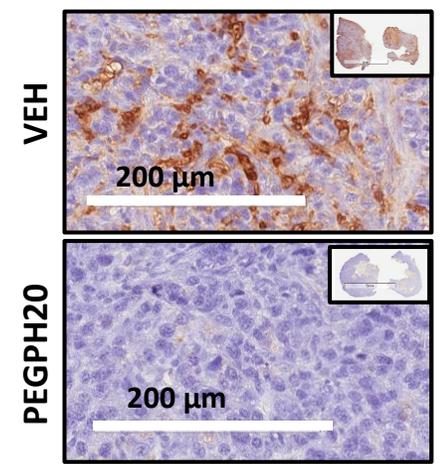
## Correlation of $K^{trans}$ derived from SSM using Individual and Group AIF.



## Treatment and MRI schedules



## IHC of tumor HA



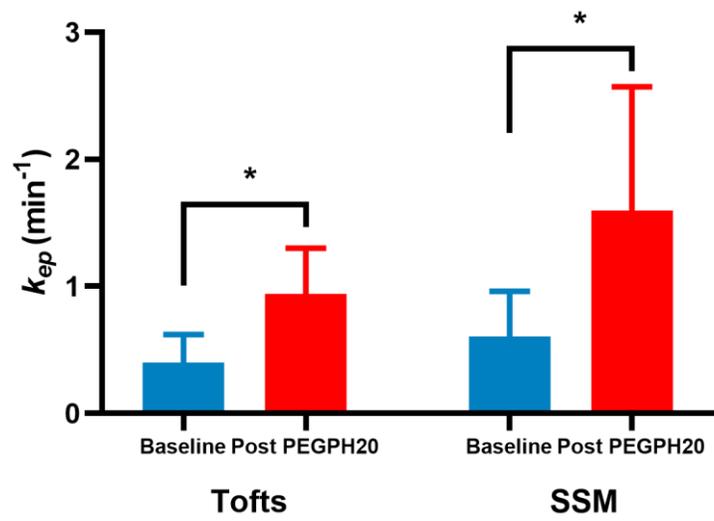
## Detailed MRI Methods

- 9.4T DirectDrive® (Agilent) interfaced with a 12-cm gradient coil.
- RF coil: 35 mm ID x 10 cm long quadrature birdcage transceiver (M2M)
- Slice groups: one slice containing the left ventricle (LV) to obtain the arterial input function (AIF); 4-7 slices covering the tumor
- $T_{10}$  ( $T_1$  before CA injection) map of tumor and blood (LV) using an ECG-gated inversion recovery technique [2].
- Contrast agent (CA): MultiHance® diluted to 10 mM of gadolinium in saline (0.2 mL) was injected in 10 sec via syringe pump into tail vein.
- DCE series: ECG-gated saturation recovery sequence
  - A total of 80 images were acquired continuously while CA was injected after first 10 images.
  - FOV=32 mm, matrix size = 64x64, effective TR= 2 x heart beats  $\approx$  200 ms, TE= 3 ms, flip angle = 90 degrees.
  - the timing of radiofrequency excitation was recorded on a micro-controller device and the record was used to correct ECG triggering errors during post processing.

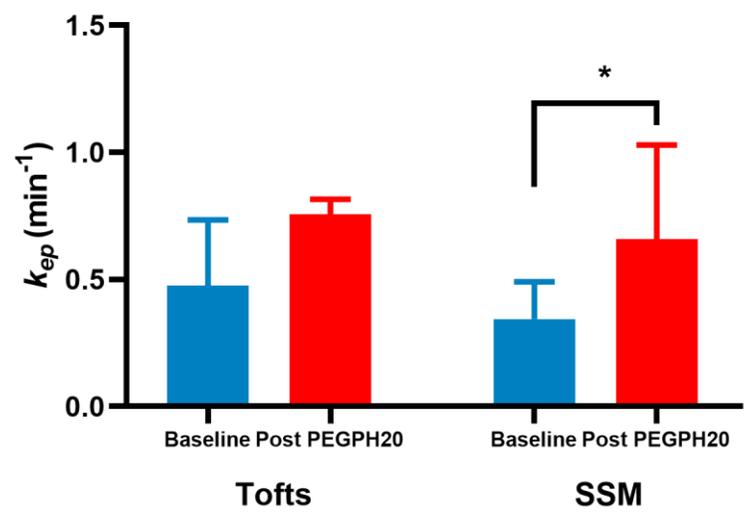
## Data Processing

- Individual AIF was extracted from LV heart of each mouse
- Group AIF was the average of 20 AIFs measured from 10 mice.
  - ✓ Each mouse contributed two AIFs (pre and post treatment).
  - ✓ AIFs were aligned by bolus-arrival time of CA before averaging.
- AIF, DCE series and  $T_{10}$  maps of the tissue were fit to a pharmacokinetic model using the least squares methods
  - ✓ Tofts model [3]
  - ✓ Modified Tofts model (M-T)
  - ✓ Shutter-speed model (SSM) [4-5]
- Pixel-wise parametric maps of  $k^{trans}$ ,  $k_{ep}$ ,  $V_e$ ,  $V_p$  and  $\tau_i$  were obtained.

Individual AIF

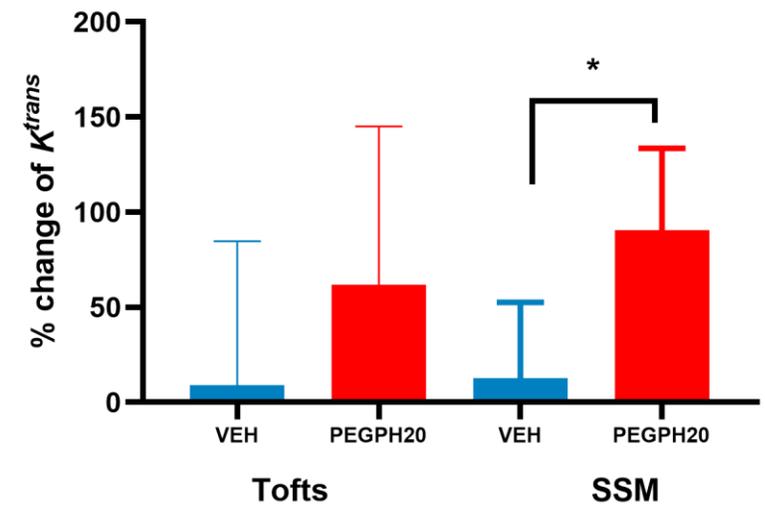
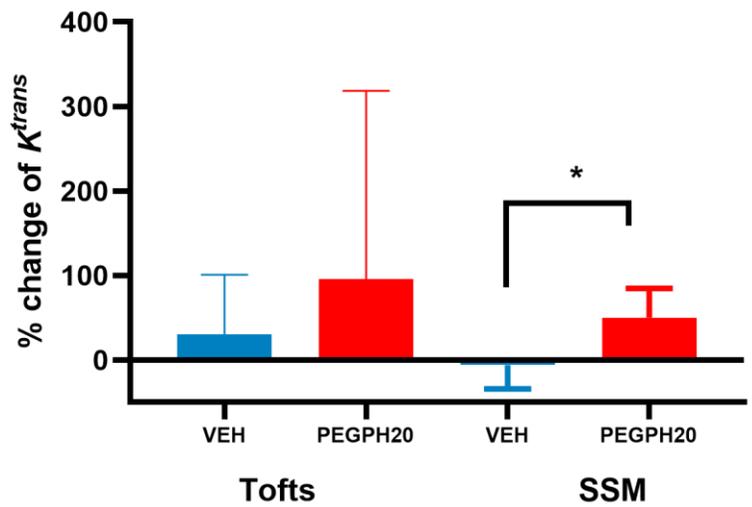


Group AIF



$k_{ep}$ metric:	Individual AIF	Group AIF
Tofts	Yes	No
SSM	Yes	Yes

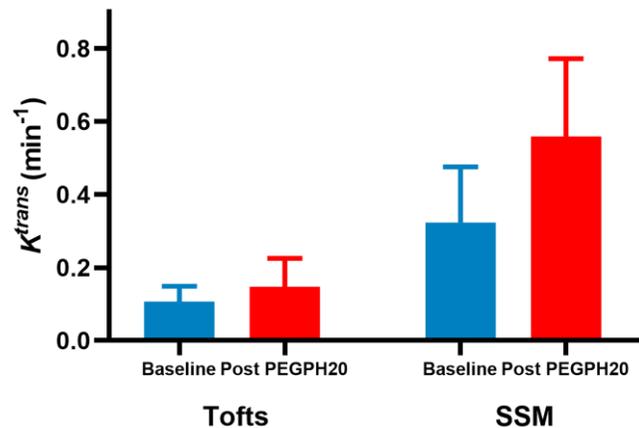
Individual AIF approach allows Tofts model to detect changes of  $k_{ep}$  induced by PEGPH20.



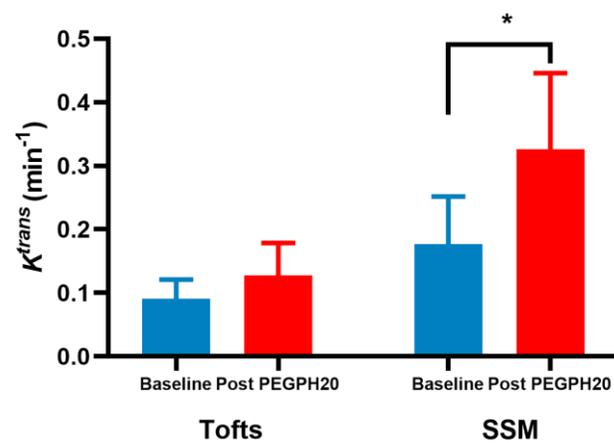
% change of $K^{trans}$ metric:	Individual AIF	Group AIF
Tofts	No	No
SSM	Yes	Yes

Both the individual and group AIF approach only allow SSM model to detect %change of  $K^{trans}$  induced by PEGPH20.

### Individual AIF

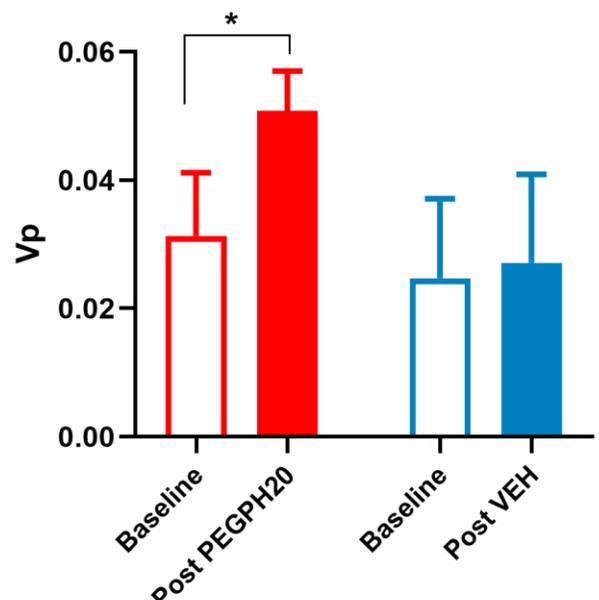


### Group AIF

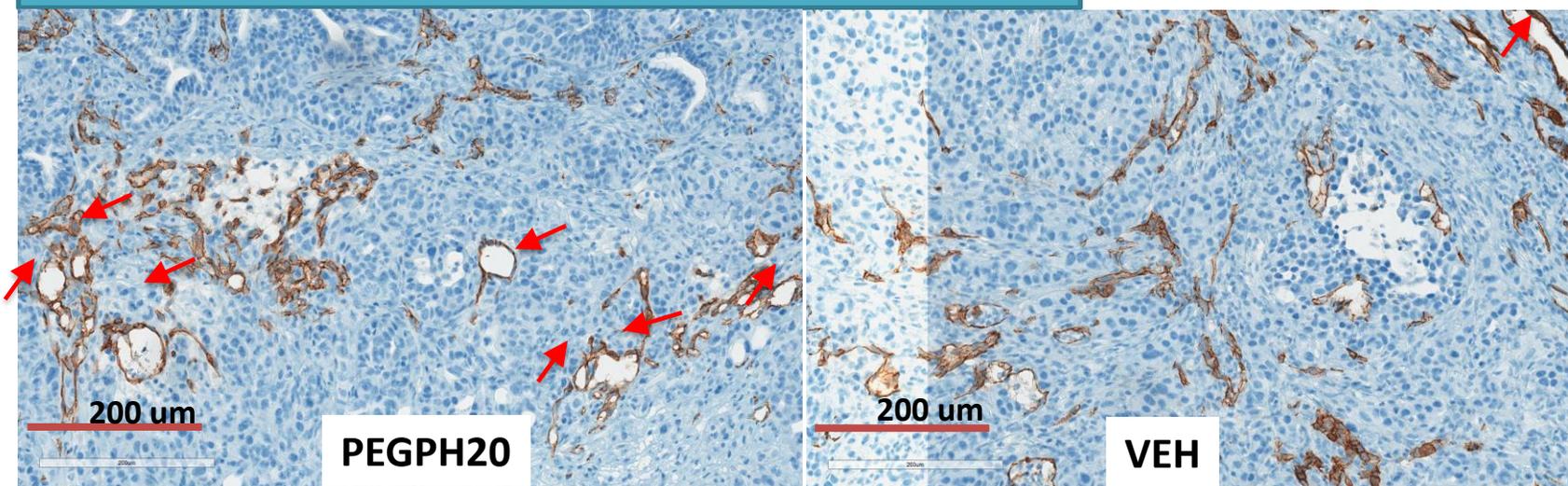


$K^{trans}$ metric:	Individual AIF	Group AIF
Tofts	No	No
SSM	No	Yes

Only group AIF approach allows SSM model to detect  $K^{trans}$  change before and after PEGPH20 injection.



### Immunostaining of CD31 (endothelial marker) in tumor



$V_p$  (fractional plasma volume) derived from fitting of M-T model using **group AIF** shows a significant increase 24 h after PEGPH20 injection.

In PEGPH20-treated tumor, a trend of increase vascular lumen area is observed (arrows) compared to VEH treated tumor although a statically significance has not been reached due to small sample size.

## Discussion and Conclusion

1. SS model appears to be more sensitive than Tofts or M-T model for detection of treatment effect when applied with either individual- or group-AIF.
2. Tofts model, however, is capable of detecting a significant increase of  $k_{ep}$  after the treatment **only** when combined with Individual-AIF approach.
3. Further validation of  $V_p$  by IHC analyses is ongoing.

## References

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