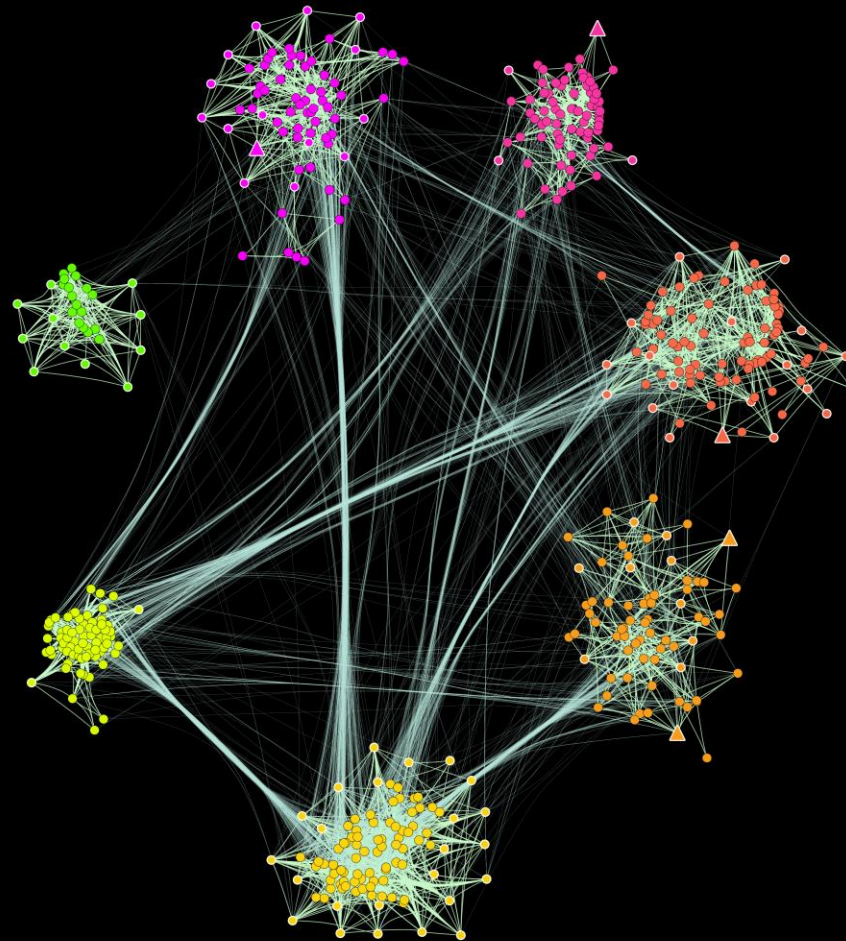
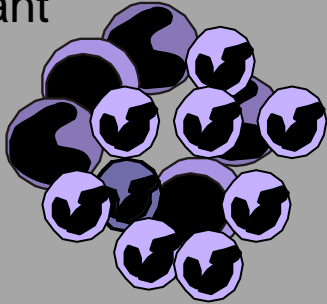


Stem cell signals in the origin, progression and therapy resistance in cancer





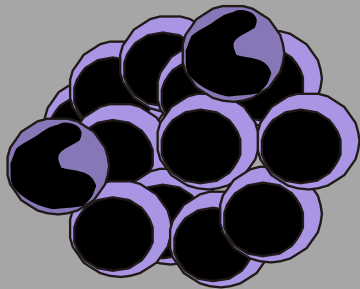
Pre-malignant



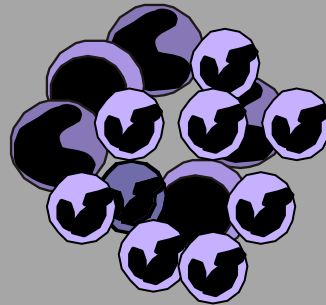
Differentiation
Arrest



Malignant

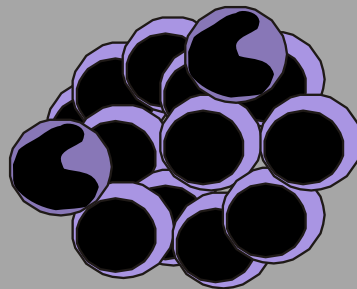


Cancer Progression



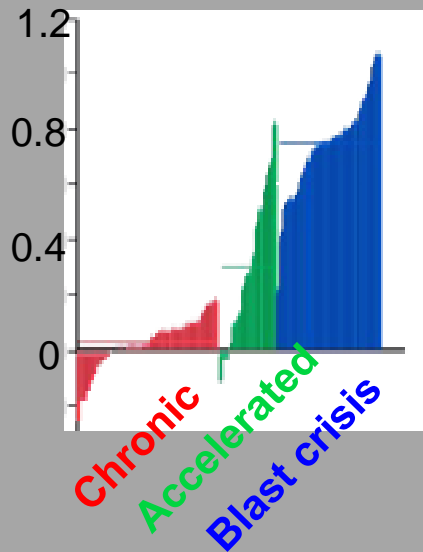
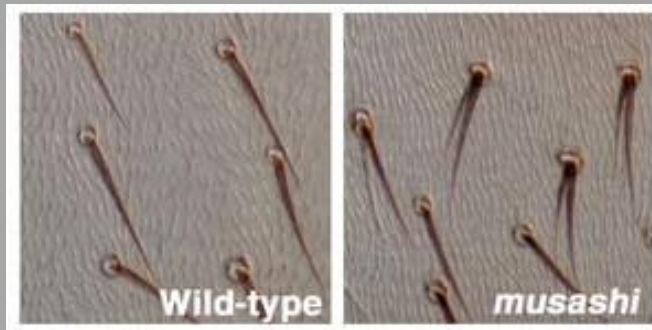
Early Detection

Interception



Cancer Progression

The fate determinant Musashi in leukemia progression



Pancreatic Cancer

Third

~~Fourth~~ leading cause of cancer related deaths

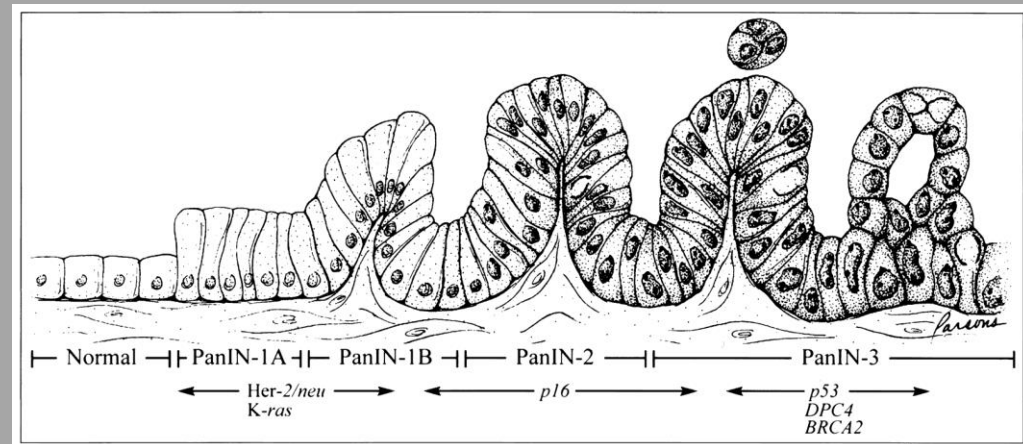
Treatments

Radiation and
Chemotherapy
Large Tumors
Distant metastases

Surgical (Whipple Procedure)

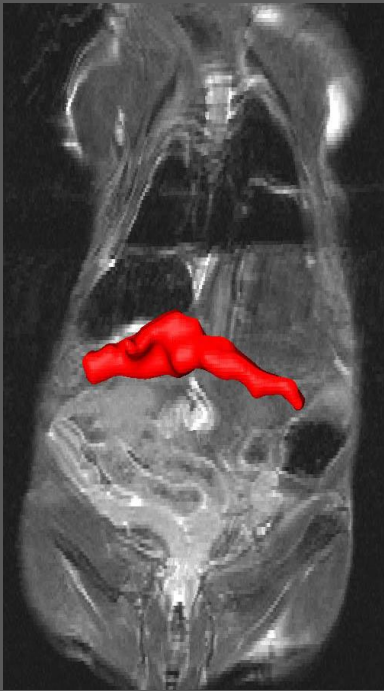
-Small localized tumor
-Only 20% of patients are candidates

Survival Rate
11% over 5
years

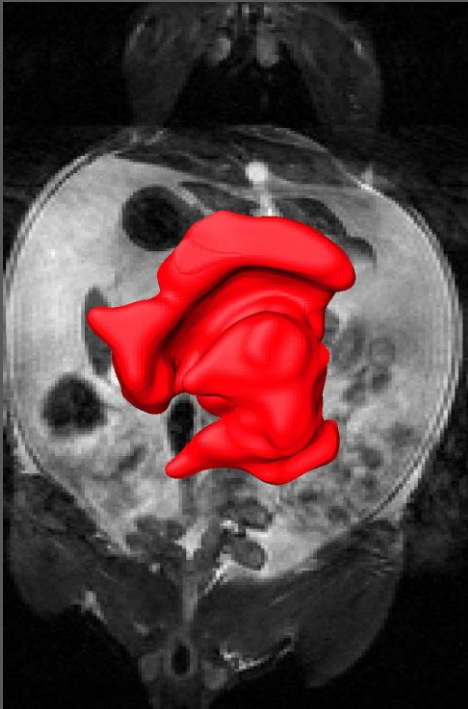


Loss of Msi leads to a significant reduction of pancreatic cancer burden

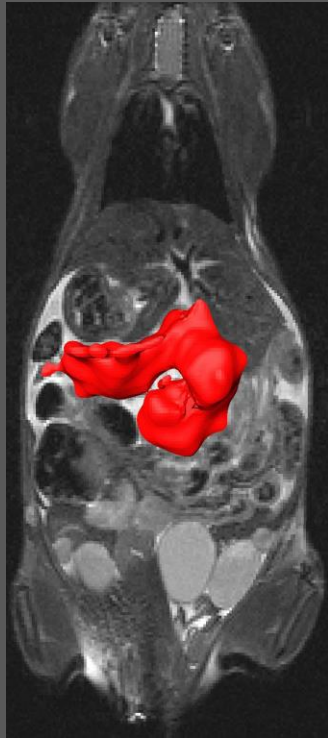
WT-Pancreas



WT-KP^{f/fC}



Msi^{-/-}-KP^{f/fC}



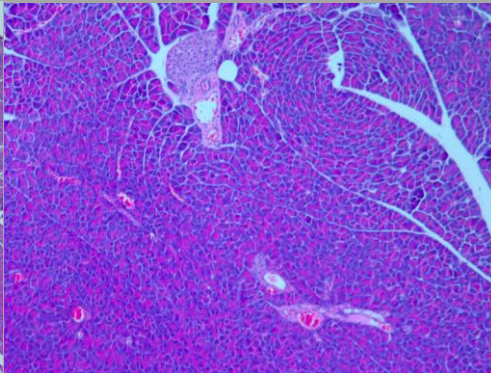
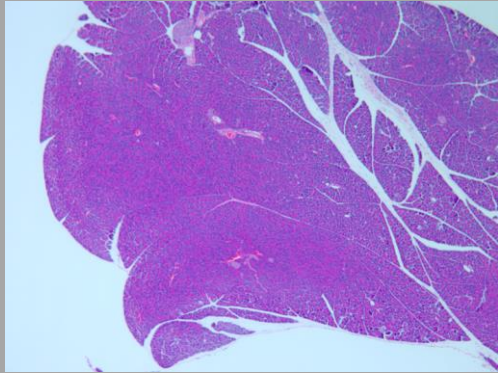
8X

5X

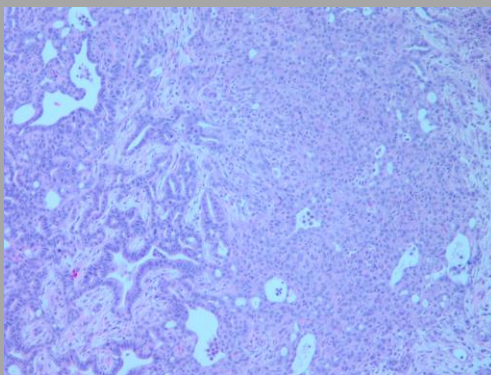
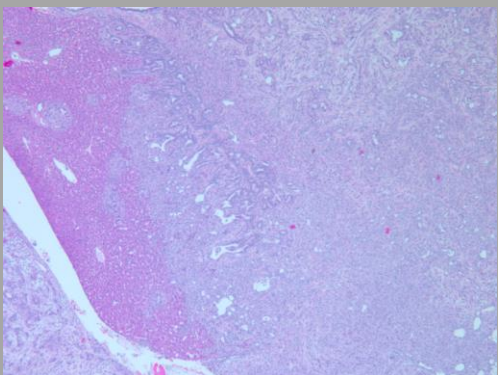
4x

10x

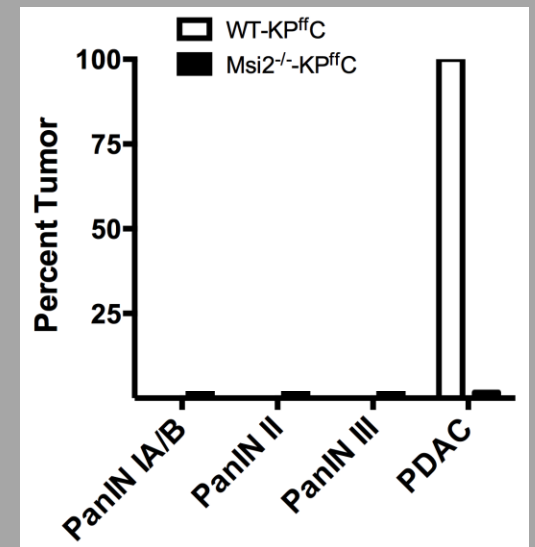
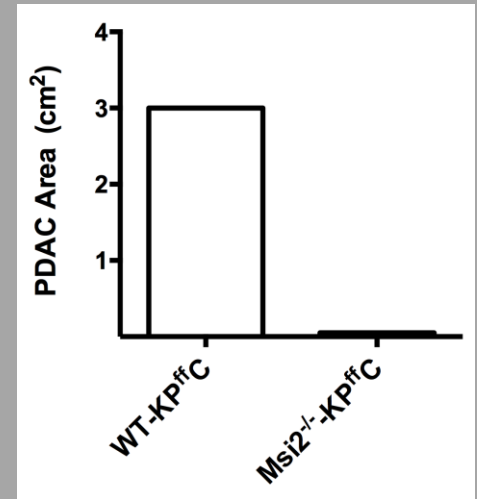
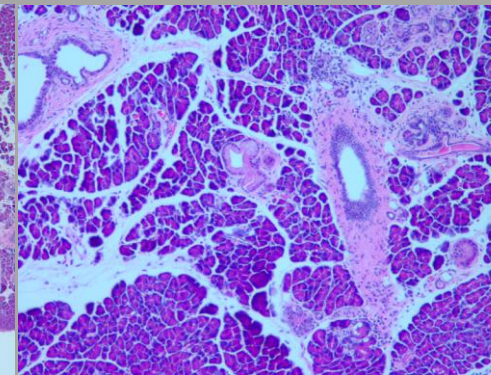
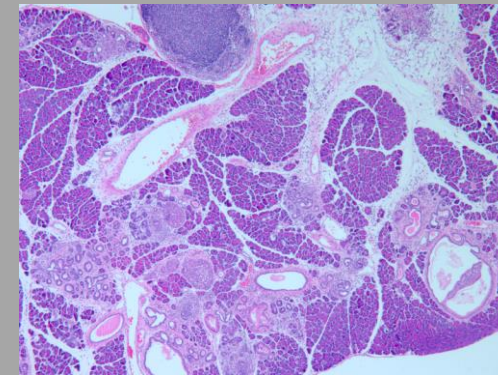
WT Pancreas

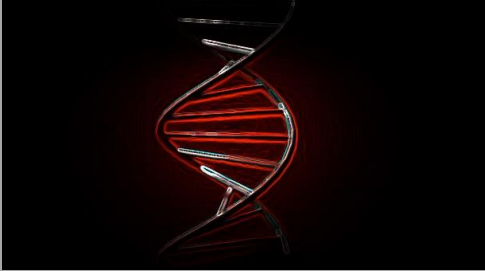


WT KP^{f/f} C

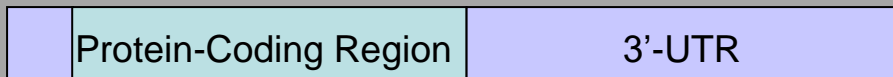
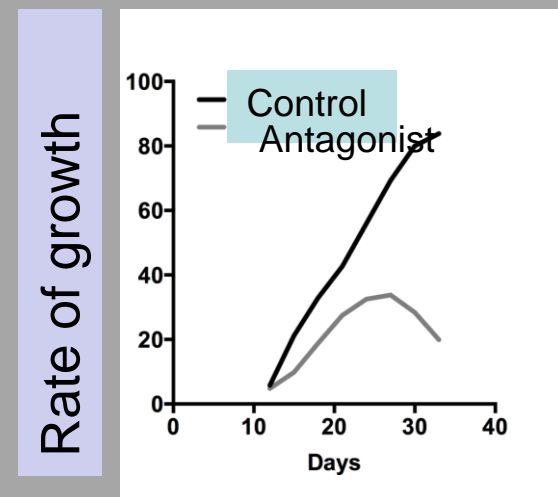
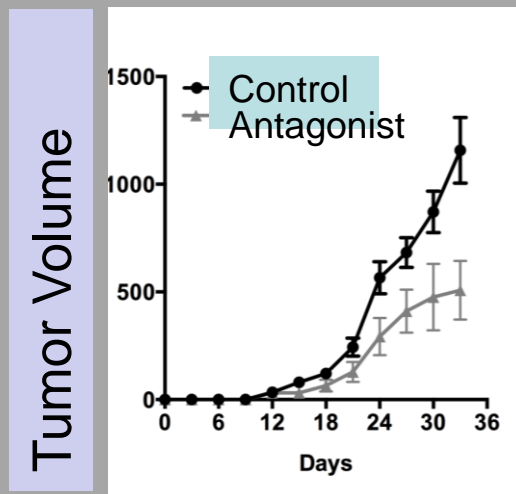
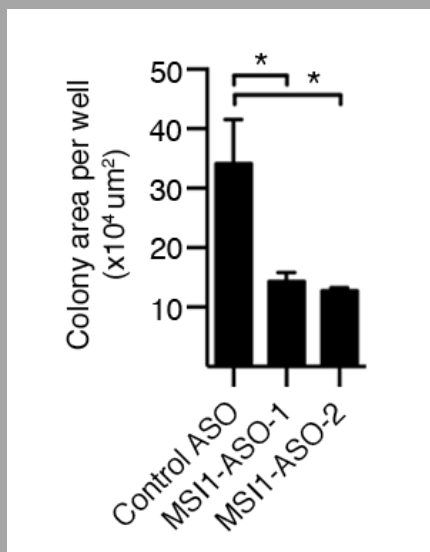


Msi2^{-/-} KP^{f/f} C





Development and delivery of an Msi - antagonist



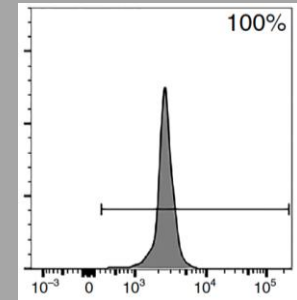
With Ionis Pharmaceuticals

Ray Fox
 Youngsoo Kim
 Robert MacLeod

Development of Msi Reporters



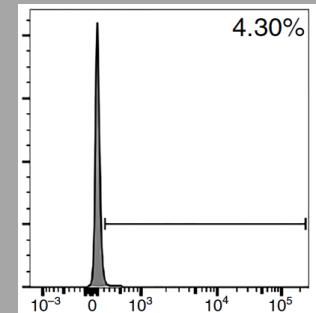
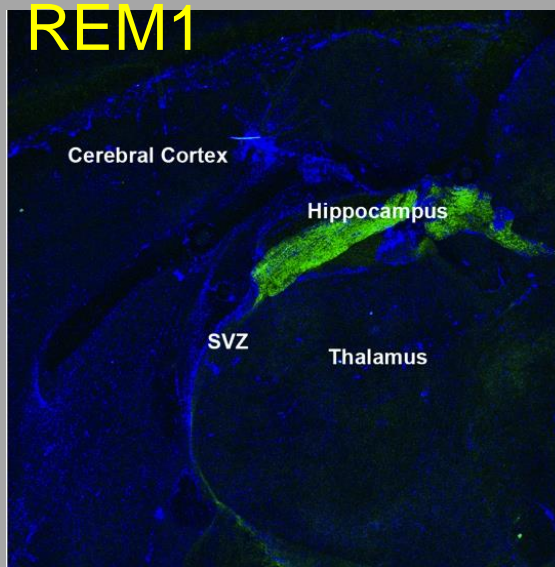
REM2



Stem Cells

Reporter Msi1 YFP
REM1

Reporter Msi2 GFP
REM2



Differentiated

Nikki Lytle

Msi Reporter+ cells are preferentially tumorigenic



REM1 or REM2

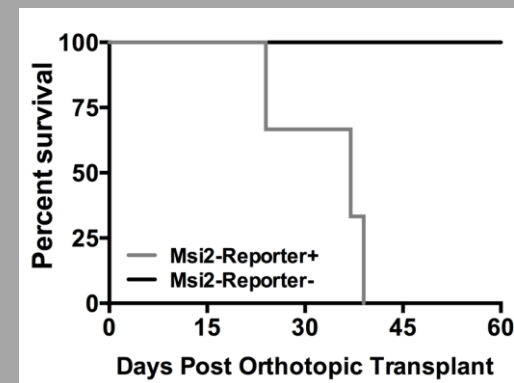
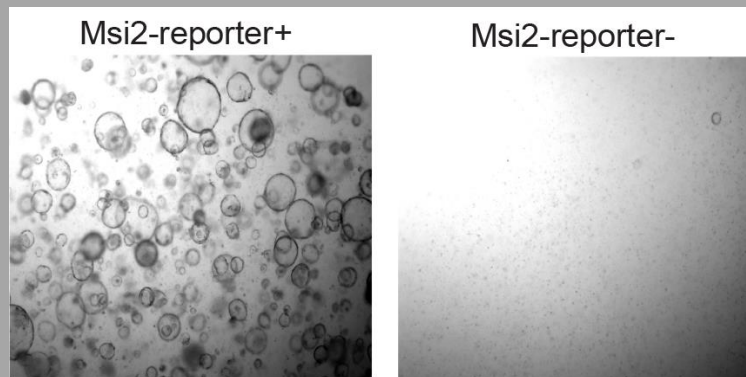
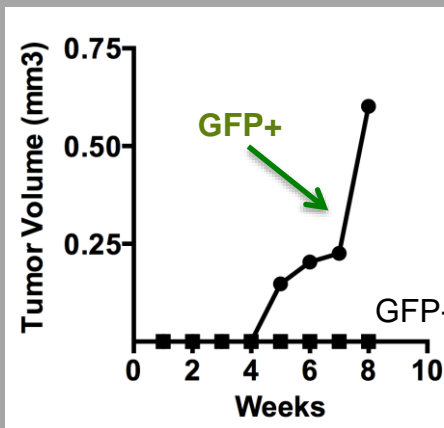
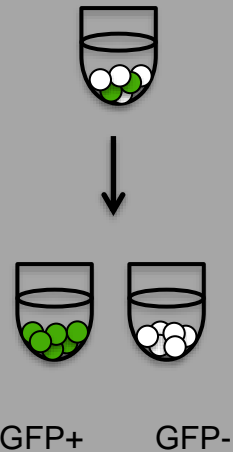
X



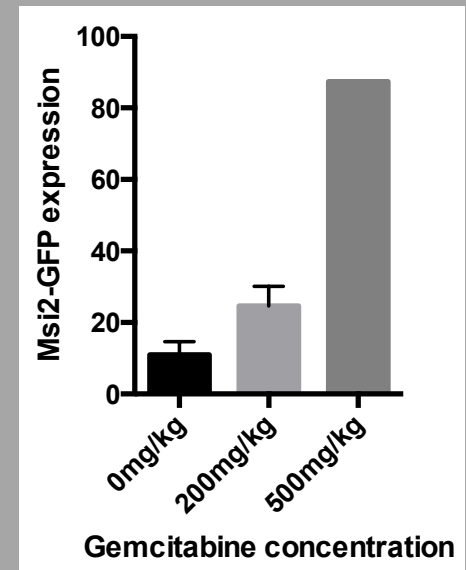
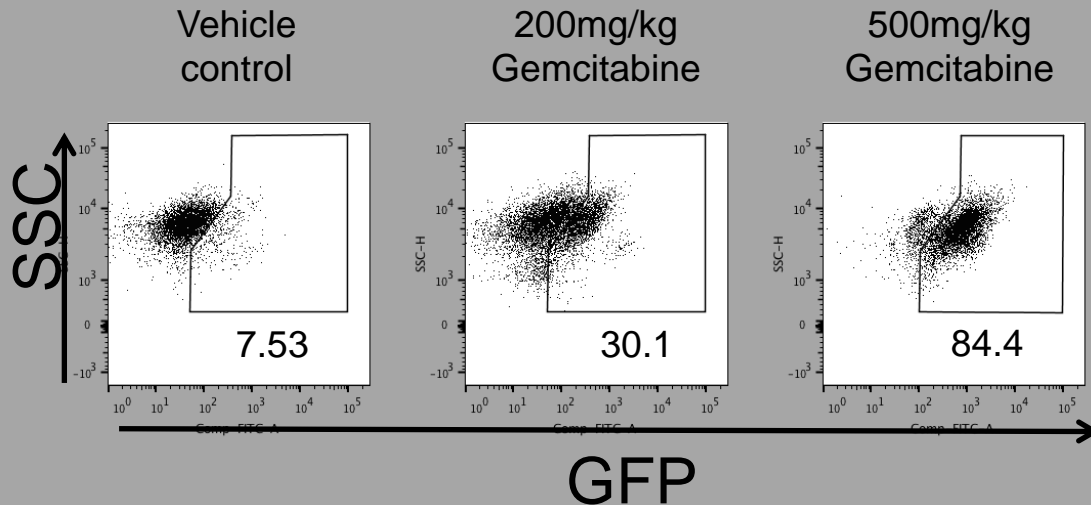
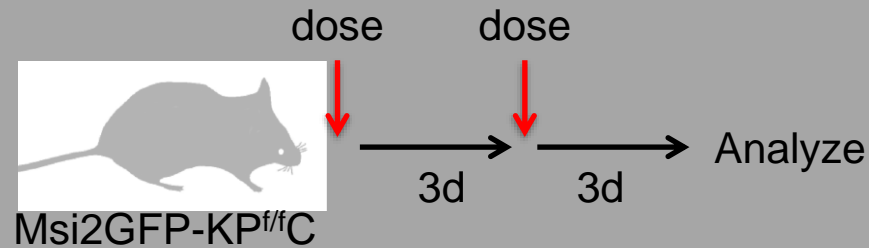
$Kras^{G12D/+}; p53^{flox/flox};$
 $ptf1\alpha-Cre$

REM1 – KP^{ff}C

REM2-KP^{ff}C



Msi Reporters are a unique tool to identify drug resistant cells



In vivo dynamics of cancer growth

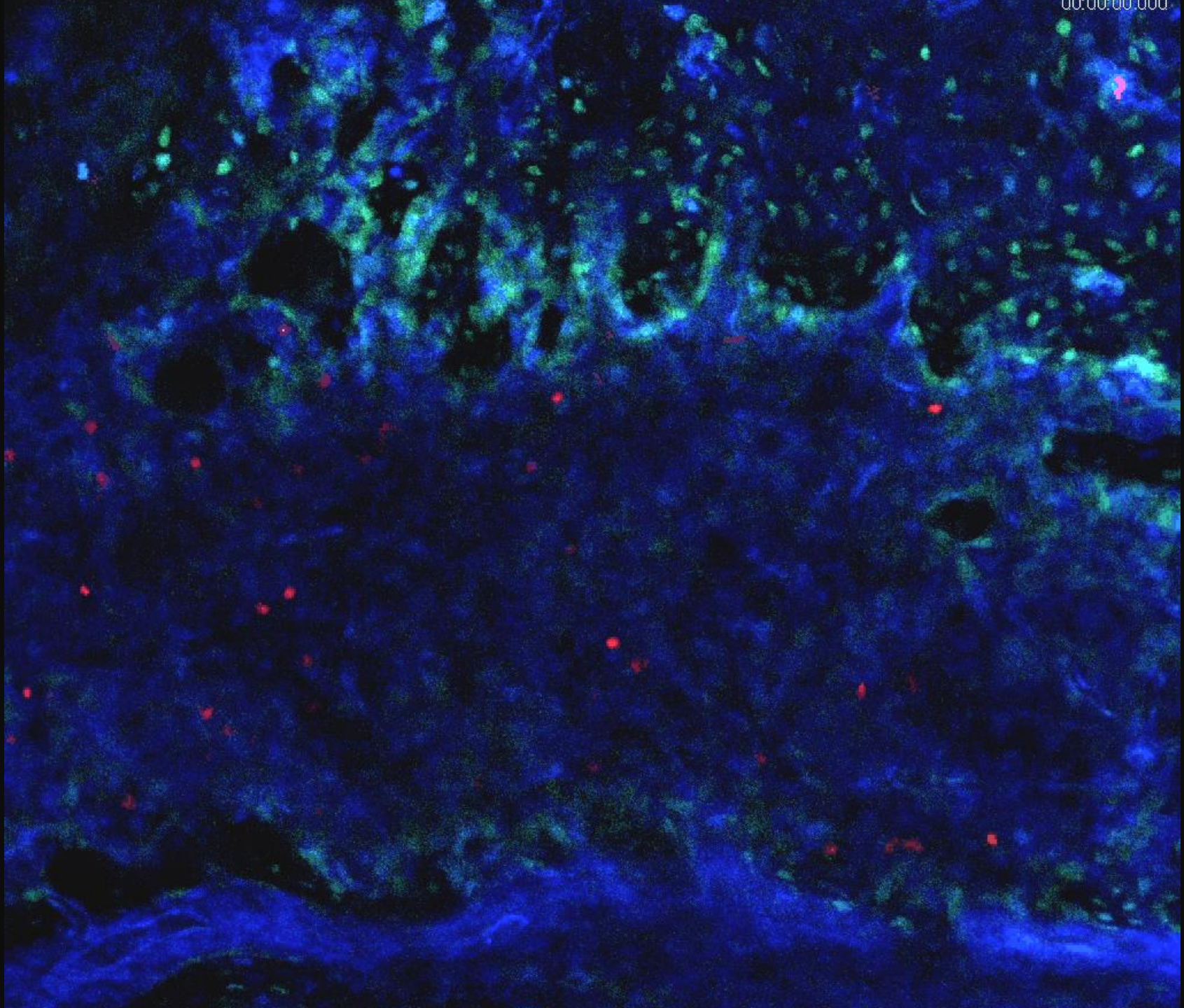


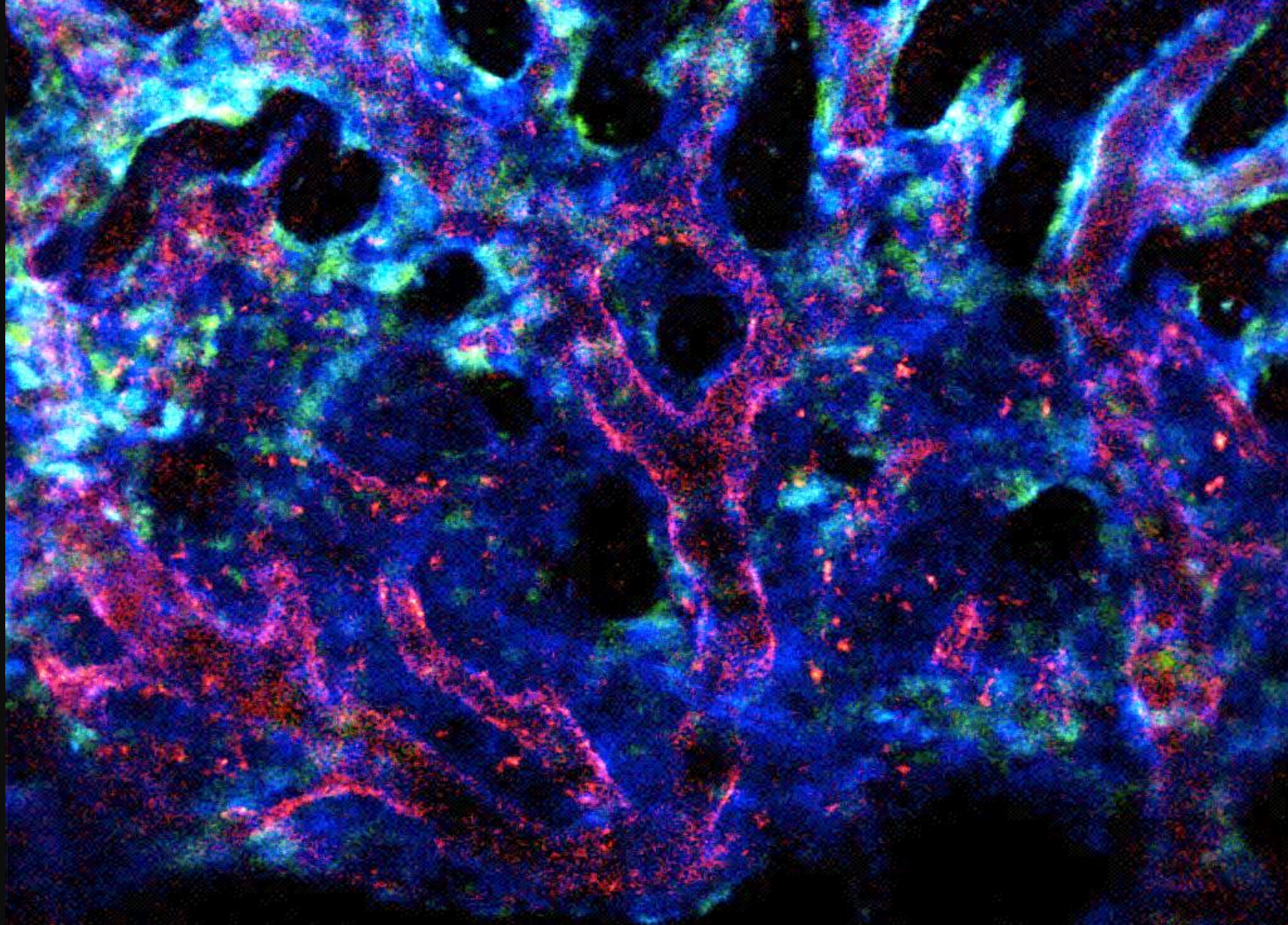
Donor

Leukemia cells



Backlit recipient





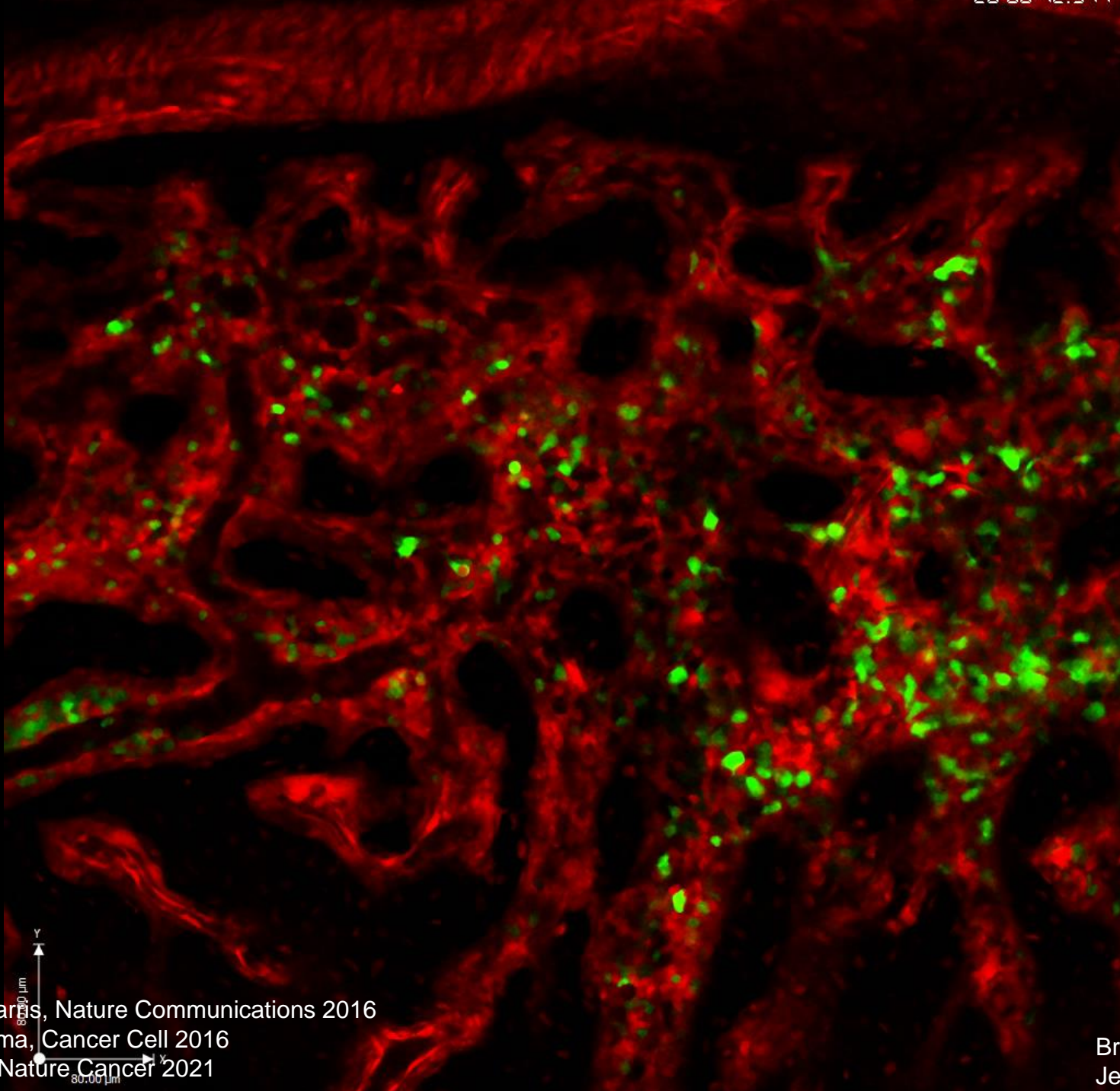
CFP

TNR

VE-
cad

Jeff Harris

100 μ m



2020-12-15 11:11

Koechlel/Harris, Nature Communications 2016

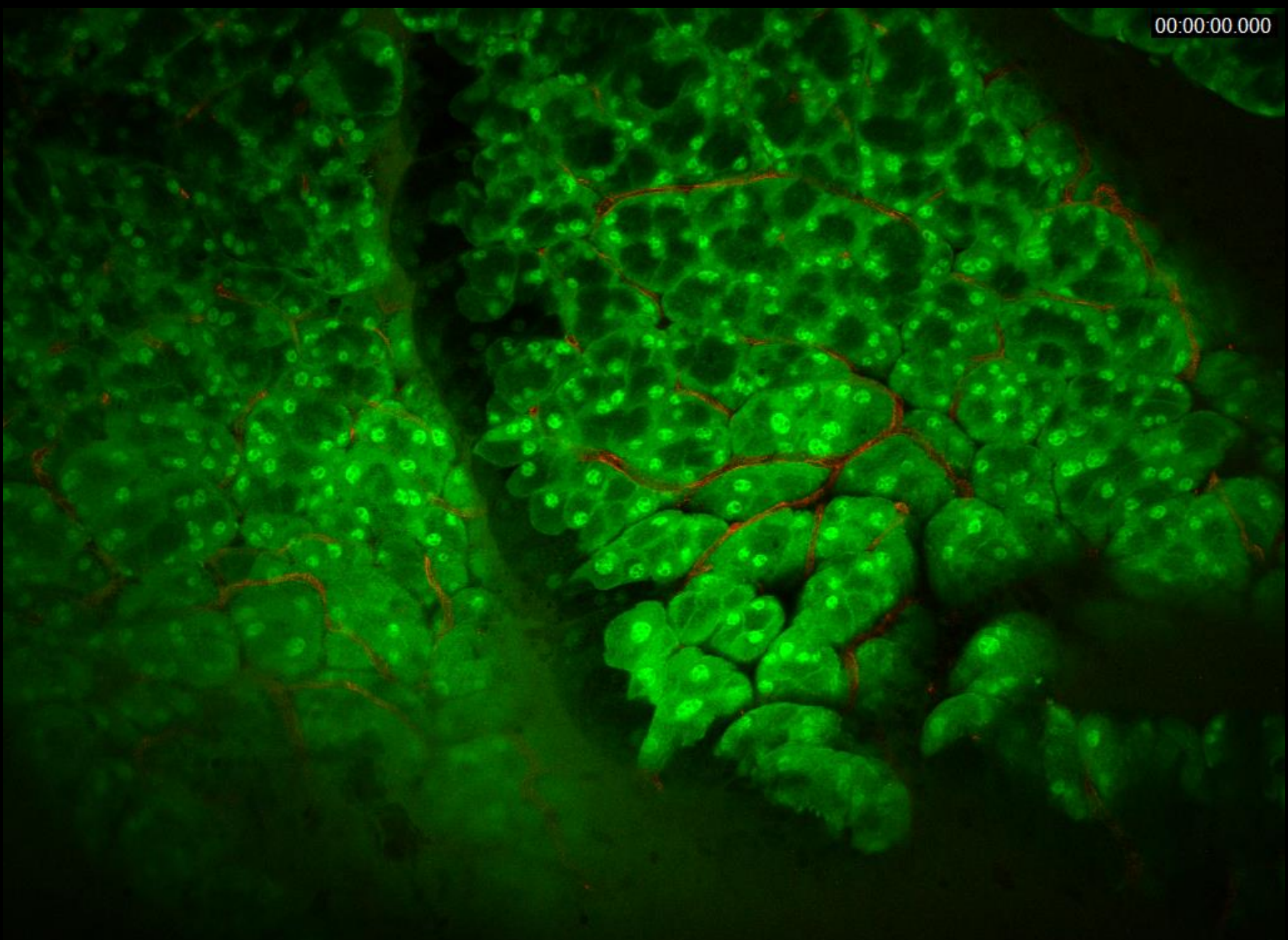
Bajaj/Konuma, Cancer Cell 2016

Bajaj et al, Nature Cancer 2021

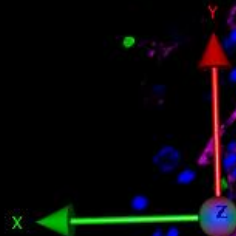


Bryan Zimdahl
Jeff Harris

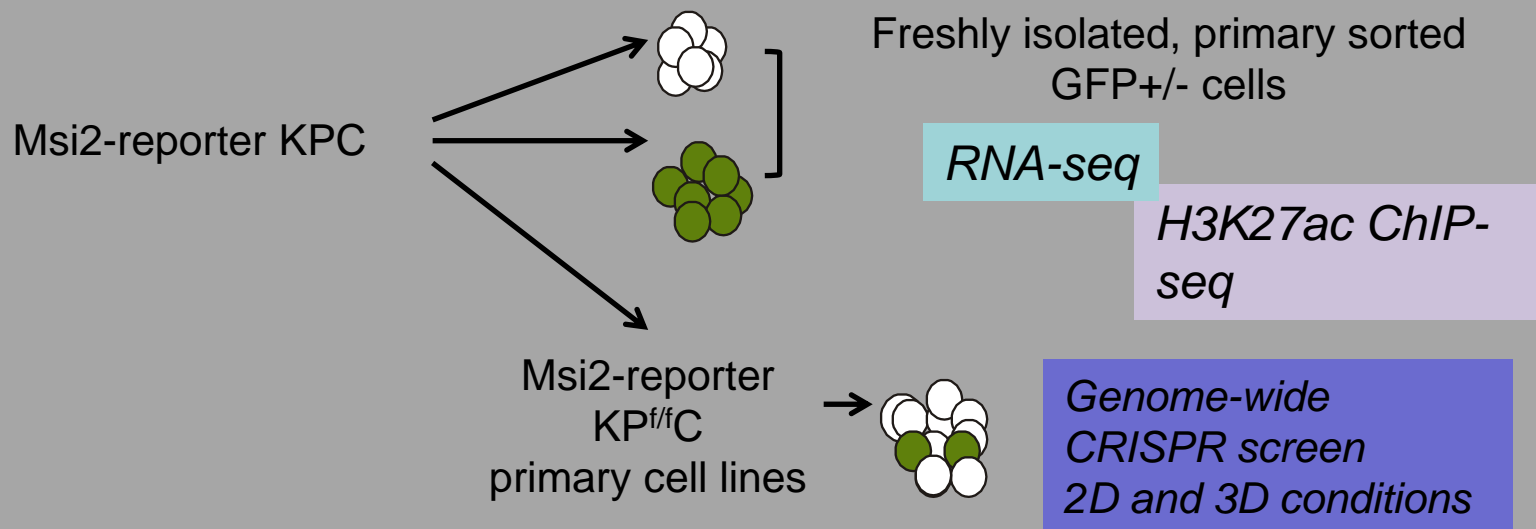
00:00:00.000



Ray Fox



Mapping dependencies of pancreatic cancer stem cells



Network map of stem cell dependencies in pancreatic cancer

Genome-wide CRISPR screen

Bioinformatics Analysis

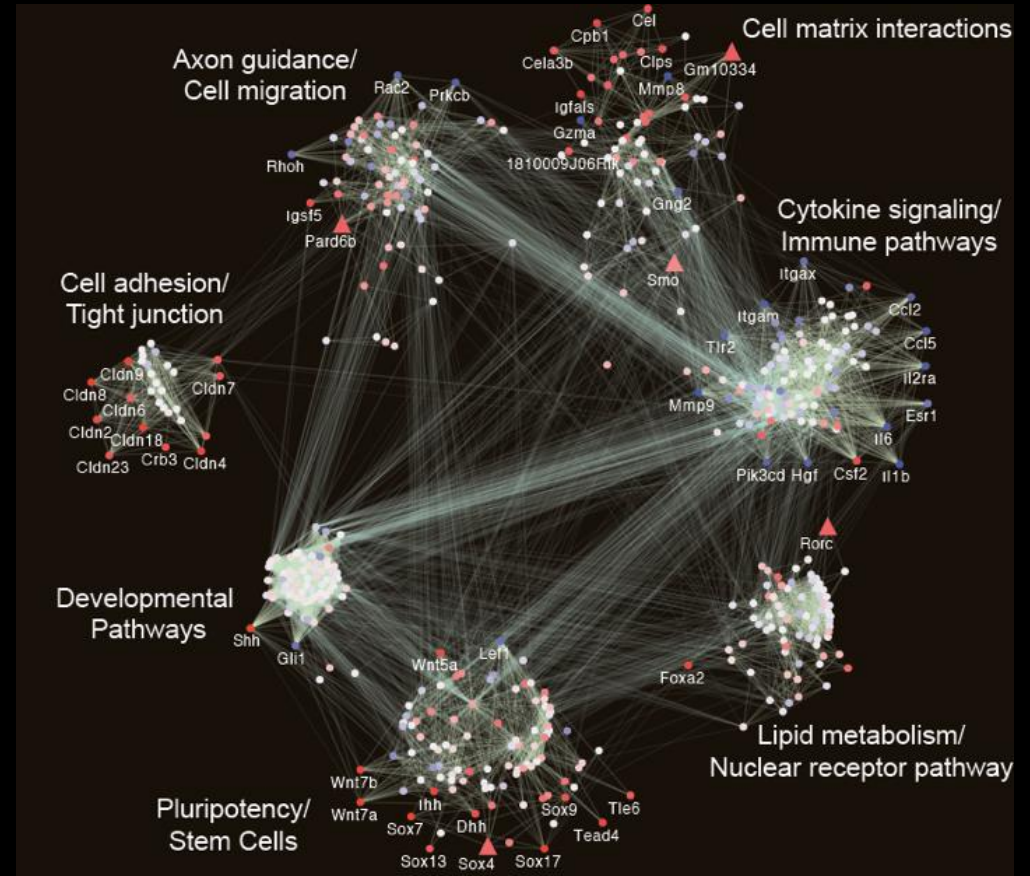
Integrate CRISPR and RNA-seq data
Identify genes enriched in and essential for growth of cancer stem cells

Network Propagation

Seed genes
STRING interactome
Build subnetworks to identify core programs

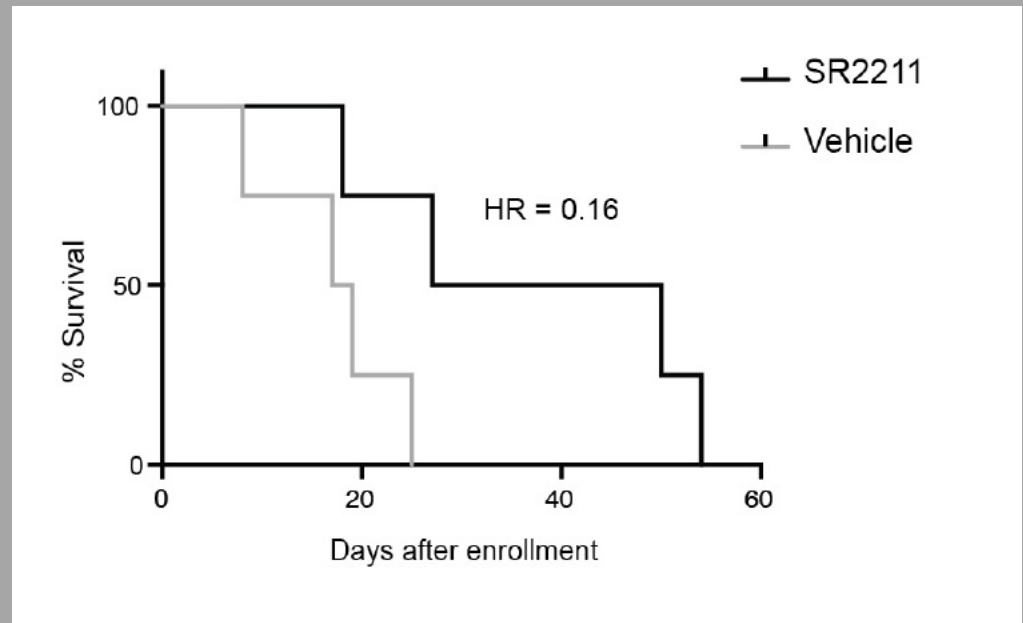
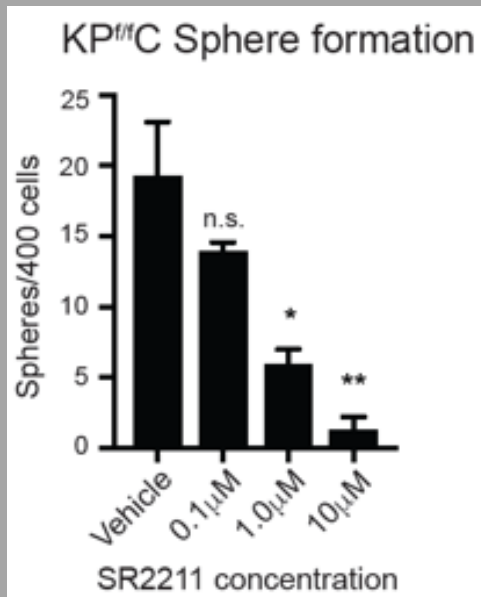
Network Map

Identify and test new stem cell dependencies



Pharmacologic blockade of ROR γ improves survival

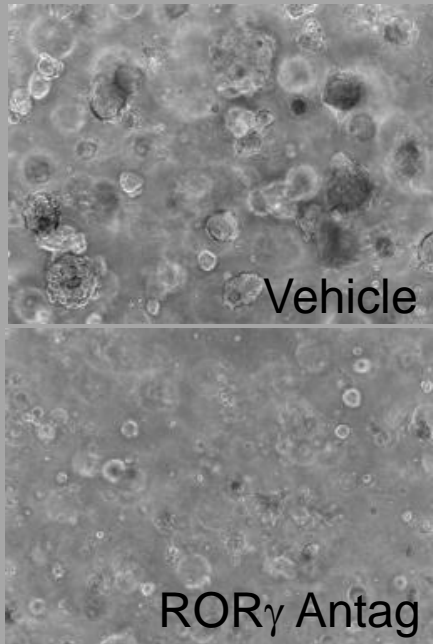
Survival of KPC autochthonous mice



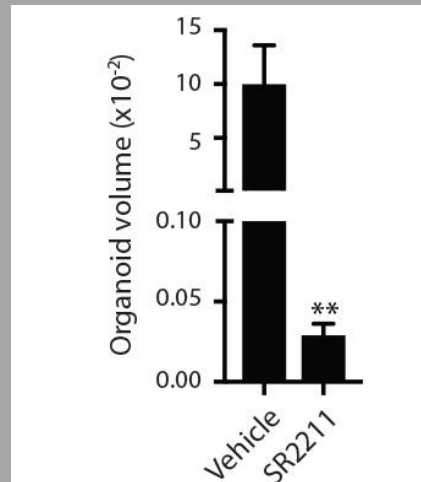
6X reduced risk of death

ROR γ inhibition blocks primary patient pancreatic cancer growth

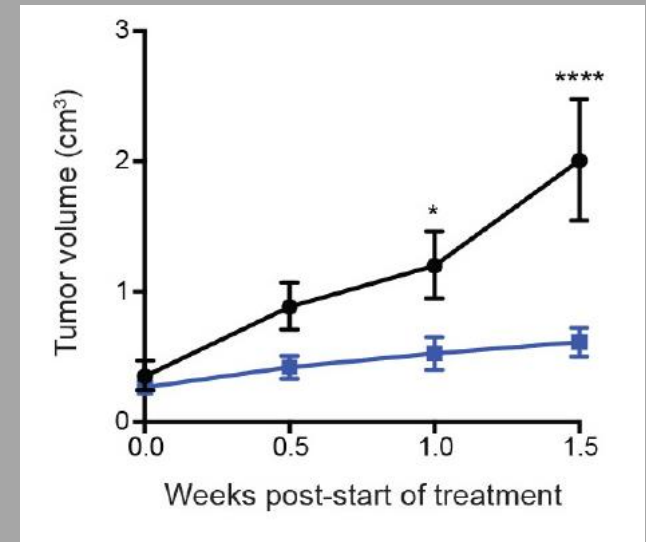
Primary patient organoid growth



Organoid size



Primary patient Xenograft growth

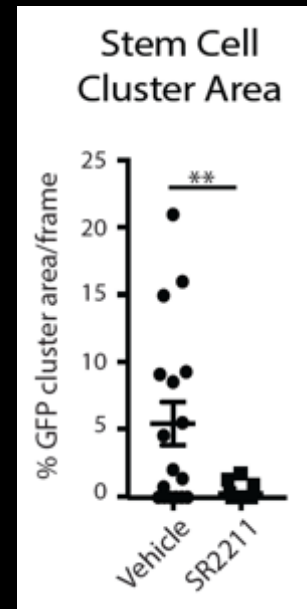
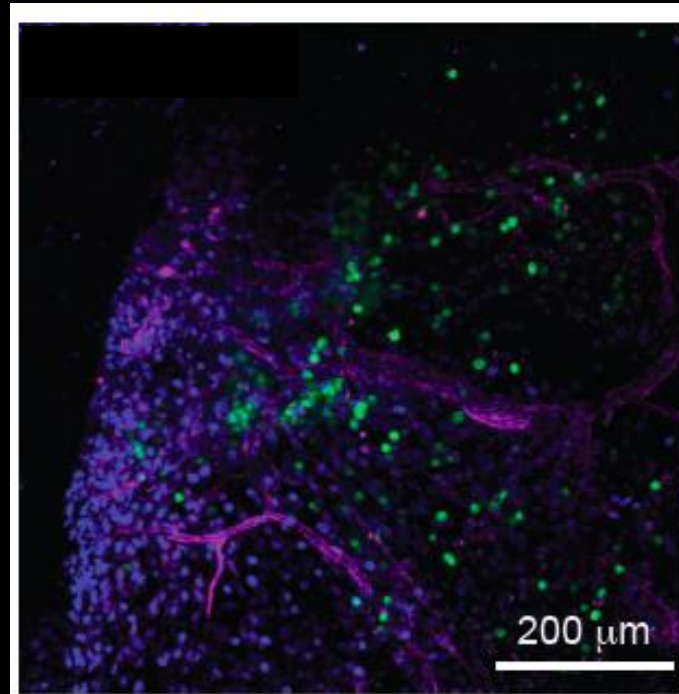
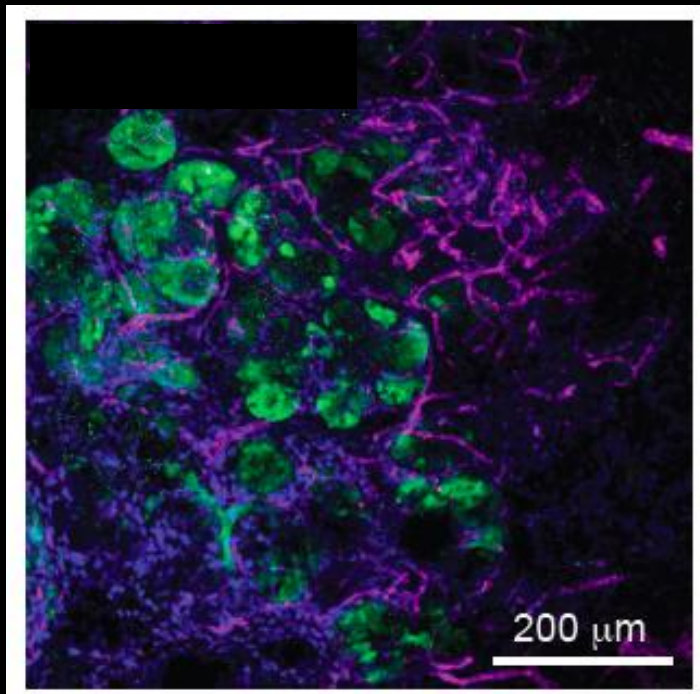


● Vehicle
■ SR2211

Pharmacologic blockade of ROR γ disrupts stem cell clusters *in vivo*

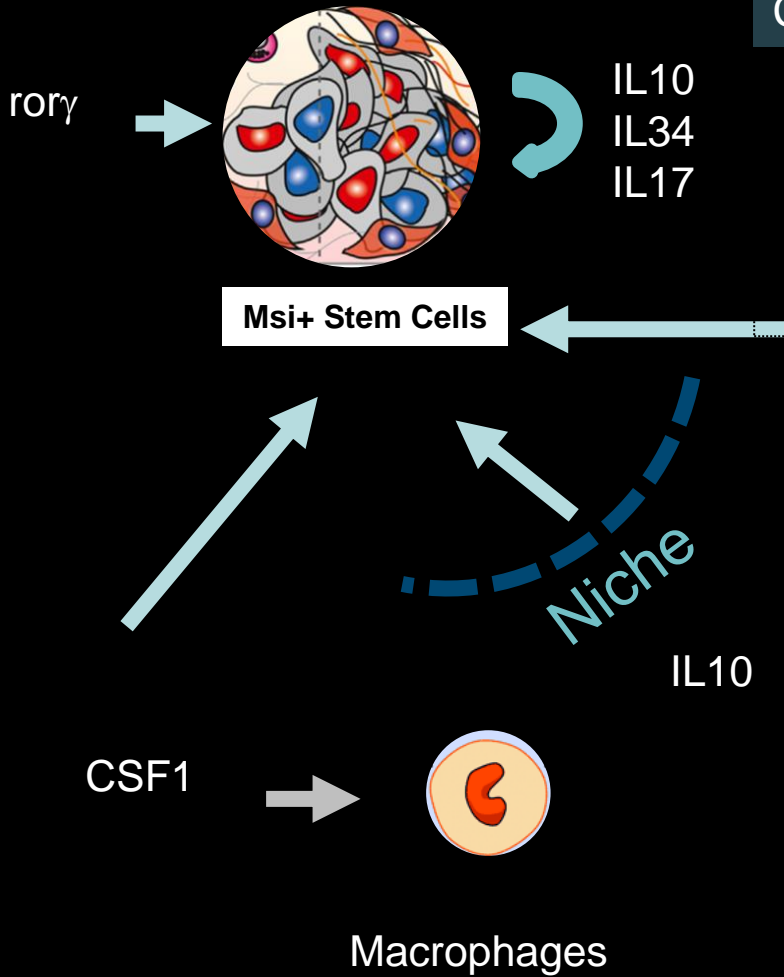
Vehicle

Ror γ antag



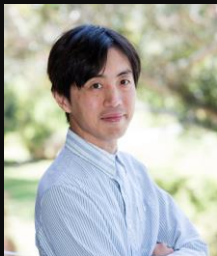
Msi2+ stem cells. VE-Cadherin. Hoechst

Co-option of cytokine-rich immunomodulatory milieu



Reposition immunomodulatory agents in pancreatic cancer

Therapies to activate the immune system may trigger regrowth of tumor cells



**-University of California-
San Diego**



**Nikki Lytle
Paige Ferguson**



**Ray Fox
Nirakar Rajbhandari
Michael Hamilton**



**Kyle Spinler
Mari Nakamura
Alison Barber
Jeevisha Bajaj
Yutaka Shima**

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Dan Von Hoff (TGEN)
Trey Ideker (UCSD)
Peter Adams (SBP)
Roman Sasik (UCSD)**

**Brin Rosenthal (UCSD)
Ani Deshpande (SBP)
Maike Sander (UCSD)
Katie Fisch (UCSD)**

**Marcie Kritzik
Emily Diaz
Matthew McDermott
Kendall Chambers**