Studying Stomach Cancer in the Lab

Gastroesophageal Cancer Symposium
Debbie’s Dream Foundation

Sandra Ryeom, Ph.D.
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 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

A

Mouse

Human

Stomach

Transverse colon

Ascending colon

Descending colon

Cecum

Taenia coli

Colon

Cecum

Haustra

Appendix

B Mouse fore and glandular stomach

C Human glandular stomach

# Different Ways to Model Cancer in Mice

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

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Healthy Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 weeks old</td>
<td></td>
</tr>
<tr>
<td>6 weeks old</td>
<td></td>
</tr>
<tr>
<td>9 weeks old</td>
<td></td>
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</tbody>
</table>

Yellow = Cancer cells
Blue = All cells

Stomach
Advanced Gastric Cancer: Metastatic Progression

Secondary stomach cancer in the lungs

Stomach cancer
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**

- Overall Survival
- Metastatic Disease

Tumors detected by imaging

Median O.S.
New Treatment Regimen is not Toxic to Mice

![Graph showing weight of mice over age with different treatments: Untreated Mice, Standard of Care (SOC), SOC + Drug X, Drug X.](image)
Survival Studies in Gastric Cancer Mice with New Therapies

*Addition of Drug X may improve survival by 6 weeks in gastric cancer*
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

<table>
<thead>
<tr>
<th>Mouse ID</th>
<th>Age (d)</th>
<th>Condition</th>
<th>CTCs</th>
<th>Lung Mets</th>
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</thead>
<tbody>
<tr>
<td>5118</td>
<td>79</td>
<td>Moribund</td>
<td>676</td>
<td>++++</td>
</tr>
<tr>
<td>5216</td>
<td>74</td>
<td>Moribund</td>
<td>25</td>
<td>+++</td>
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<tr>
<td>5223</td>
<td>70</td>
<td>Good</td>
<td>4</td>
<td>none</td>
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Screening Mouse Urine and Feces For Early Signs of Gastric Cancer

Serial Collection of Mouse Urine and Feces

Fecal analysis

Urinalysis

9 weeks
7 weeks
5 weeks
3 weeks

Kamimura et al. Sci, Reports, 2018
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