

# MR Imaging as Predictive and Prognostic Biomarker

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Harnessing Imaging Tools to Guide  
Immunotherapy Trials



# Disclosure

- *I do not have any relevant financial relationships with any commercial interests*
- *Will be discussing off label use of an FDA approved drug*

# Overview

- Focus on inflammation in tumor → Tumor associated Macrophages (TAM)
- Noninvasive imaging → tool to quantify TAM density within tumors

# Inflammation & Cancer

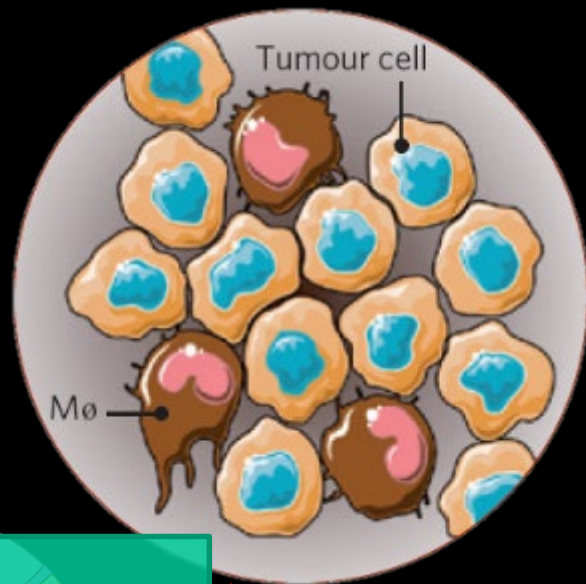
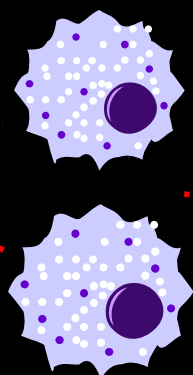
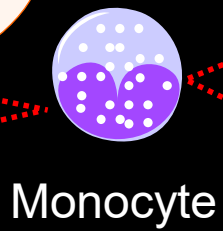
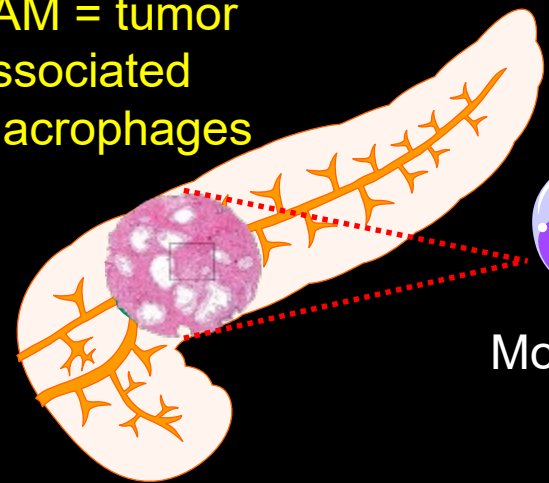
- 1863 Rudolf Virchow → white blood cells or leukocytes → in neoplastic tissues → connection of inflammation and cancer
- Harold Dvorak → inflammation and cancer → share development mechanism (angiogenesis) and tissue infiltrating cells (lymphocytes, **macrophages** and mast cells)

# Inflammation & Cancer

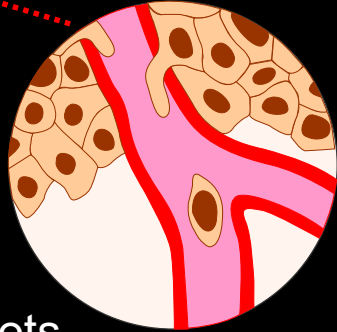
- Tumors act like Wounds that Do Not Heal

- Inflammatory component of Cancer Microenvironment has NOT been exploited → imaging

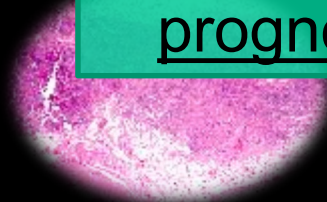
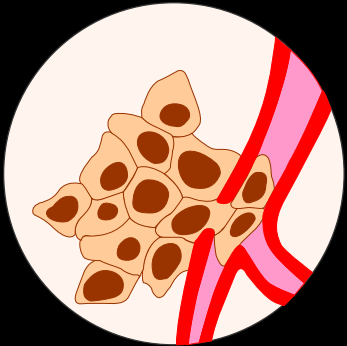
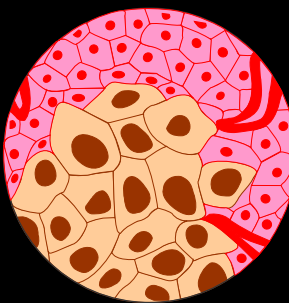
TAM = tumor associated macrophages



• High number of Tumor Associated Macrophages (TAM) in tumor → tumor progression and overall poor prognosis

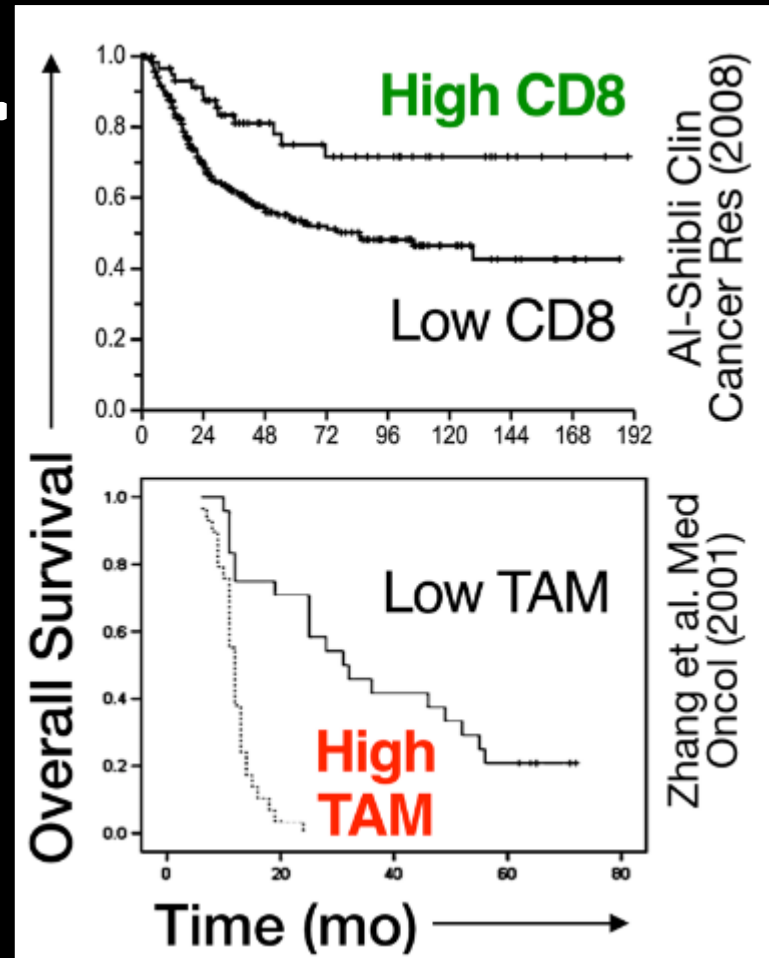


Distant Mets



# Tumor Associated Macrophages (TAM)

- Role in
  - Tumorigenesis
  - Angiogenesis
  - Matrix modelling
  - Metastases



# Therapeutics Targeting TAM


- Tumor-associated macrophage (TAM) levels vary across patients and tumor regions → correlate with resistance to immune checkpoint blockade
- New therapeutic drugs targeting TAM → lead to durable and predictable response → BRAF inhibitor therapy, PDL1 targeted antibody therapy



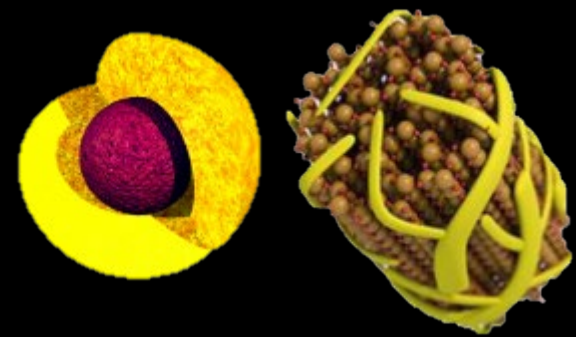
# TAM targeted Therapies

- Identify tumors → density of TAM
  - Stratify patients
    - TAM modulating therapies
  - Monitor treatment response → test that can be performed repeatedly

# TAM Detection and Quantification

- Gene expression analysis
  - Immunohistochemistry
  - Fluorescent MRI
- 
- Invasive
  - Lack of clinical availability
- Noninvasive test; easy to perform and interpret

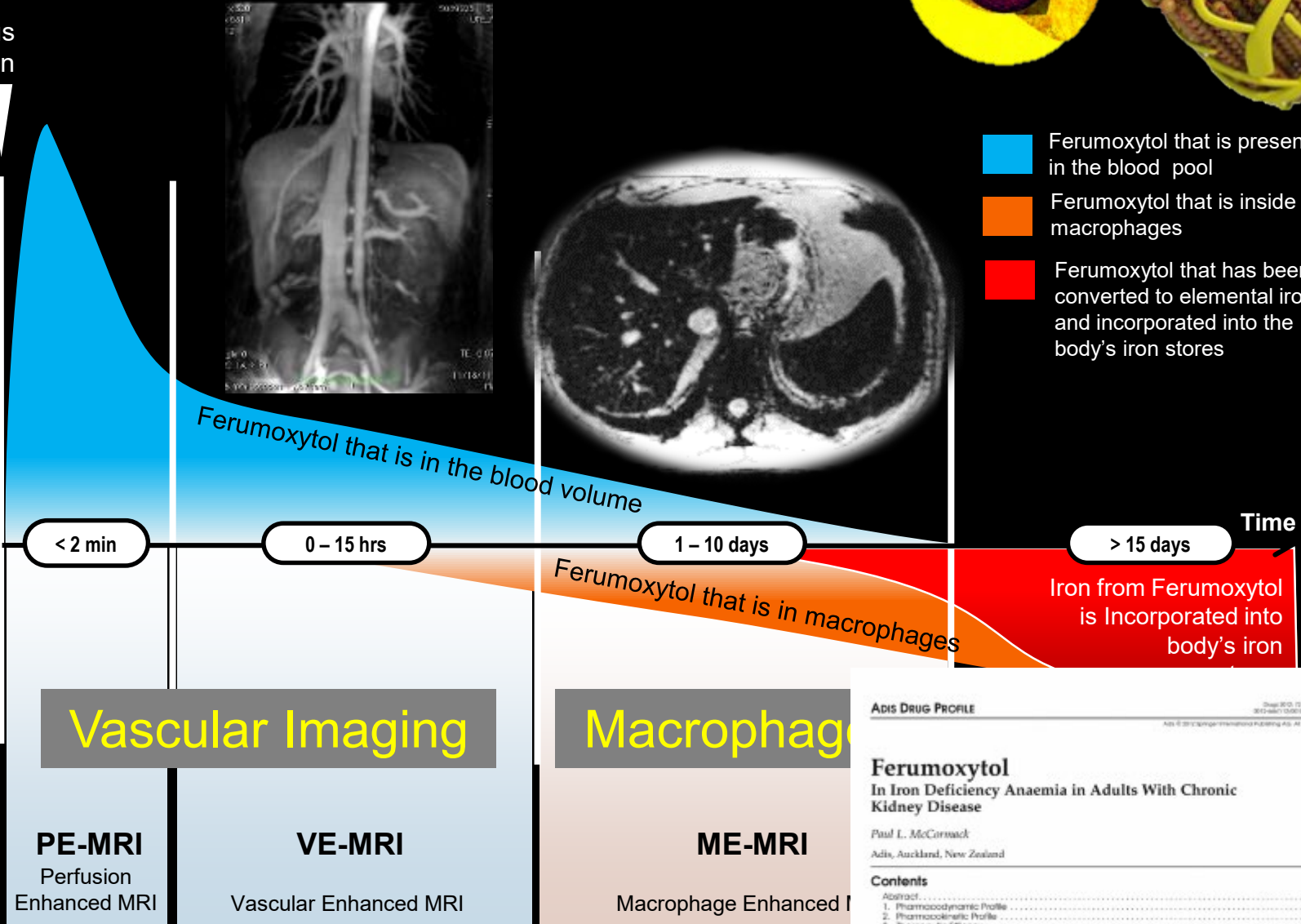
# Ferumoxytol Biodistribution



17 sec Bolus Injection

↑ increasing Concentration in blood

↓ Increasing Concentration in Tissue



**Vascular Imaging**

**Macrophage**

**PE-MRI**  
Perfusion Enhanced MRI

**VE-MRI**  
Vascular Enhanced MRI

**ME-MRI**  
Macrophage Enhanced MRI

**MODES OF MAGNETIC RESONANCE IMAGING**

**ADIS DRUG PROFILE**

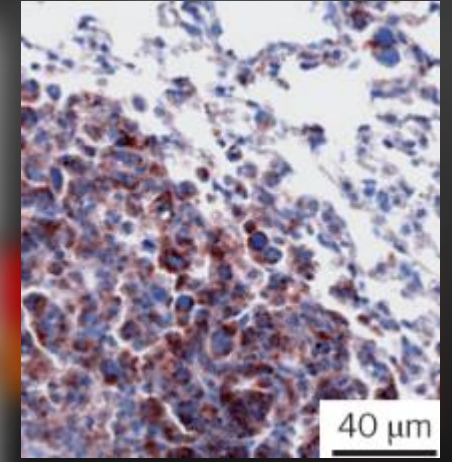
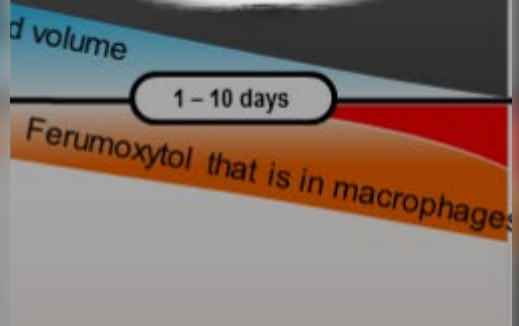
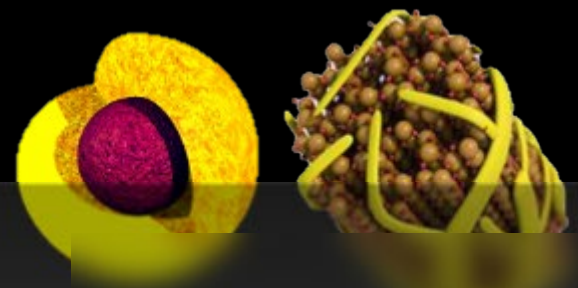
**Ferumoxytol**  
In Iron Deficiency Anaemia in Adults With Chronic Kidney Disease

Paul L. McCormack  
Adis, Auckland, New Zealand

**Contents**

Abstract	2018
1. Pharmacodynamic Profile	2018
2. Pharmacokinetic Profile	2018
3. Therapeutic Efficacy	2018
4. Tolerability	2018
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# Ferumoxytol Biodistribution

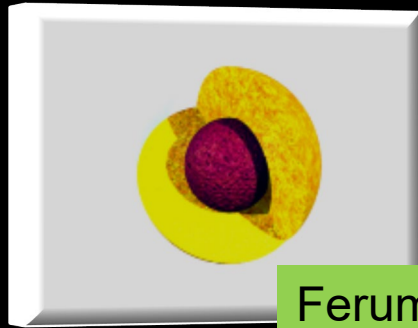


## Macrophage Imaging

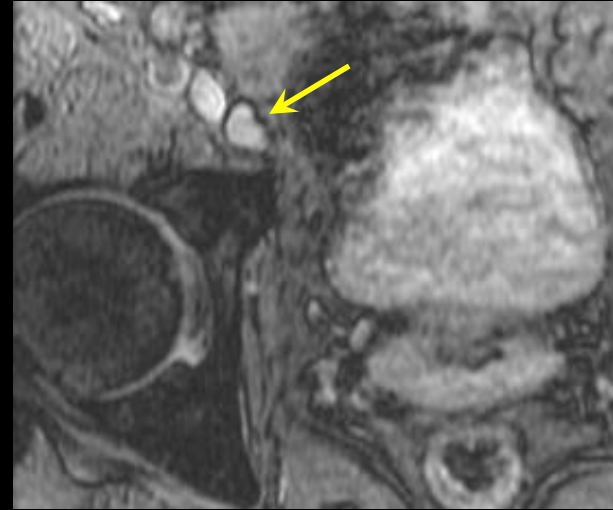
**ME-MRI**

Macrophage Enhanced MRI

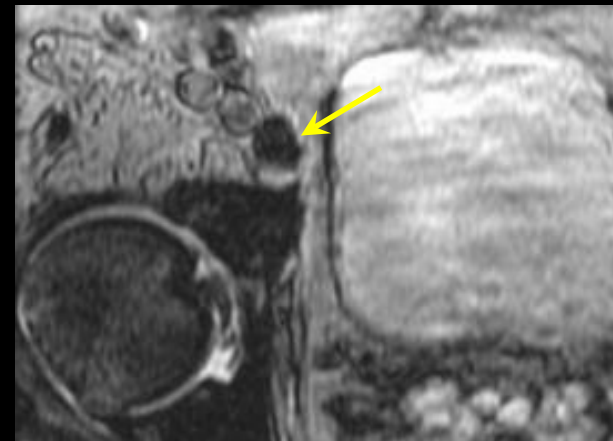
# Ferumoxytol



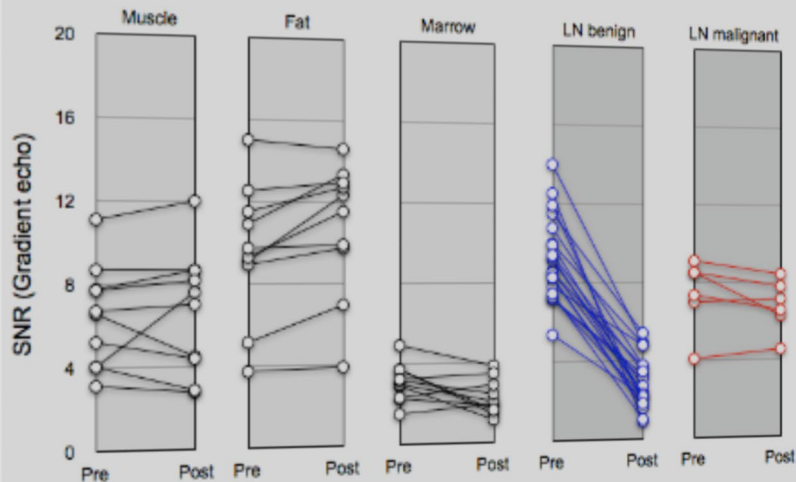
Ferumoxytol



Baseline



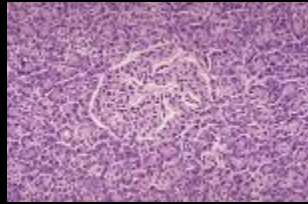
24 hours



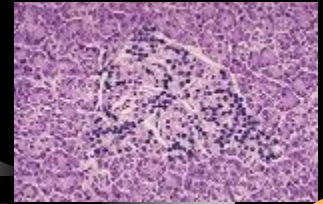
# Imaging Inflammation

- Type 1A diabetes (T1D)
  - Autoimmune Disease
- Noninvasive method to visualize T1D at the target organ level in patients with active insulinitis

Insulitis is associated with inflammatory infiltrate and capillary "leak"



"Leak"



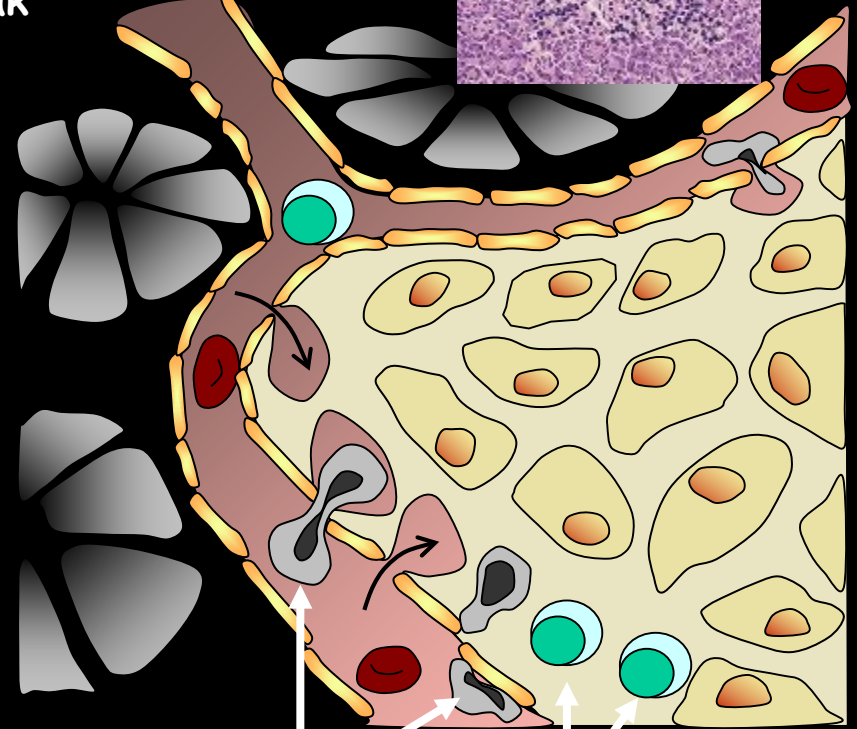
Exocrine pancreas

RBC

Blood vessel

$\beta$  cells

Healthy pancreatic islet



Monocytes

Lymphocytes

Insulitic islet

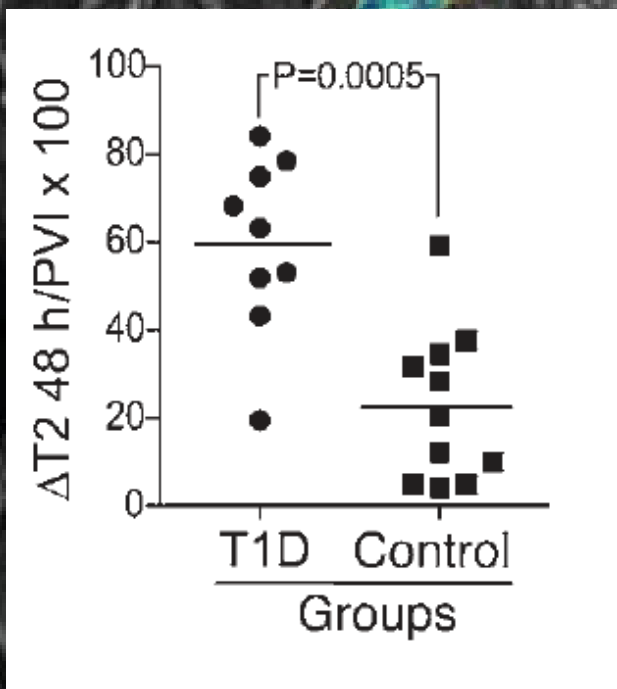
Controls

Pre

48 hr post

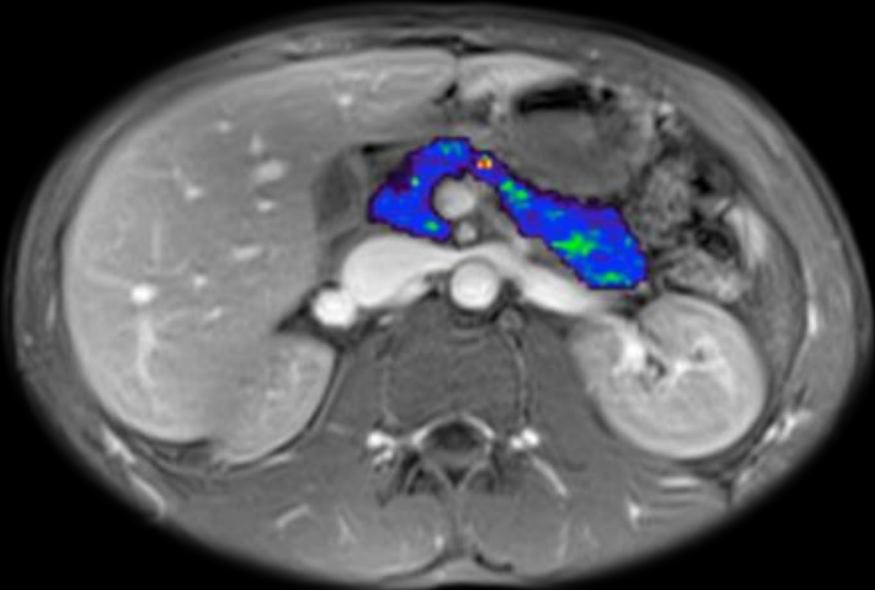
Diabetic Patients

48 hr post

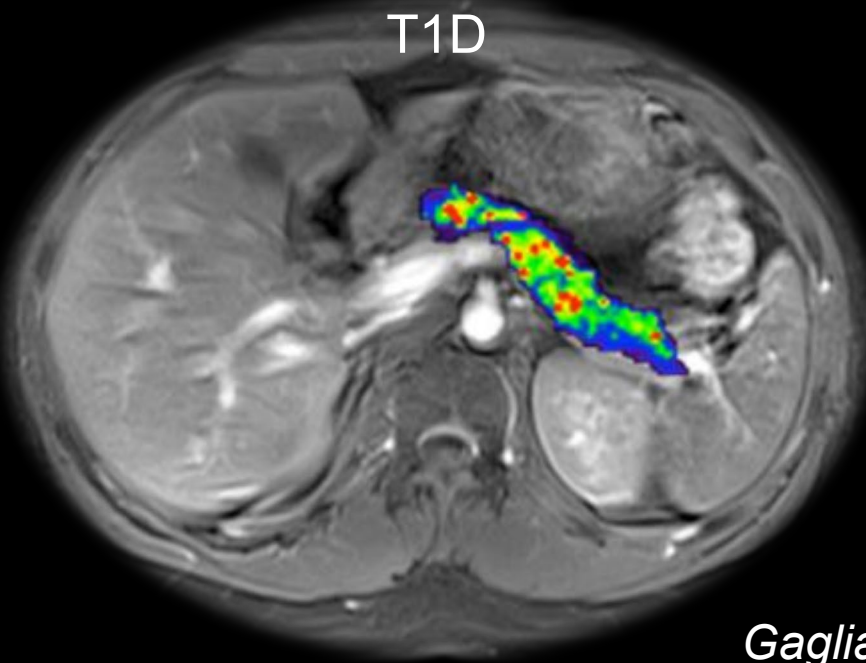




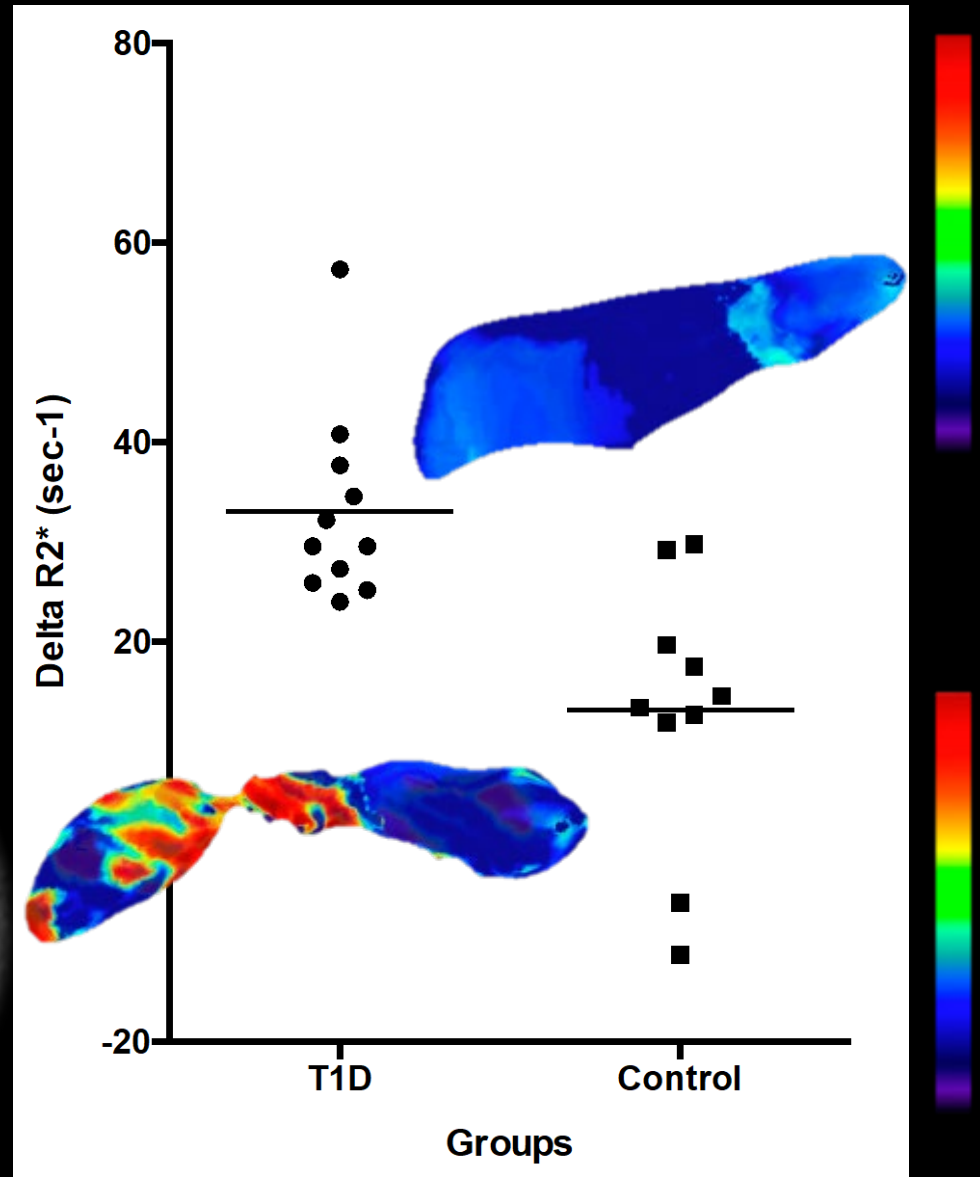
Control

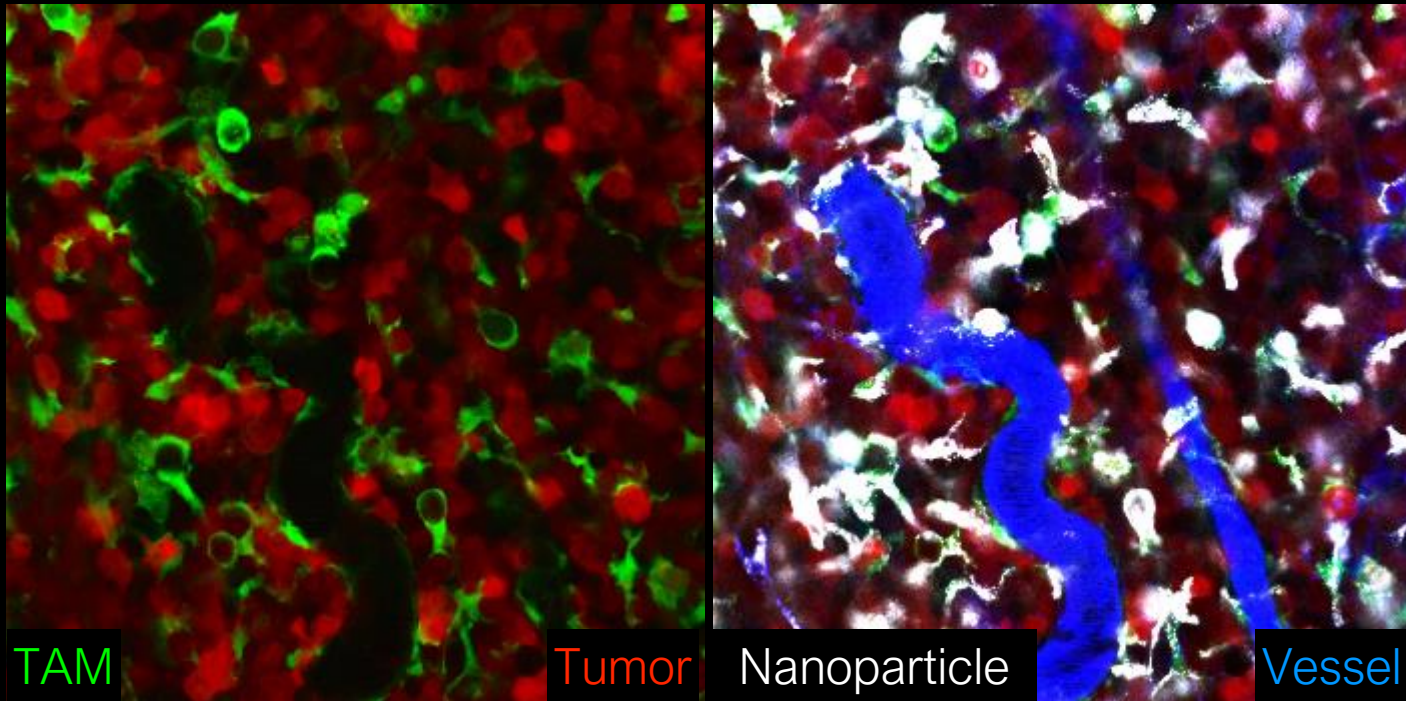


T1D



Delta R2\* Entire Pancreas



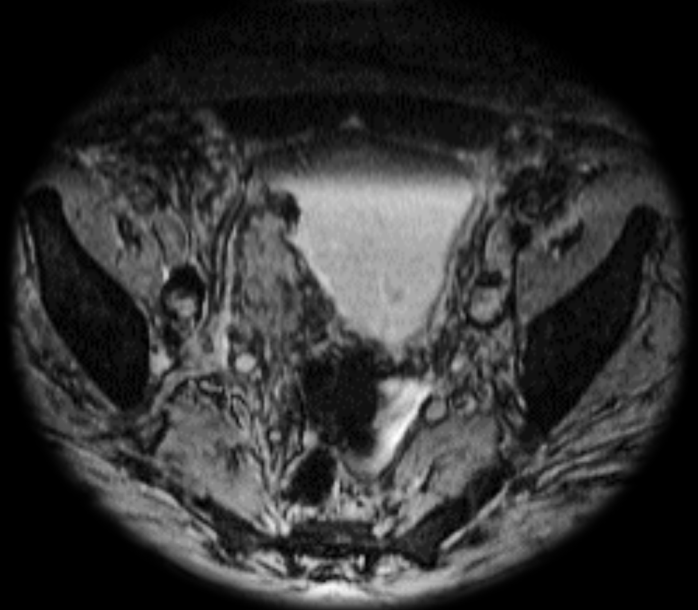
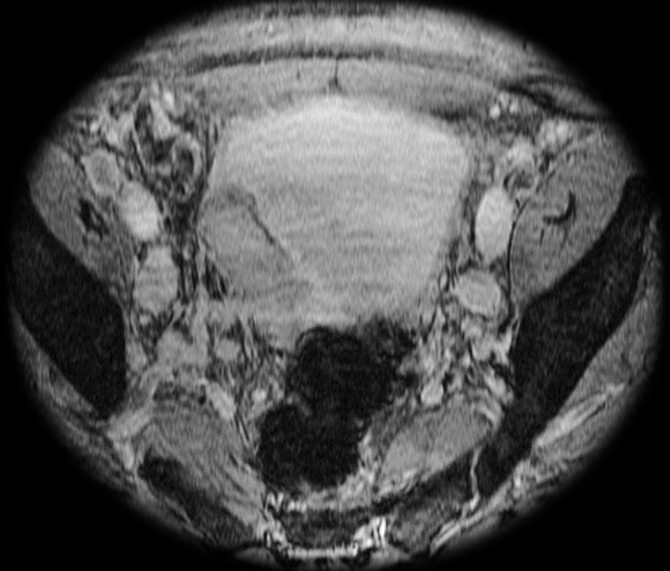
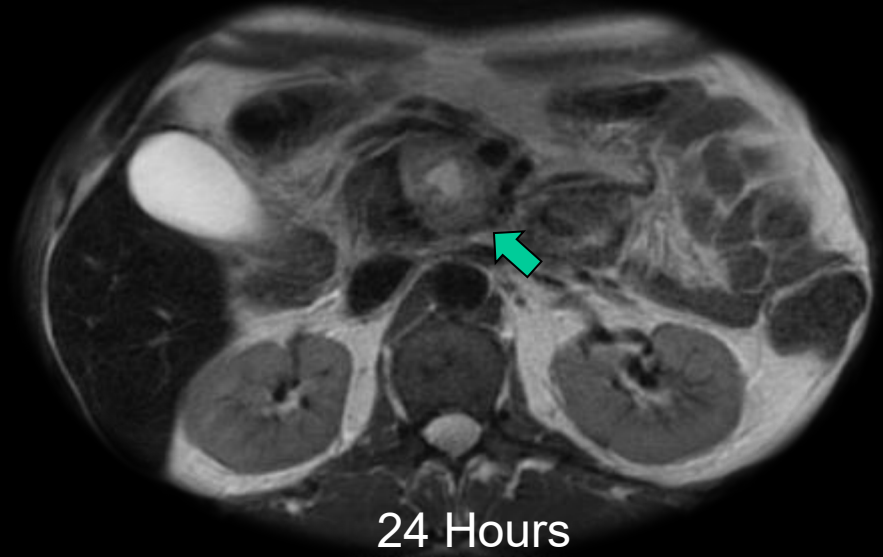


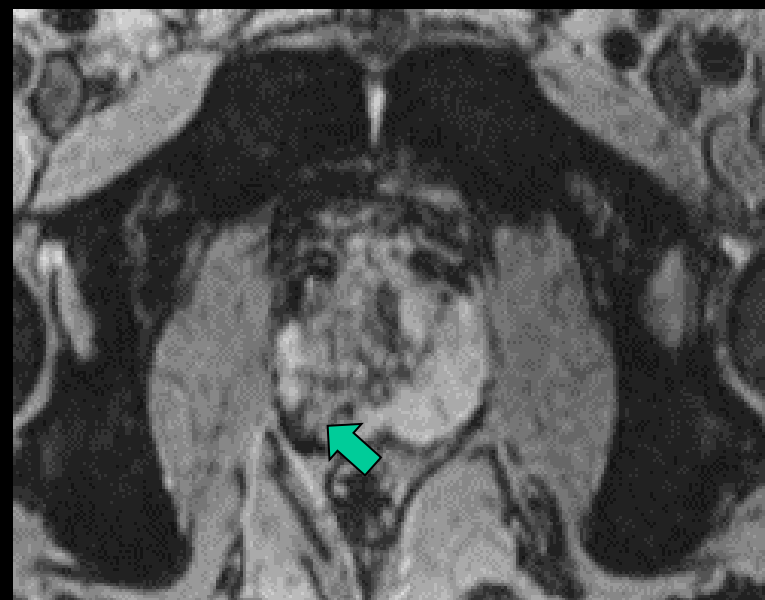
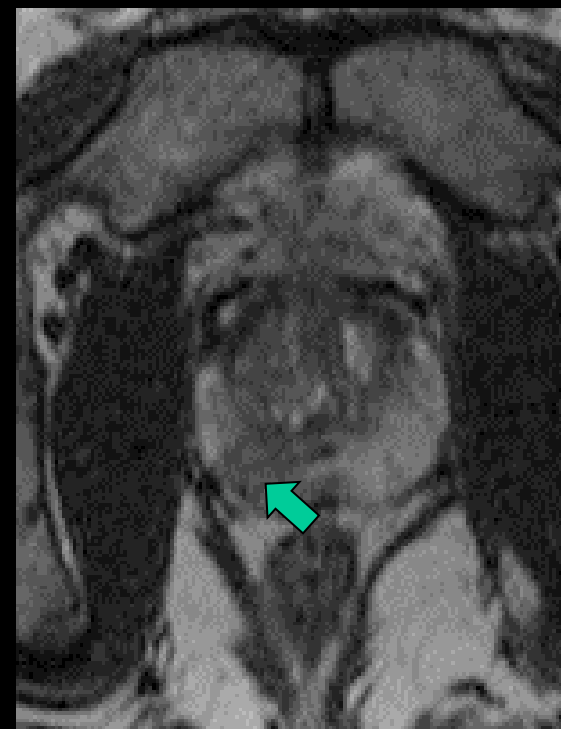
mer-TK mouse

Flt3 mouse

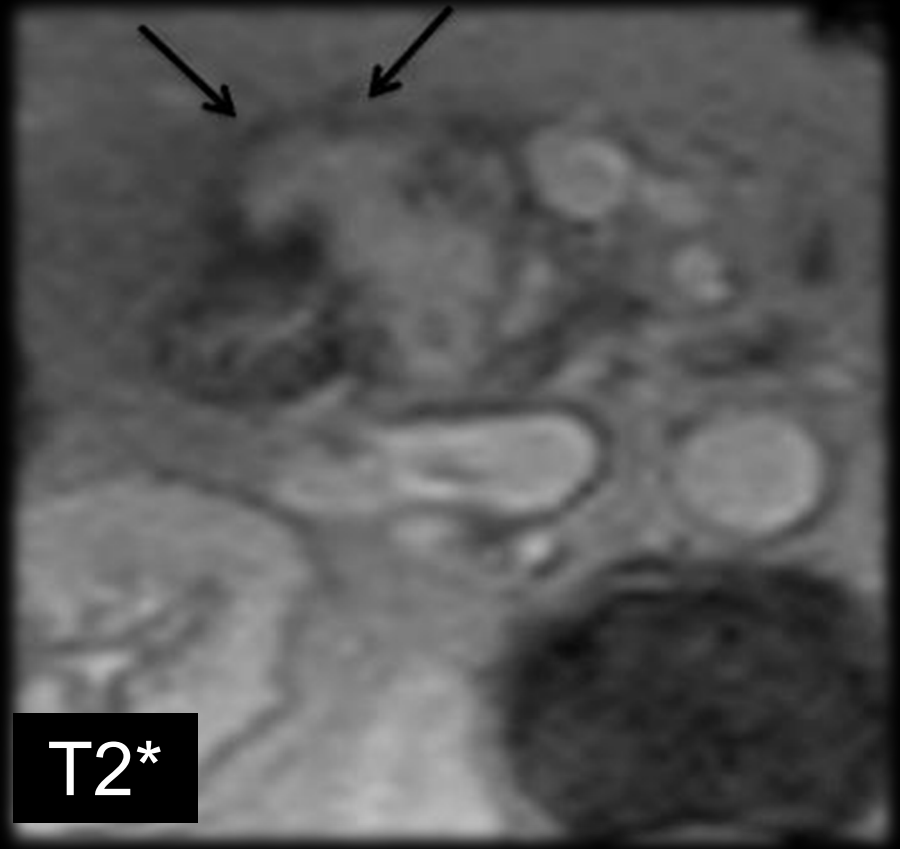
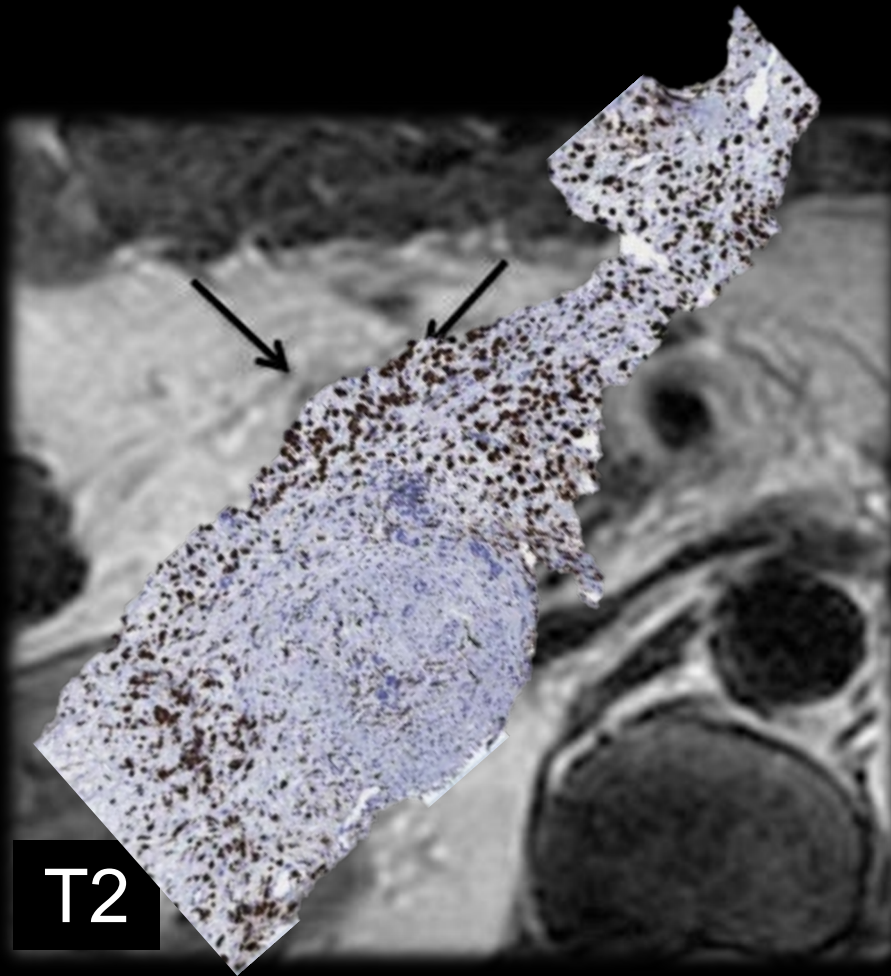
white: ferumoxytol  
red: E14-apple cells  
green: merTK-GFP  
blue: pacific blue dextran

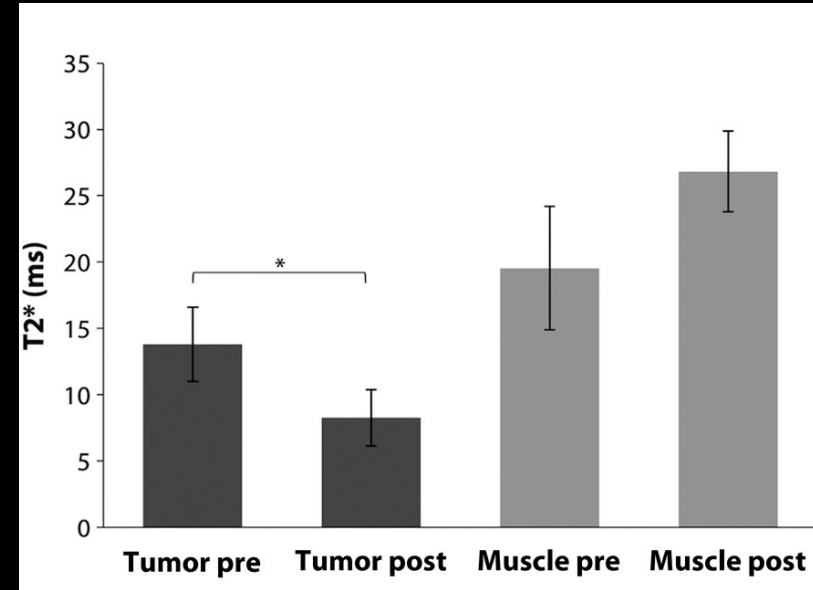
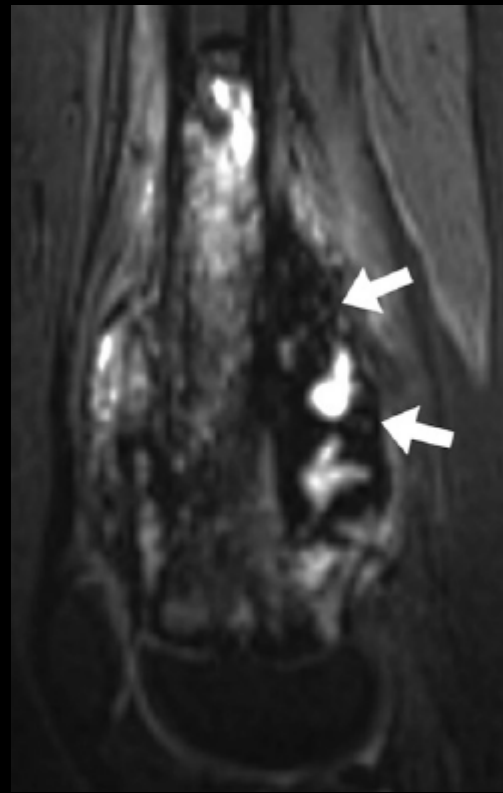
# Can Ferumoxytol → TRAM imaging





# PDAC





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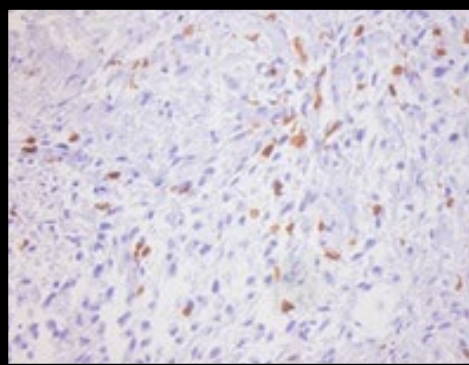
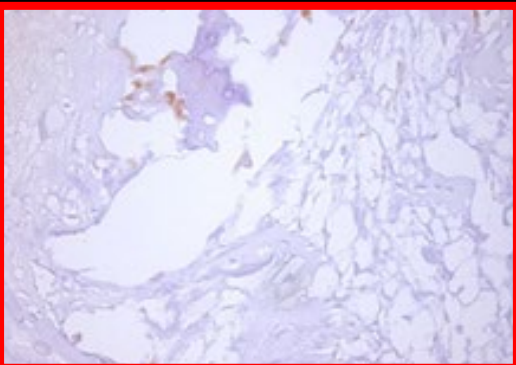
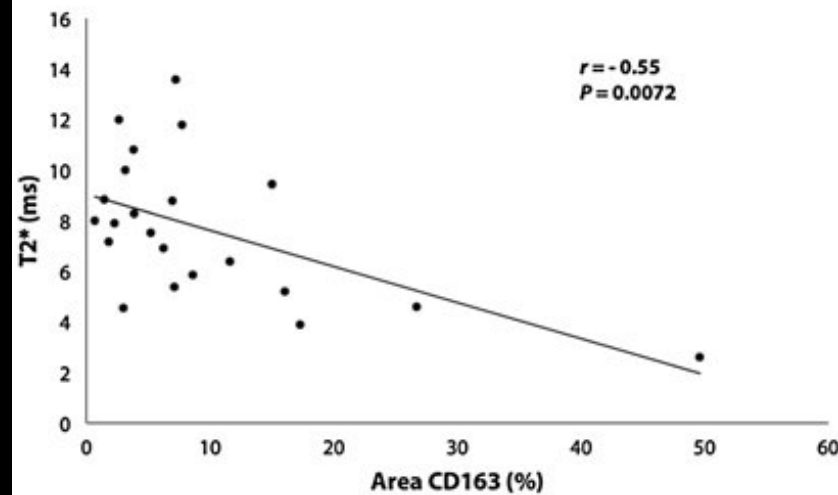
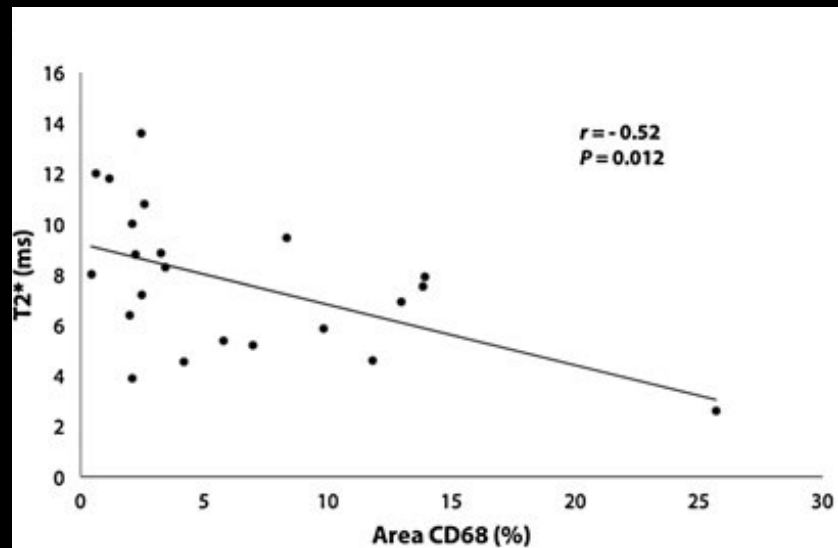
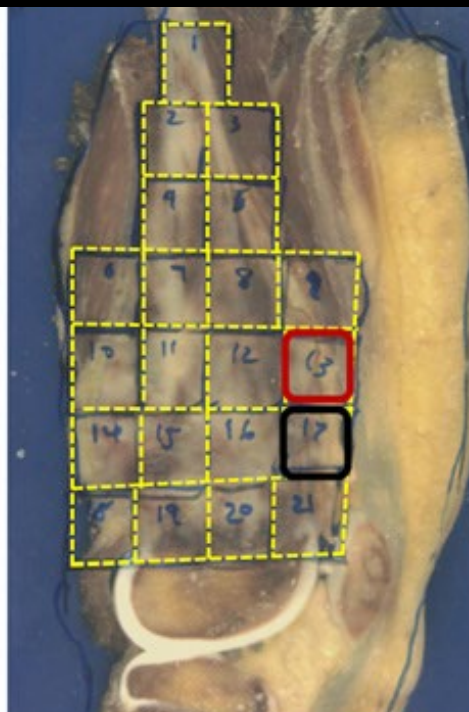
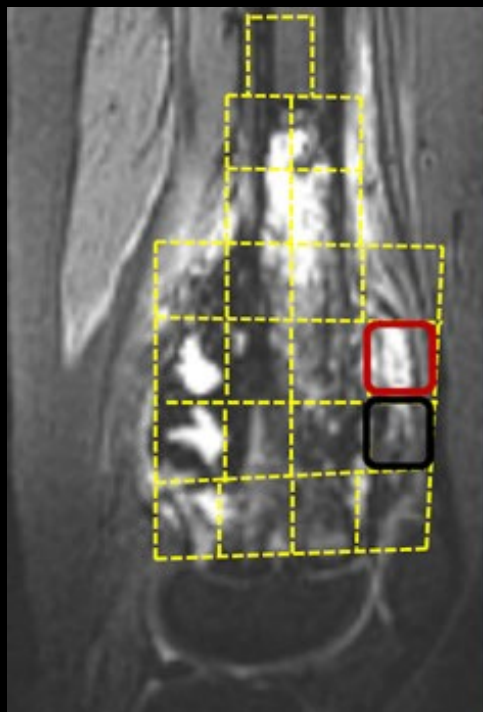
Precision Medicine and Imaging

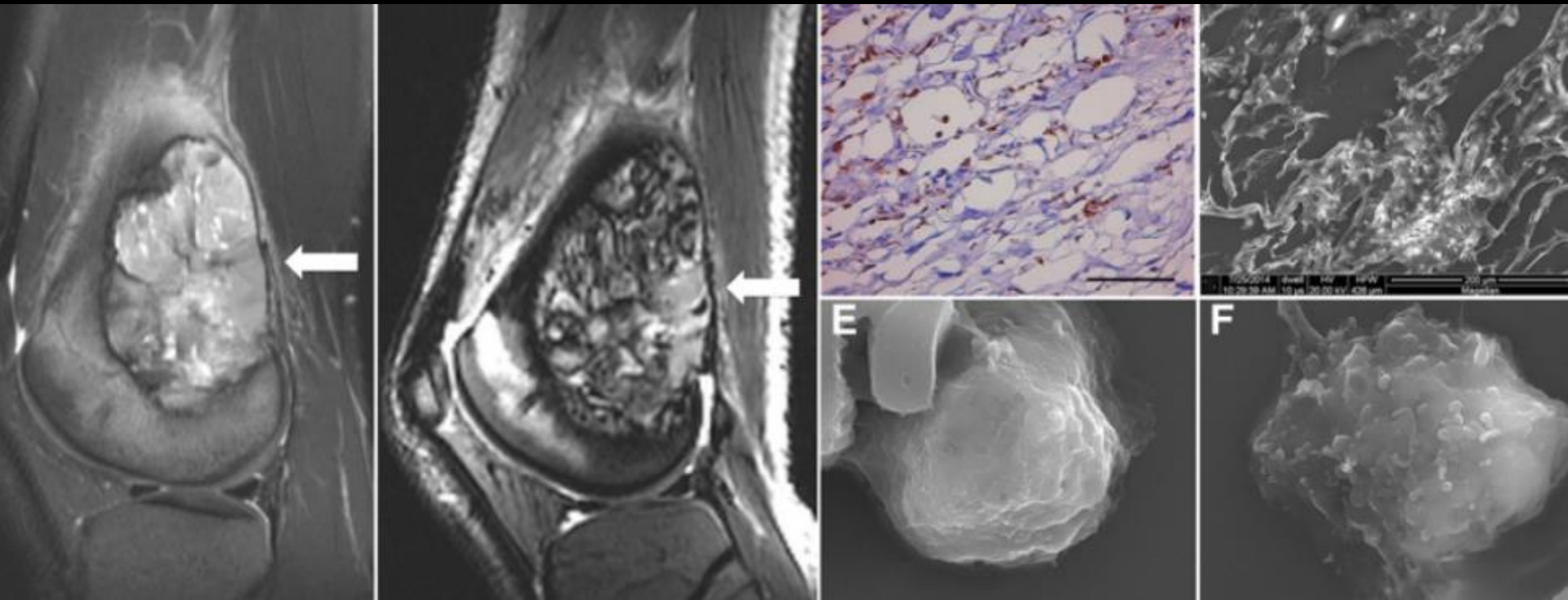
Clinical  
Cancer  
Research

## Magnetic Resonance Imaging of Tumor-Associated Macrophages: Clinical Translation

Maryam Aghighi<sup>1</sup>, Ashok J. Theruvath<sup>1,2</sup>, Anuj Pareek<sup>1</sup>, Laura L. Pisani<sup>1</sup>, Raphael Alford<sup>1</sup>, Anne M. Muehe<sup>1</sup>, Tarsheen K. Sethi<sup>1</sup>, Samantha J. Holdsworth<sup>1</sup>, Florette K. Hazard<sup>5</sup>, Dita Gratzinger<sup>3</sup>, Sandra Luna-Fineman<sup>4</sup>, Ranjana Advani<sup>2</sup>, Sheri L. Spunt<sup>4</sup>, and Heike E. Daldrup-Link<sup>1,4</sup>





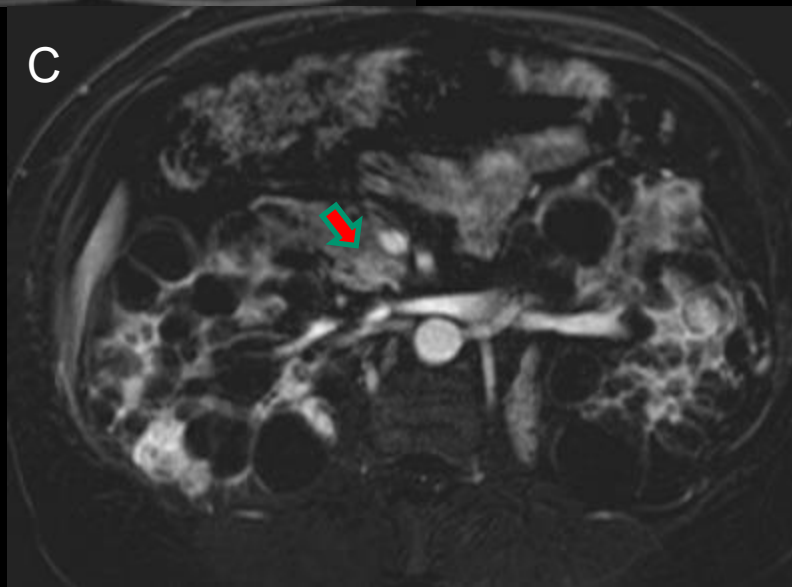
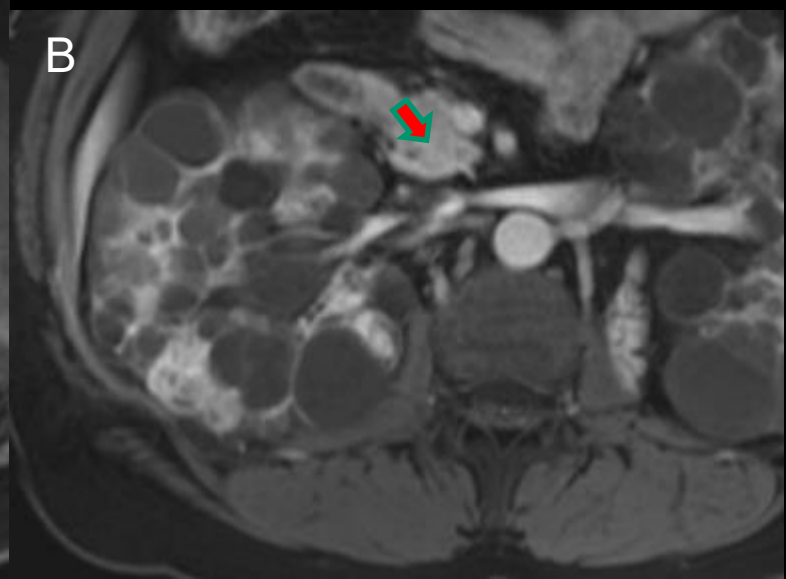
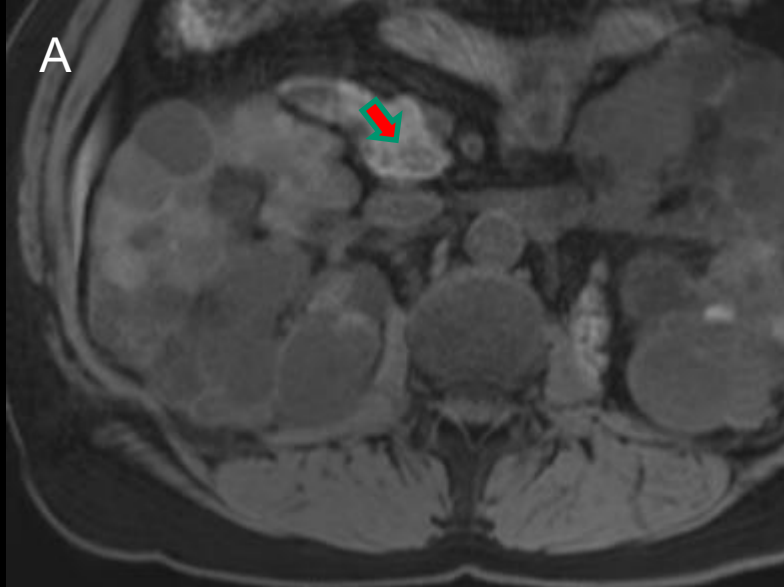


**Tumor Ferumoxytol enhancement on MRI correlated with TAM density in the tumors**

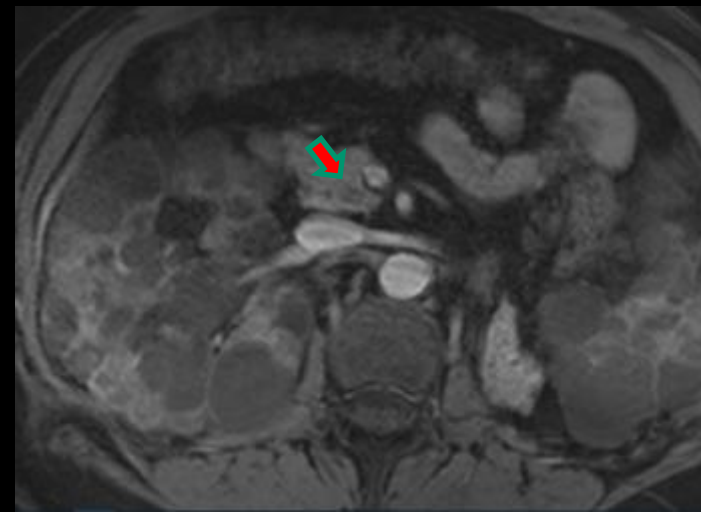
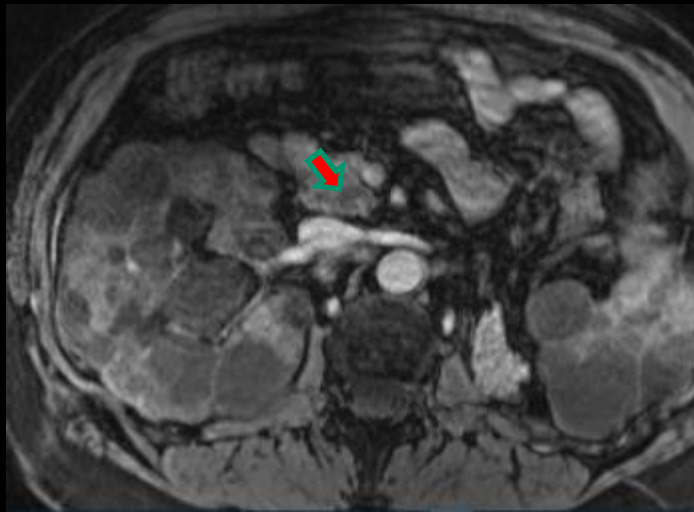
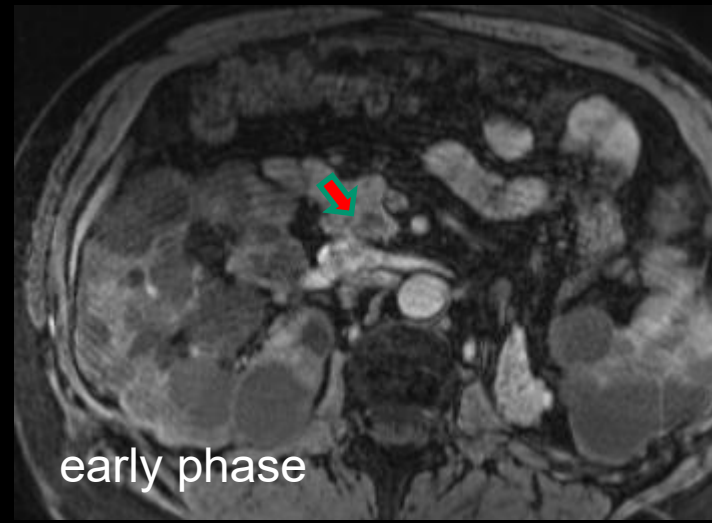
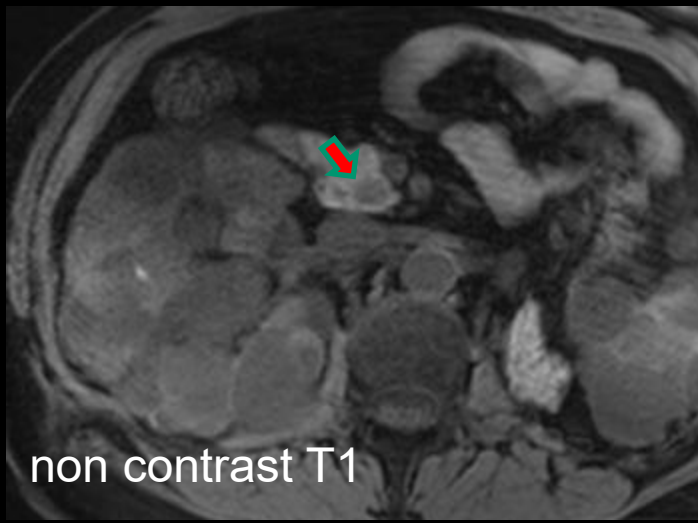


# Ferumoxytol MRI for TAM

- FDA approved therapeutic (off label)
- Noninvasive and easy to perform
- Minimal training
- Single dose expensive
- Temporal macrophage localization → 24 hrs. delayed post contrast
- Differentiate bone from contrast uptake if only post is done



Gadolinium enhanced MRI in a patient with VHL shows enhancing lesion in pancreatic uncinus process (B,C)



Ferumoxytol enhanced MRI in a patient with VHL shows T1 hypointense lesion in pancreatic uncinus process (top left), which does not demonstrate enhancement in delayed phase images (bottom)

# Conclusion

- Ferumoxytol enhanced MRI
  - Surrogate biomarker for TAM
  - Potential to study effect of immune responses on tumor progression and outcomes
  - Biomarker for monitoring new TAM targeted therapies