FORECASTING *H. PYLORI*-ASSOCIATED GASTRIC DISEASE PROGRESSION TO IMPROVE SCREENING MODALITIES FOR EARLY GASTRIC CANCER INTERVENTION

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IMO WORKSHOP 2014
GASTRIC CANCER – 2\textsuperscript{ND} MOST CANCER RELATED DEATHS WORLDWIDE

> 70% cases associated with H. Pylori
H. PYLORI IS ASSOCIATED WITH CHRONIC INFLAMMATION THAT MOBILIZES AND RECRUITS GSCs

Houghton et al. Science 306, 2004
Expression of Stem Cell Markers **CD44** and **Musashi-1** increases during the progression from gastritis, IM, dysplasia and invasive cancer stages.

Wang et al., Br J Cancer. 105(5), 2011
Hypothesis

Stem cells play a pivotal role in the progression from normal to metaplasia, dysplasia, and carcinoma.

The fraction and spatial distribution of stem cells in gastric biopsies may serve as a prognostic factor for disease progression and suggest meaningful screening intervals.
Quest: Develop a mathematical model of H. Pylori-associated Carcinogenesis
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Dysplasia/Cancer
Goblet Cells
Gastric Stem Cells
Mucosal Cells
Secretory Cells (Chief, Parietal, G Cells)
Crypt Dynamics

Crypt size

Cummul. Cancer Risk

# Stem Cells
AIM 1.

Develop a *mechanistic mathematical* model of gastric crypt homeostasis and *H. Pylori* induced inflammation and facilitation of carcinogenesis.

*Calibrate* the model with *stem cell* numbers and their spatial distribution at different gastric disease stages with retrospective tissue data from *H. Pylori*-associated disease (Cali, Columbia; n=30) and *non H. Pylori*-associated disease (Moffitt; n=30) provided by Dr. D. Coppola.
AVAILABLE DATA

Gastric biopsy tissue samples from different disease stages (normal, hyperplasia, metaplasia, cancer)

- H. Pylori-associated; Cali (n=30)
- Non H. Pylori-associated; Moffitt (n=30)

To be done: staining for GSC: CD44, Musashi-1

Quantification by Aperio system in the Analytic Microscopy Core at MCC to count the positive GSCs and to correlate their number to the surface area evaluated per tissue sample.
AIM 2!

Use the calibrated model to predict patient-specific disease progression dynamics using sequential screening samples from endoscopic gastric biopsies (n=10; Dr. D. Coppola).

We will randomize the retrospective data into training and test cohorts to validate the predictability of the disease progression model to suggest personalized screening schedules for early intervention.
AVAILABLE DATA

Single patient (n=10) gastric biopsy tissue samples from different disease stages (normal, hyperplasia, metaplasia, cancer)

To be done: staining for GSC: CD44, Musashi-1
MODEL DESIGN

• Collect patient specific data
• Use as initial condition for math model
• Use derived **parameter distributions** to predict disease progression within ‘cone of uncertainty’
• Use subsequent patient samples to re-calibrate the model and forecast disease progression with a smaller ‘cone of uncertainty’
Suggested screening

Normal

Metaplasia

Low Grade Dysplasia
• We are proposing an integrated mathematical model parameterized by clinical samples to identify *H. pylori* infected patients who are at greater risk to develop gastric dysplasia and carcinoma

• The model, initialized to patient-specific data, will suggest personalized screening schedules
BUDGET

• IHC on available retrospective data
  $20,000

• 50% effort Postdoc for model calibration and validation
  $30,000
THANK YOU.