Penn Medicine

Studying Stomach Cancer in the Lab

Gastroesophageal Cancer Symposium
Debbie's Dream Foundation

Sandra Ryeom, Ph.D.

the cure is within
ABRAMSON CANCER CENTER

From Bench to Bedside

Scientific Discoveries

- basic science research
- animal models

Clinical Trials

- Phase I, II, III trials to test new therapies for patients

Treating patients

- New drugs

Why mice?

99.5% genetic similarity

96-99% genetic similarity

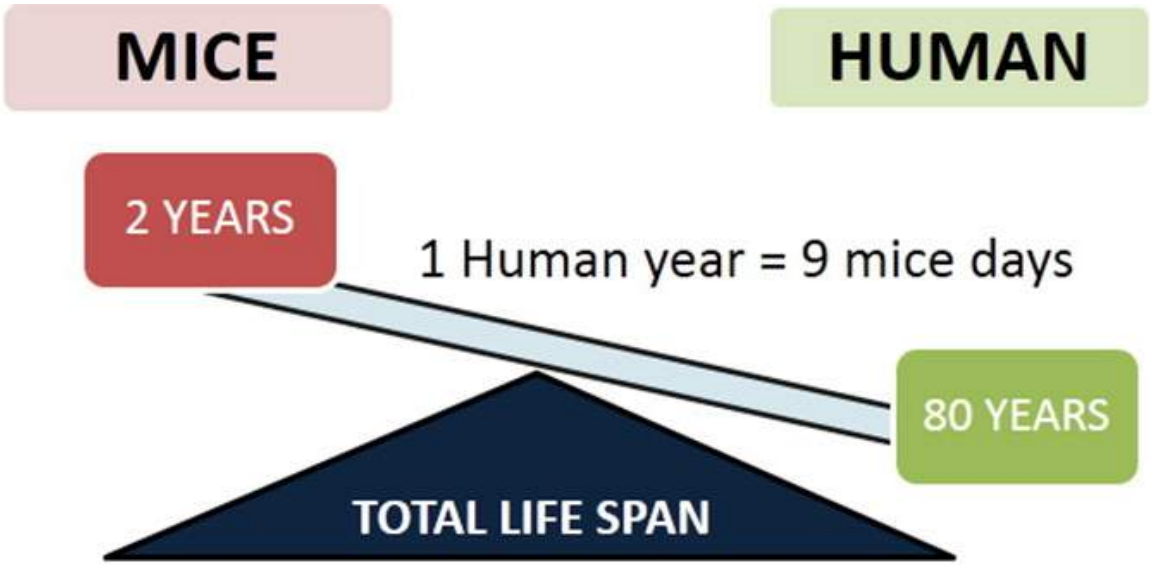
90% genetic similarity

80% genetic similarity

Mouse Models to Study Cancer

- Mice have 75% genetic similarity to humans but 99% of mouse genes have human analogs
- Small size
- Easy to breed
- Numerous genetic manipulations possible
- Experiments are completed quicker and are more tightly controlled than human studies

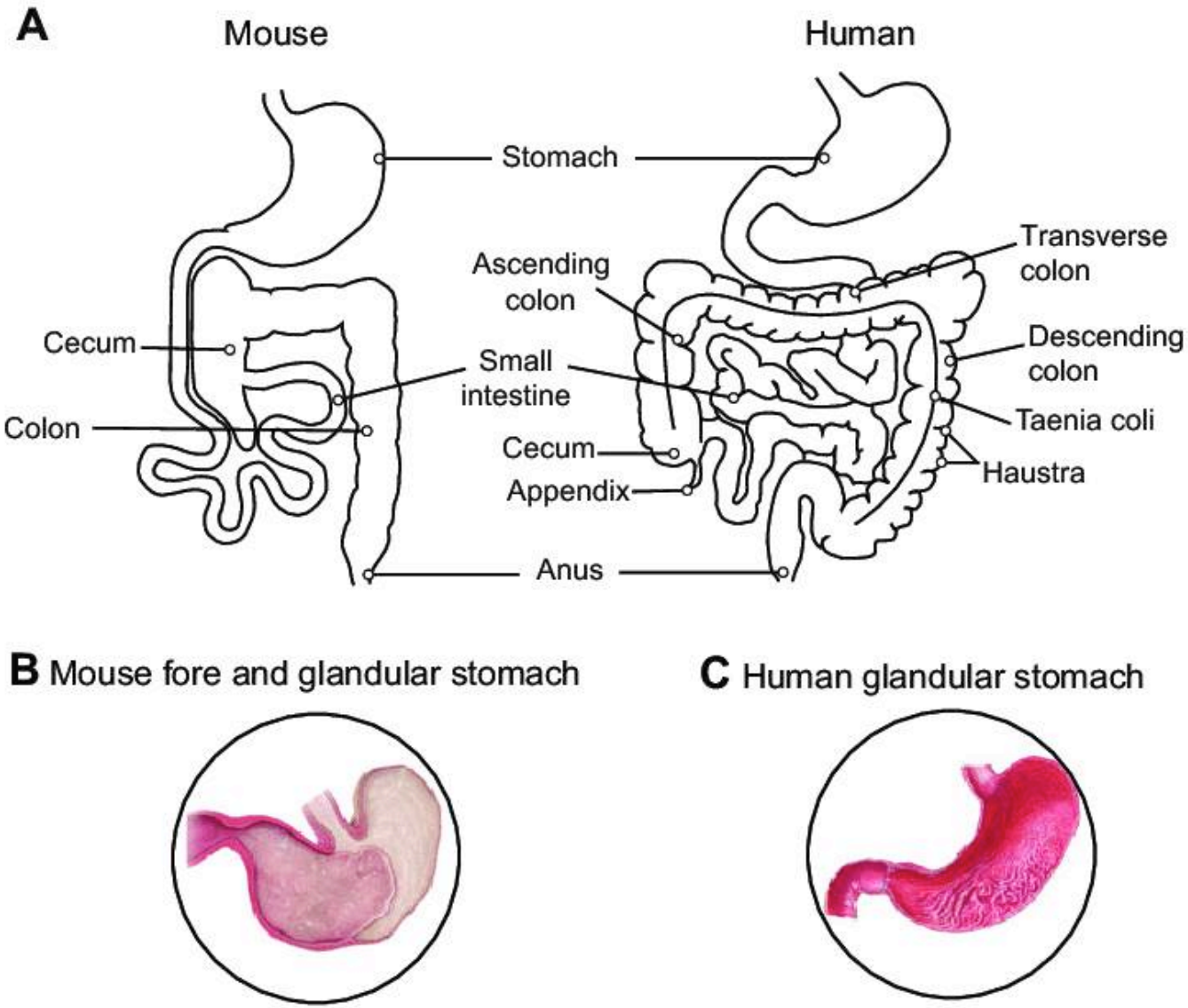
Correlation Between Mice and Human Age



Correlation between mouse and human age changes at different stages (weaning, puberty, adulthood, reproductive senescence…)

Dutta et al. Life Sciences 2016

Mice and Humans have Similar Anatomy

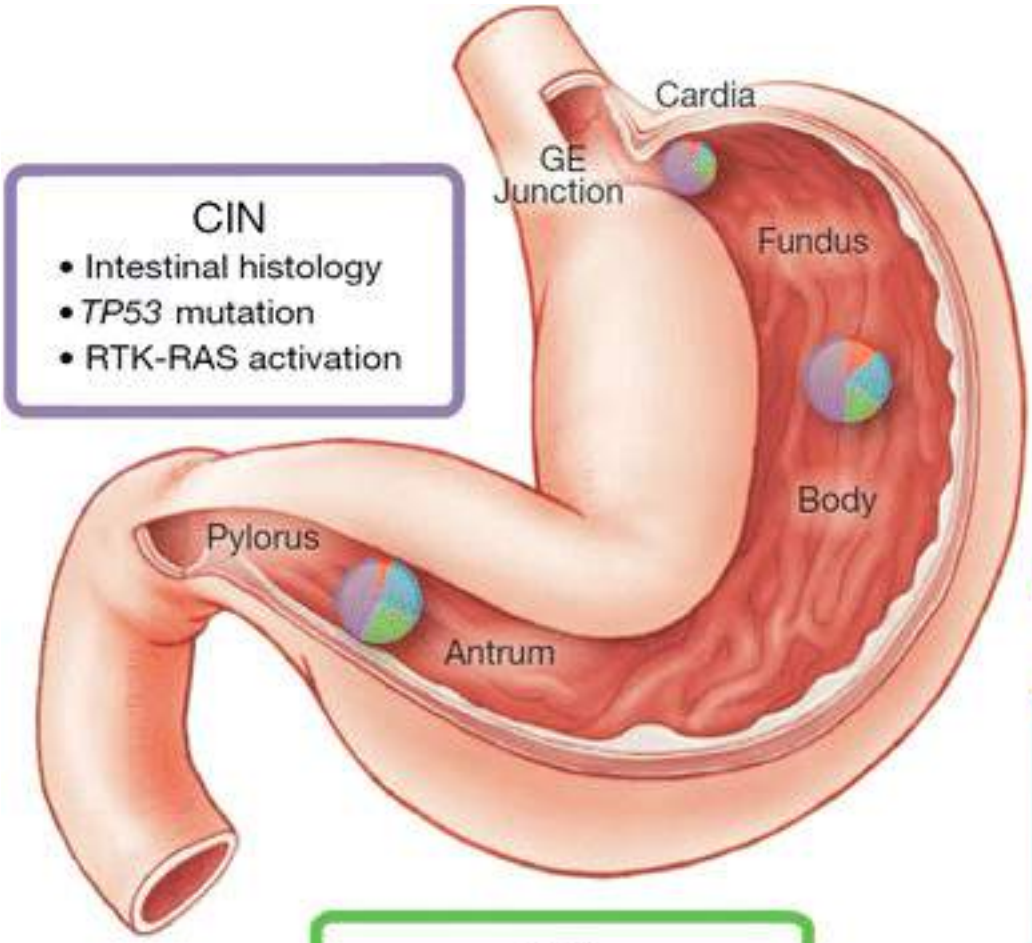


Nguyen A, et al. Disease Models & Mech. 2015

Different Ways to Model Cancer in Mice

Cancer Model	Approach	Pros	Cons
Carcinogen induced	Expose mouse to carcinogen	Carcinogens promote tumor formation	Unknown genetic alterations, variable tumor development
Xenograft transplant	Inject human or mouse tumor cells into mice	Can easily measure/watch tumor growth	Incompatible mouse host and human tumor cells
Orthotopic transplant	Inject tumor cells into tissue of origin	Tumors grow in proper environment	Not possible in all organs, large number of tumor cells injected
Transgenic	Genetically engineer mouse tumors (GEMM)	Recapitulates mutations in human tumors	Takes a long time to generate
Patient-derived xenograft	Inject human tumors directly from patients into mice (PDX)	Can study human tumors in vivo	Difficult to obtain human tumors

Gastric Cancer Subtypes



CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

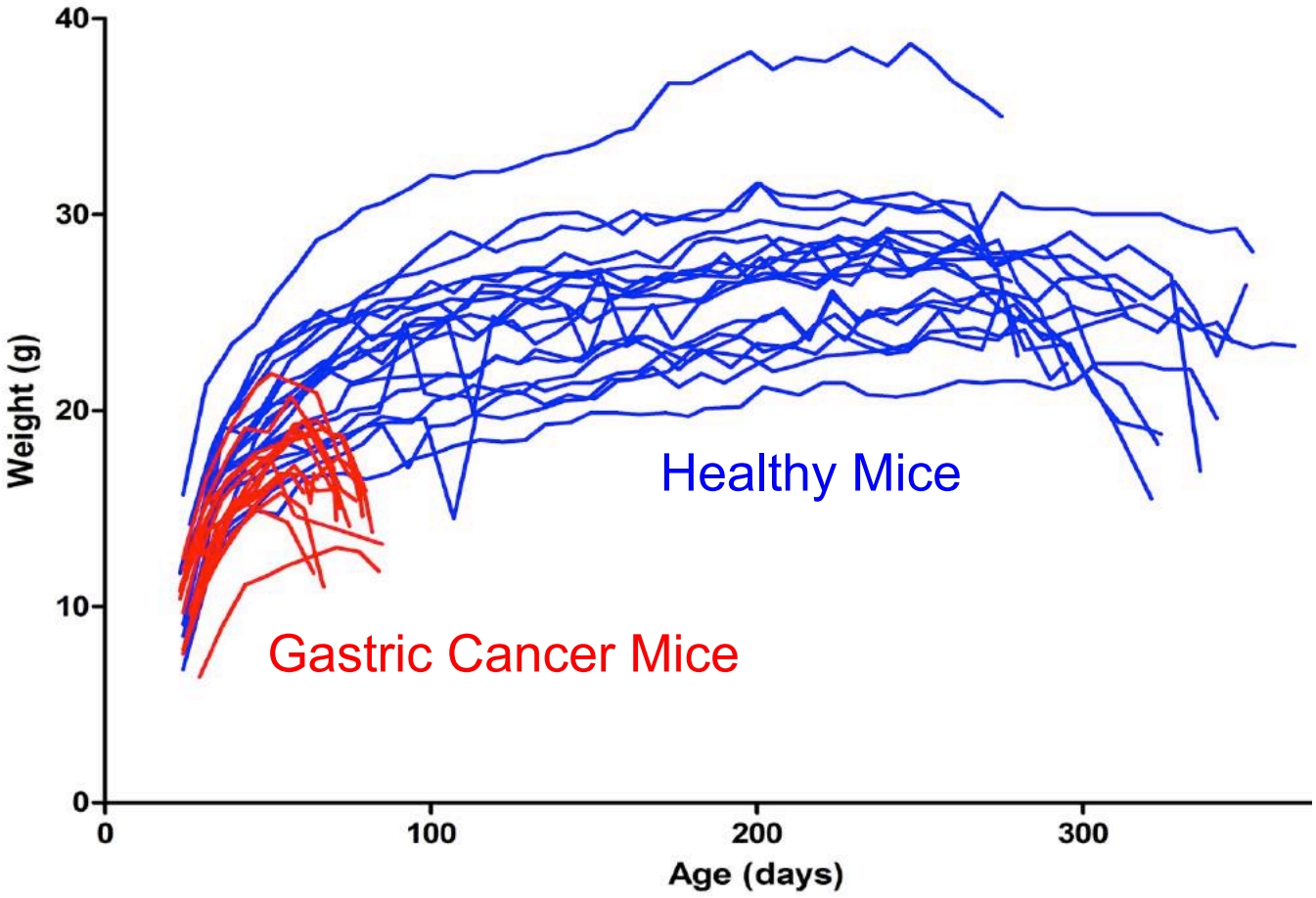
EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

Van Cutsem, et al. The Lancet, 2016

Monitoring the Weight of Gastric Cancer Mice

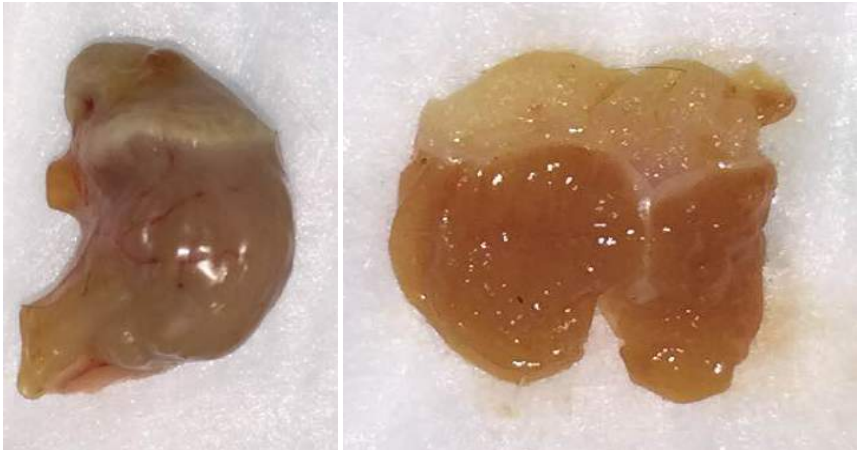


Average lifespan of mouse 2 years (~80 yo human)

Gastric Cancer in Mice- Linitis Plastica

- Gastric cancer mice with enlarged dysmorphic stomach
- Thick, rigid, and whitened
  - Similar to Linitis Plastica or Leather Bottle stomach seen in patients

Healthy Mouse Stomach

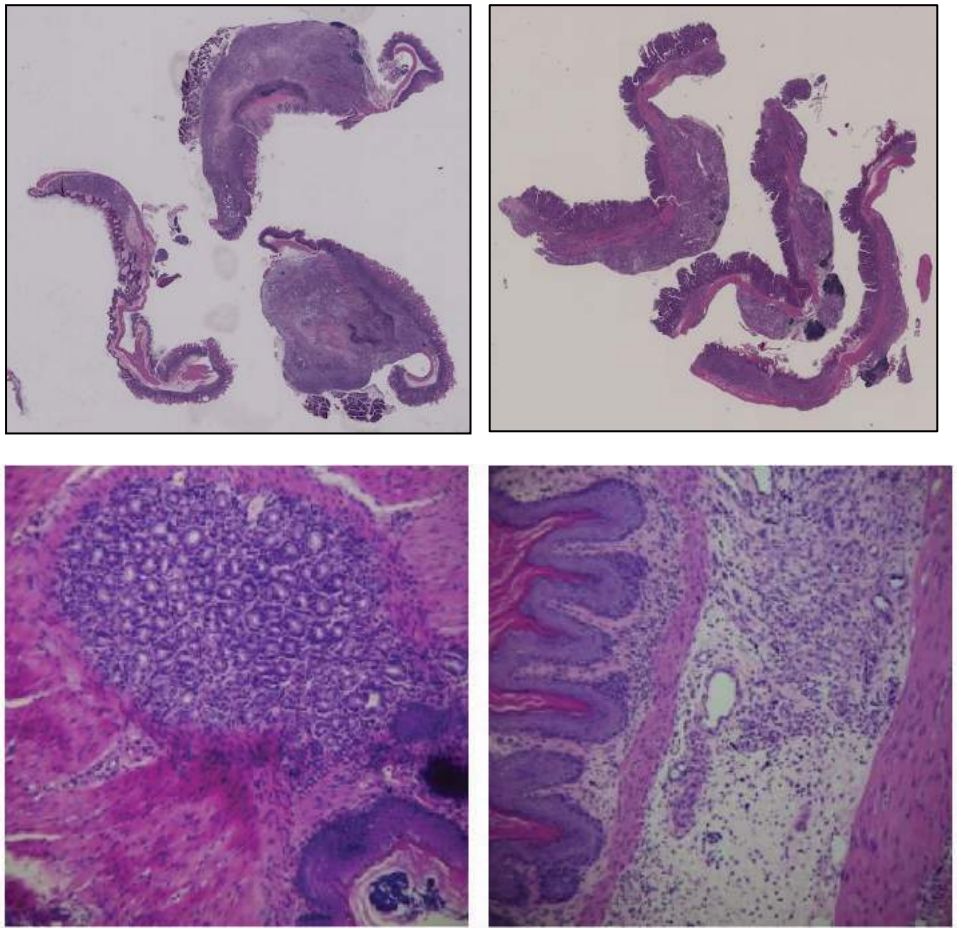


Gastric Cancer Mouse Stomach

Pathology of Gastric Cancer Mouse Models is Similar to Human Gastric Cancer

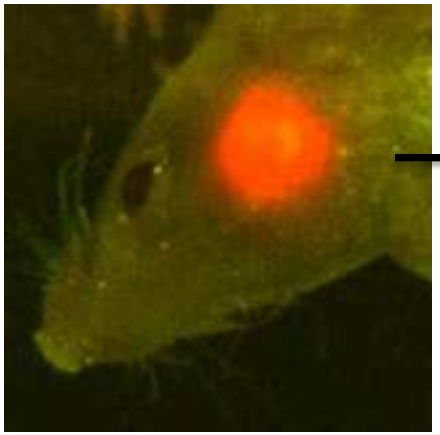
Intestinal Type

Diffuse type

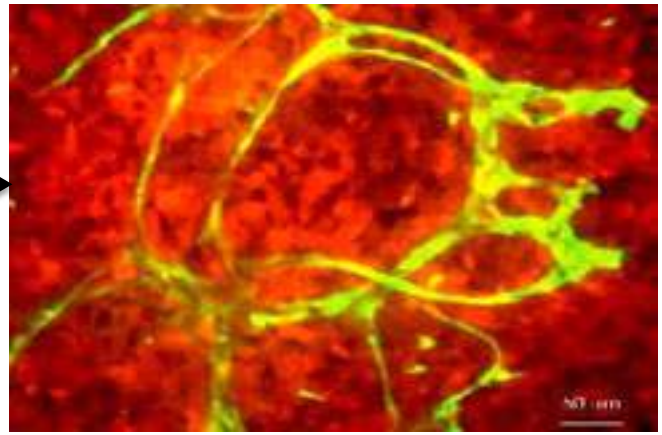


Mice Can be Engineered with Molecular Markers to Follow Cancer Progression

GFP mouse



Brain tumor



RED = tumor cells
GREEN= blood vessels from mice

Zimmer et al. 2015

We can Monitor Gastric Cancer Progression in our Mice

Yellow Protein labeled Gastric Cancer Mice

Healthy Mouse

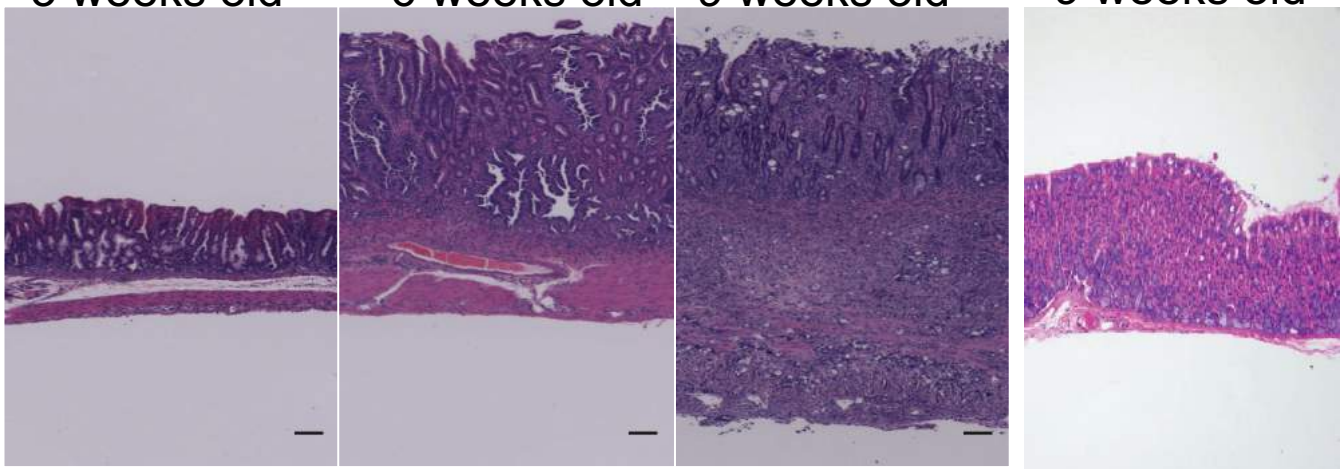
3 weeks old

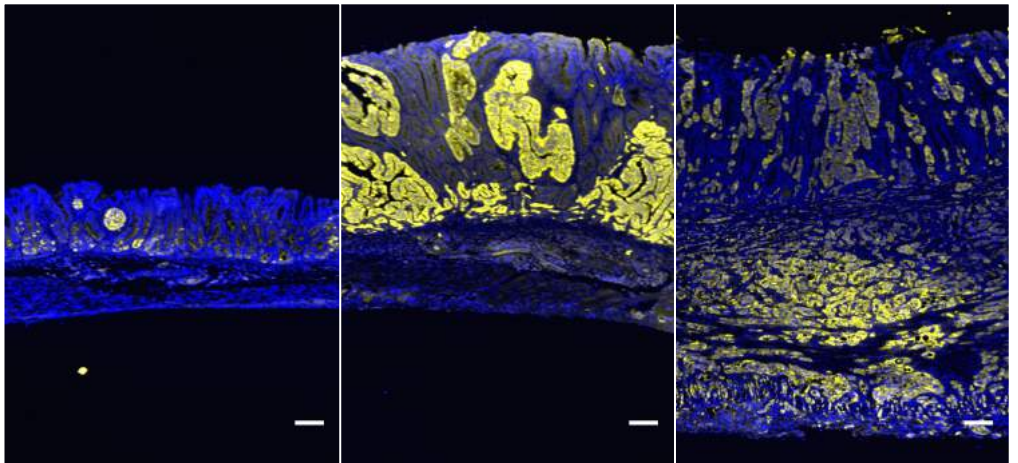
6 weeks old

9 weeks old

9 weeks old

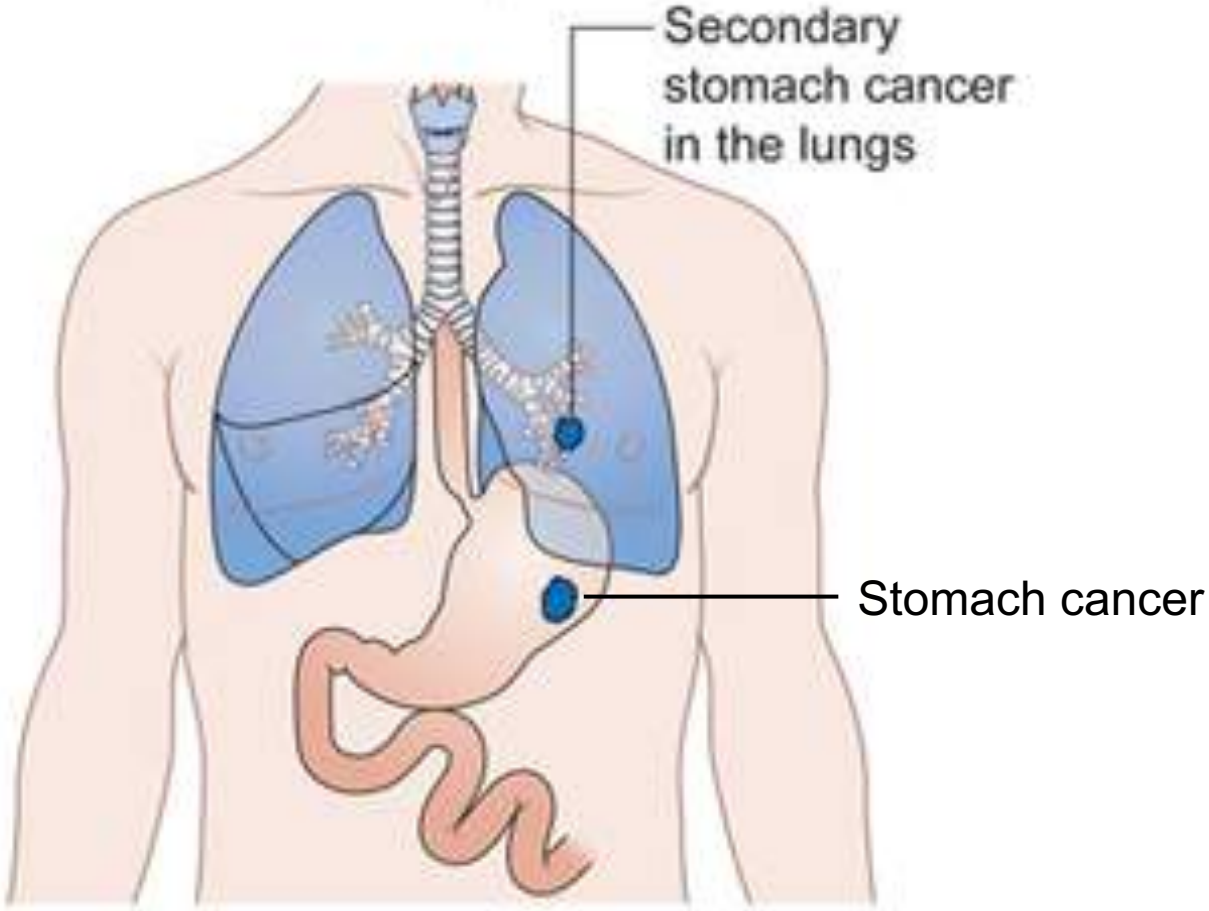
Stomach





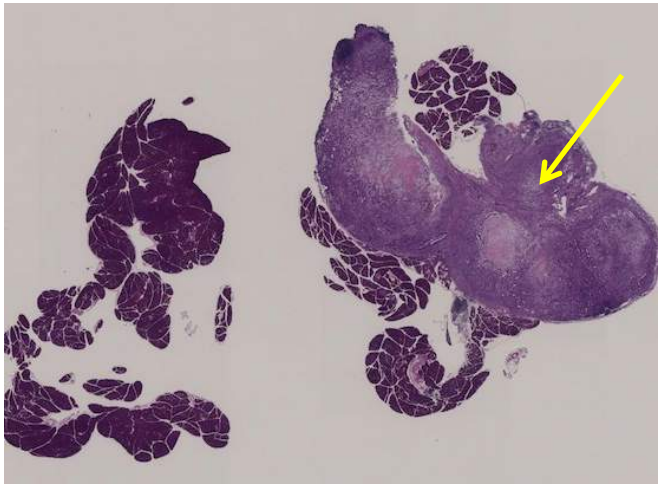
Yellow= Cancer cells
Blue = All cells

Advanced Gastric Cancer: Metastatic Progression

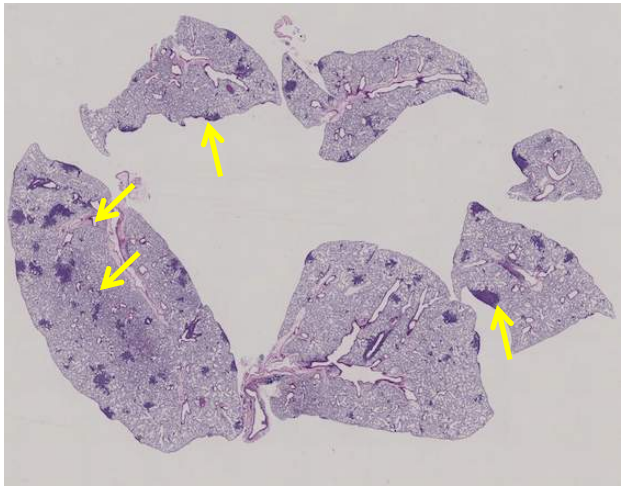


Gastric Cancer Mice Metastasize to Lymph Nodes, Lung and Liver

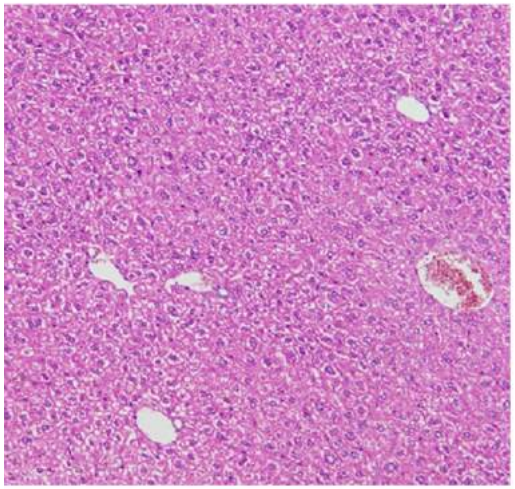
Perigastric Lymph Node Mets



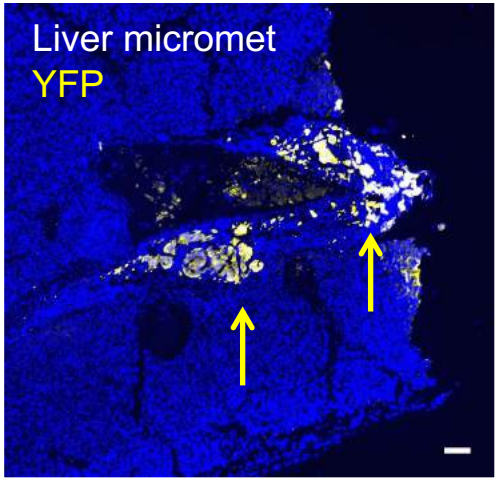
Lungs Metastases



Liver Micrometastases



Liver mets
not detected
by imaging



Yellow= Cancer cells
Blue = All cells

What are we studying in our Gastric Cancer mouse models?

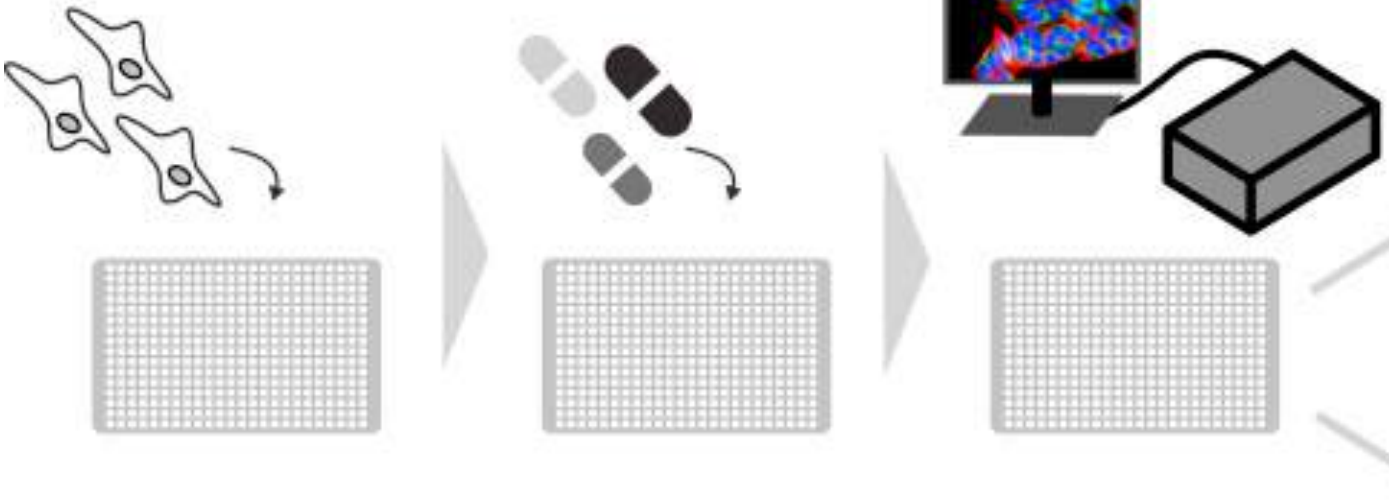
- New treatments to slow/prevent metastases or spread of disease
- Biomarkers for early detection
- Biological pathways that drive gastric cancer

Drug Discovery for New Treatments for Gastric Cancer

Gastric Cancer Cells (from mice)

Add FDA- Approved Drugs (screen 3000 drugs)

Automated Readout for Drugs that Kill Cancer Cells



Test Drugs in mice:

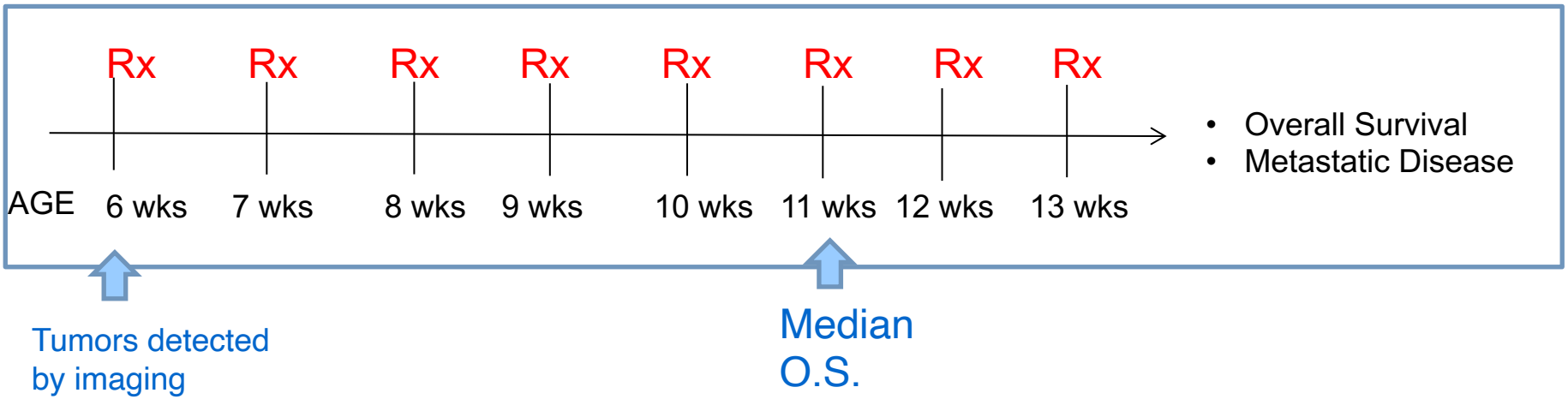
- Toxicity
- Efficacy

Clinical Trials in Gastric Cancer Mice

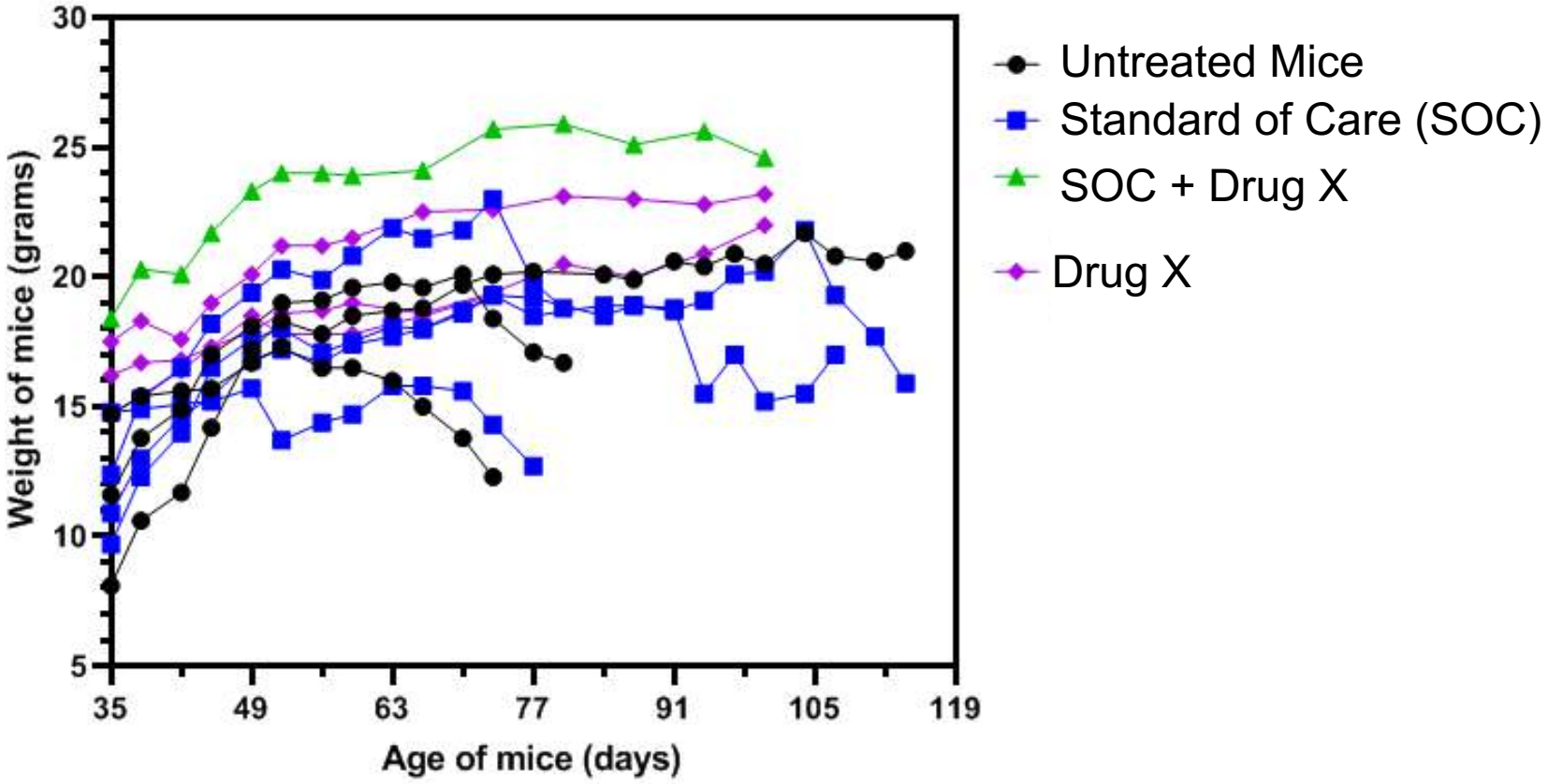
ARM I: 5FU + Oxaliplatin
Standard of Care

ARM II: 5FU + Oxaliplatin + Compound X
Experimental Arm

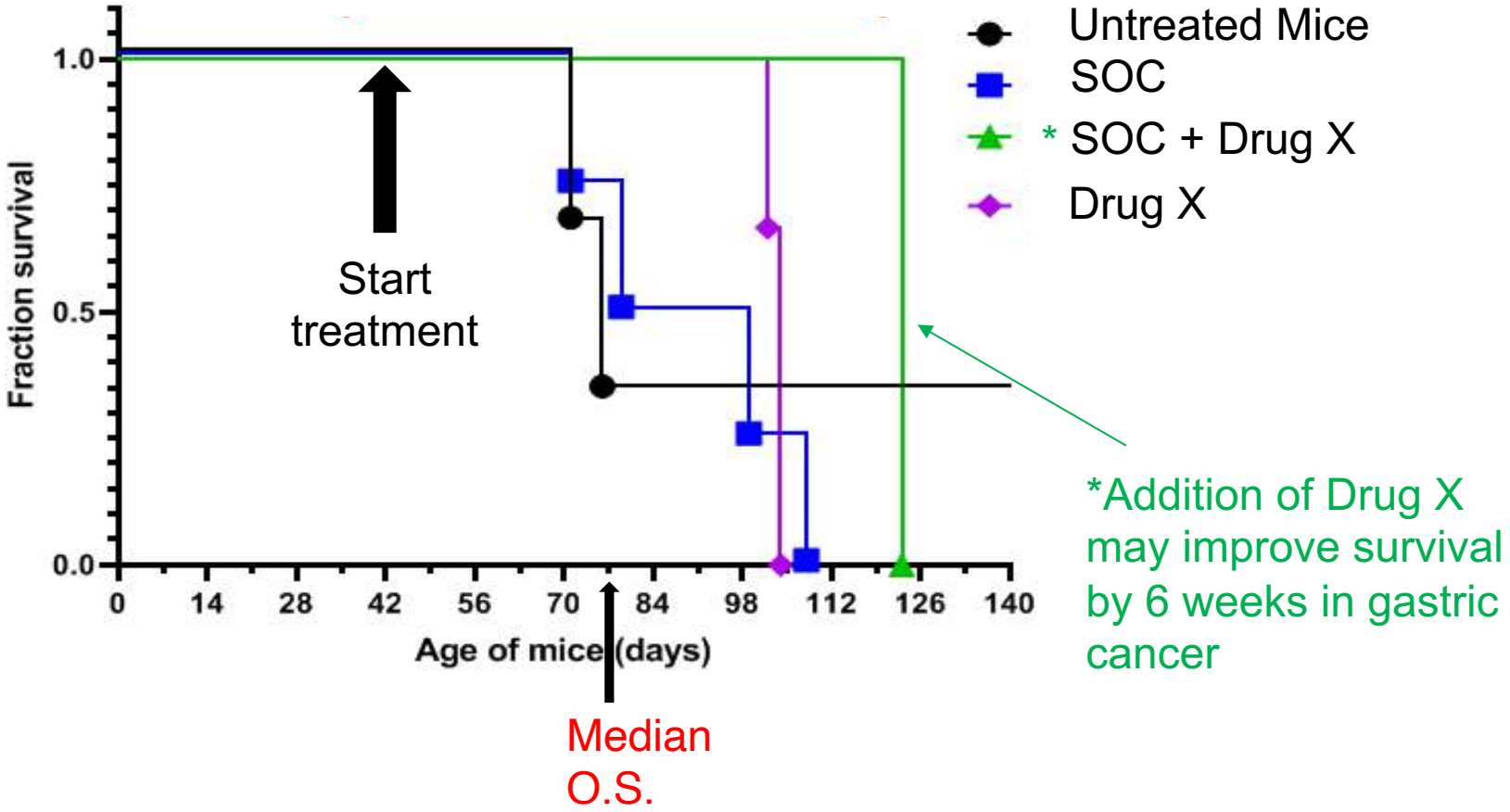
Experimental Schema



New Treatment Regimen is not Toxic to Mice

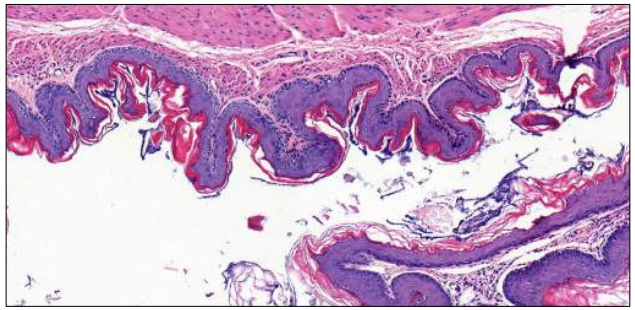


Survival Studies in Gastric Cancer Mice with New Therapies

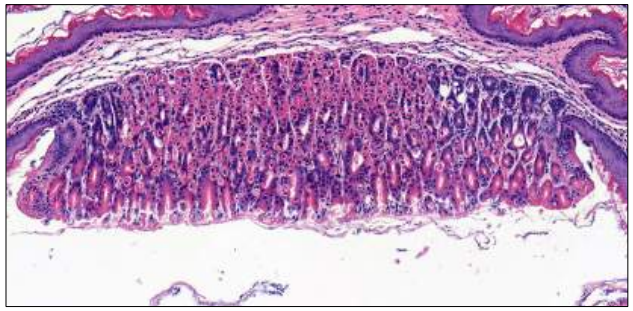


Gastric Organoids to Model Stomach Cancer and screen new drugs

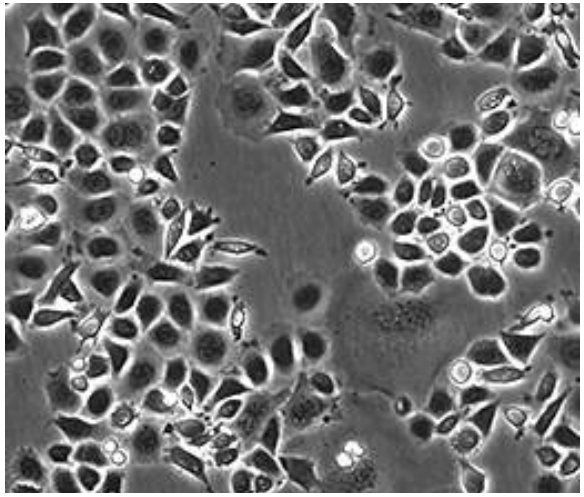
Normal Mouse Stomach



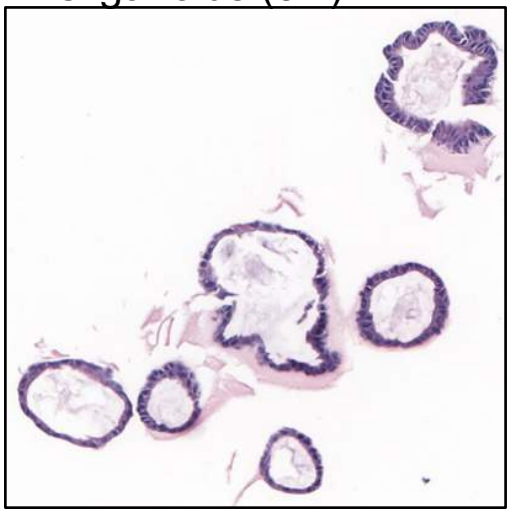
Mouse Stomach Tumor



Gastric Cancer Cells (2D)



Gastric Cancer Organoids (3D)

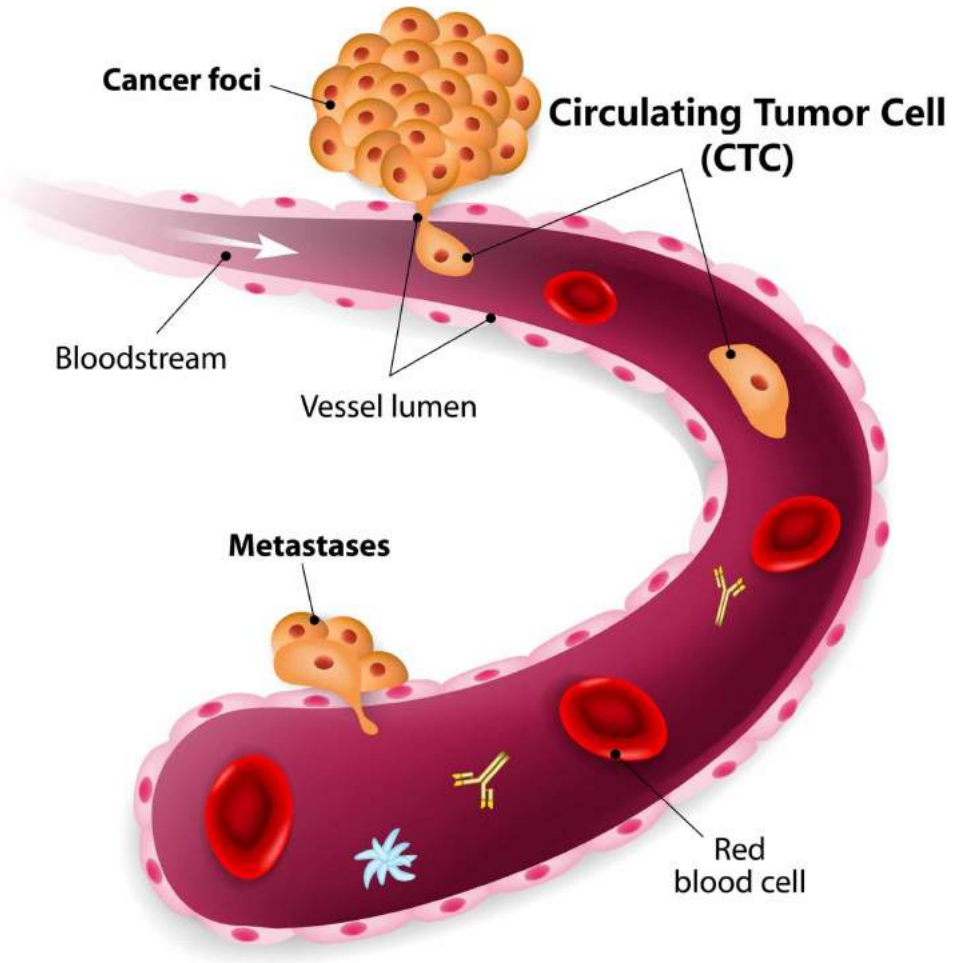


- Drug Screen
- Personalized Medicine

How can we detect gastric cancer before we can visualize it?

- Liquid Biopsies
  - Blood (Circulating tumor cells, tumor DNA)
- Stool and Urine
  - Tumor proteins, tumor DNA
- Gastric Lavage
  - Tumor proteins, tumor DNA

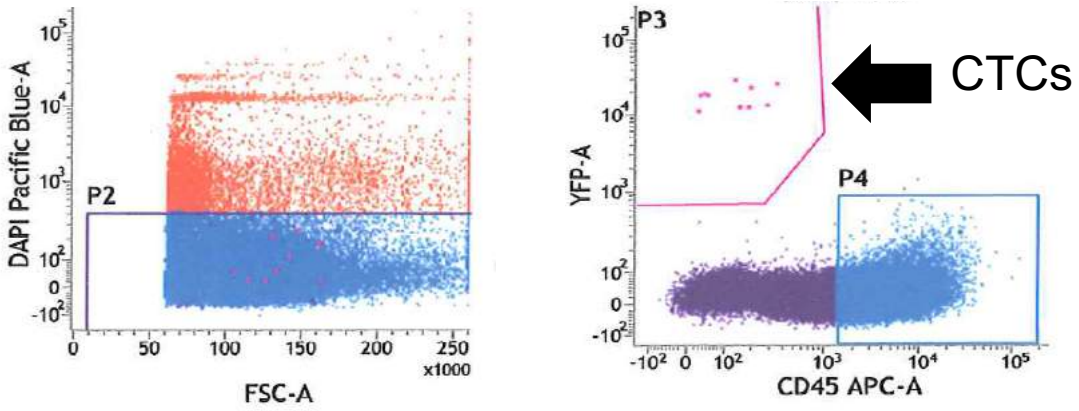
Do Gastric Cancer Cells Circulate in the Blood When Tumors are Small?



https://www.vycap.com/application/circulating-tumor-cells/

Circulating Tumor Cells may Correlate with Metastatic Disease

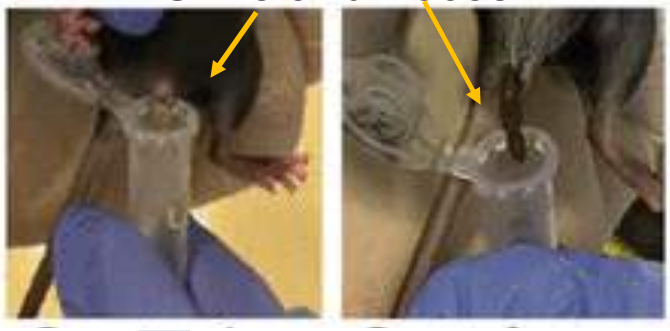
CTCs in the blood can be detected by their Yellow marker



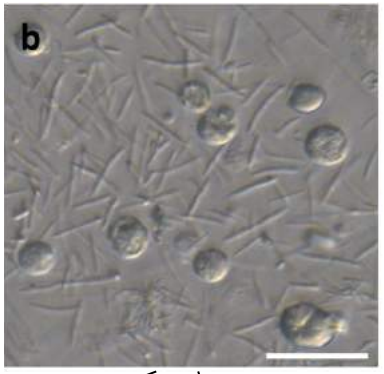
Mouse ID	Age (d)	Condition	CTCs	Lung Mets
5118	79	Moribund	676	+++++
5216	74	Moribund	25	+++
5223	70	Good	4	none

Screening Mouse Urine and Feces For Early Signs of Gastric Cancer

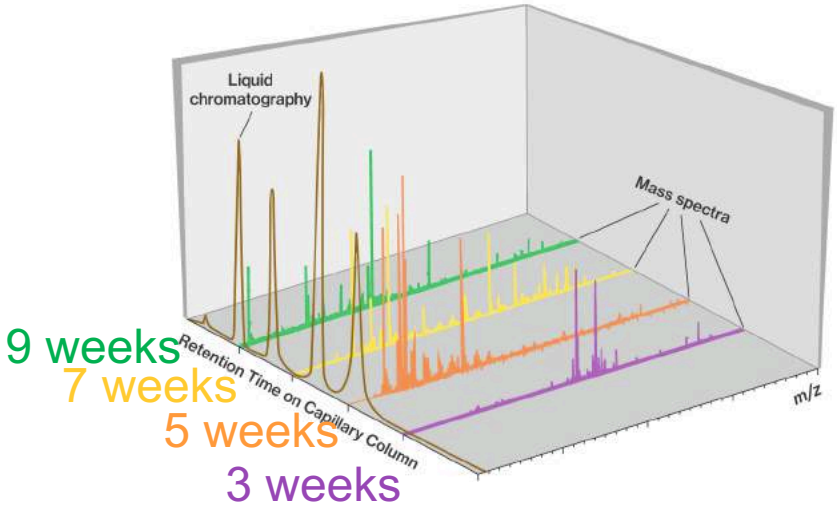
Serial Collection of Mouse Urine and Feces

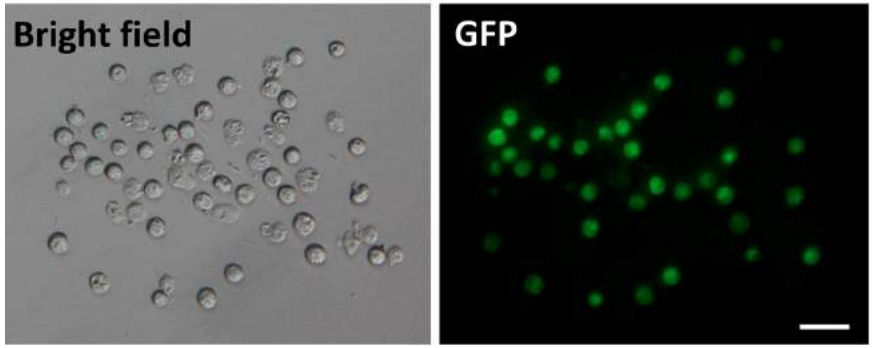


Fecal analysis



Urinalysis





Kamimura et al. Sci, Reports, 2018

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