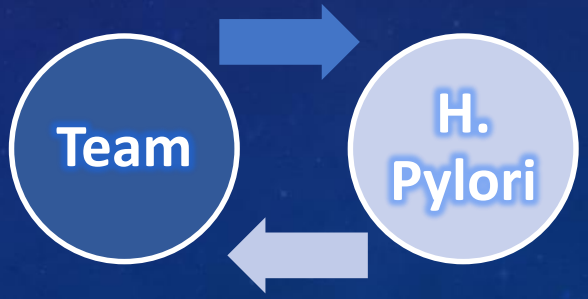
FORECASTING *H. PYLORI*-ASSOCIATED GASTRIC DISEASE PROGRESSION TO IMPROVE SCREENING MODALITIES FOR EARLY GASTRIC CANCER INTERVENTION

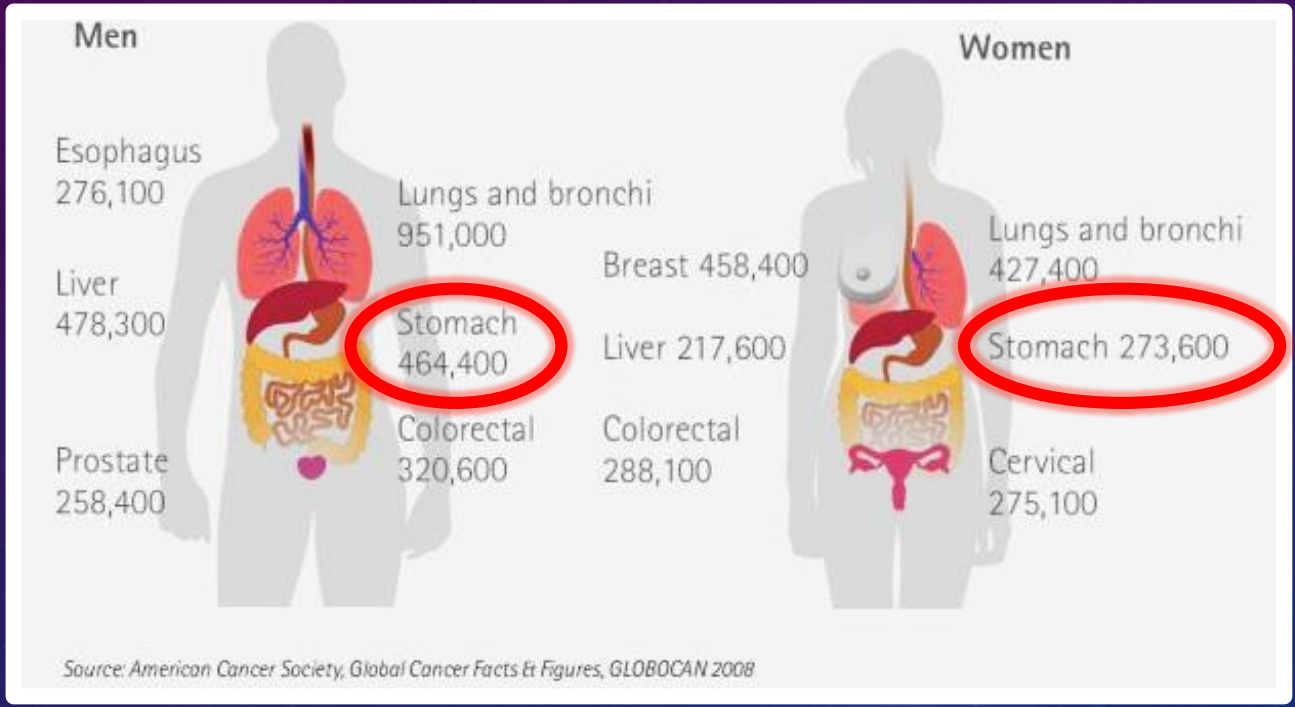
Hema, Radhia, Alicia, Derek, Ziv, Zayar, Artem, Bin, Tuhin, Yougan, Leah, Jose, Domenico, Heiko

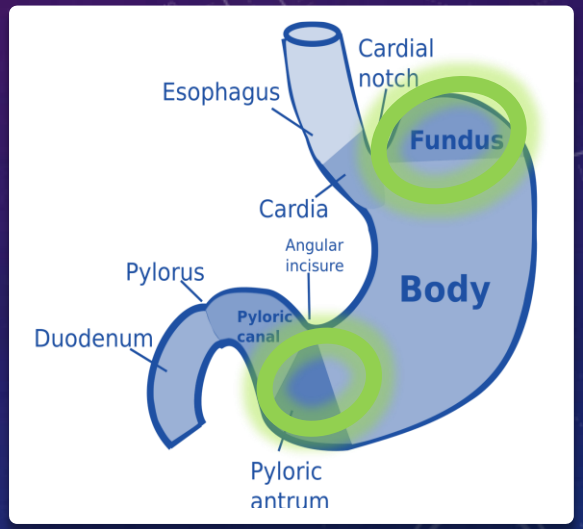


IMO WORKSHOP 2014

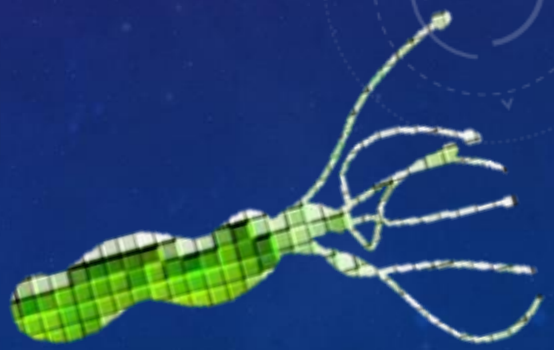

Team
H.
Pylori

GASTRIC CANCER – 2ND MOST CANCER RELATED DEATHS WORLDWIDE

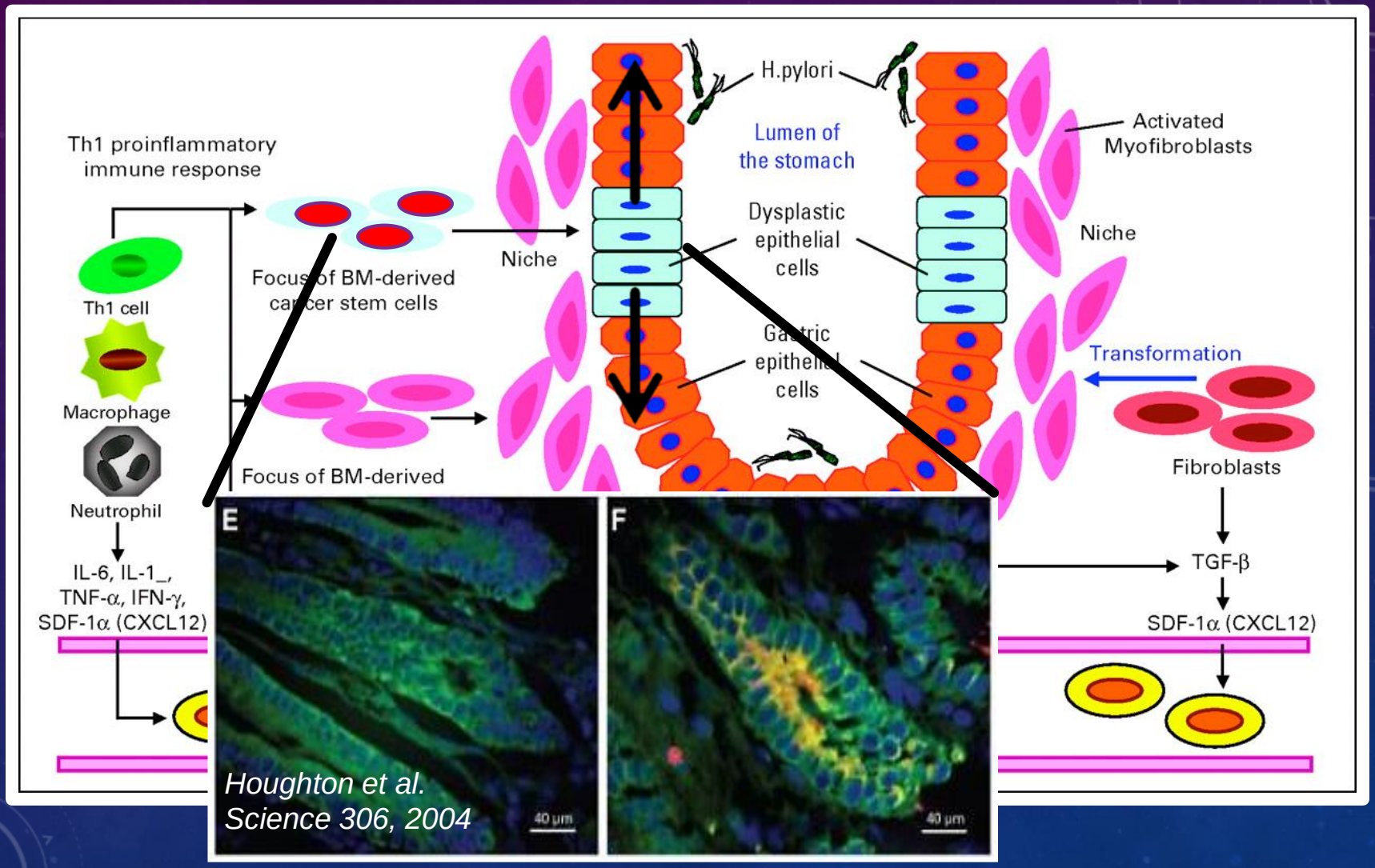




> 70% cases associated with H. Pylori



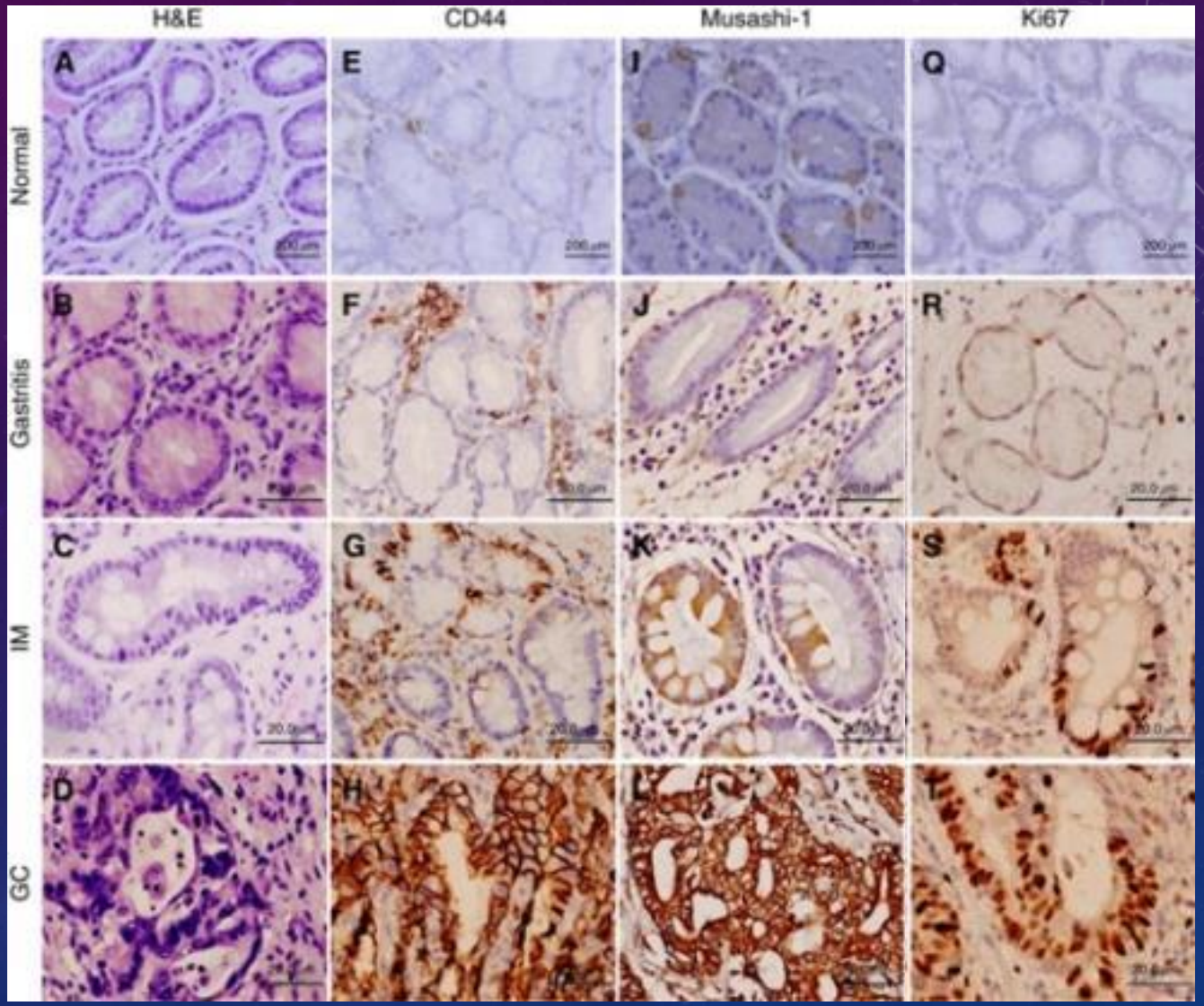
H. PYLORI IS ASSOCIATED CHRONIC INFLAMMATION THAT MOBILIZES AND RECRUITS GSCs



J Clin Oncol. 26(17), 2008

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

time



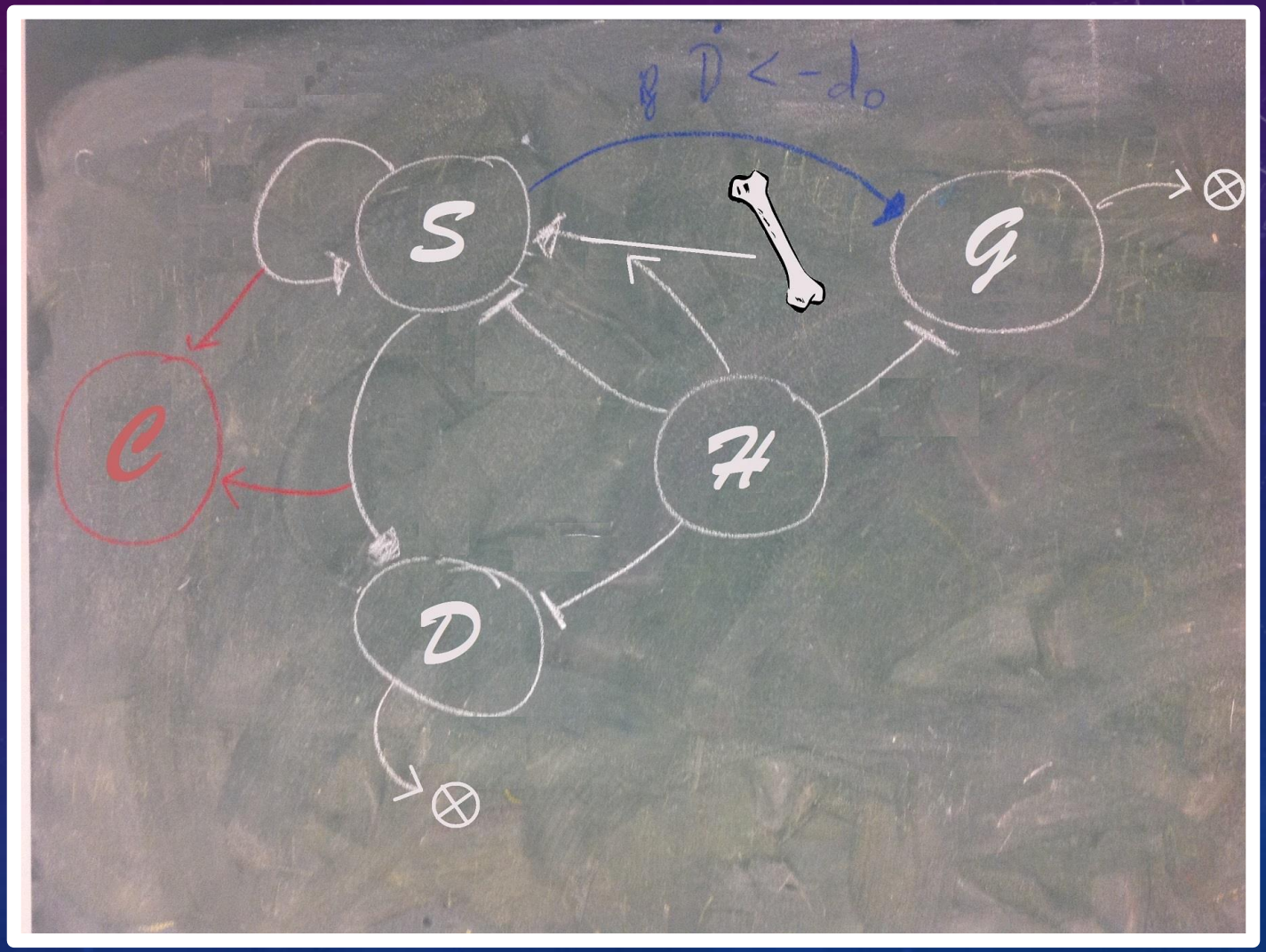
Wang et al., Br J Cancer. 105(5), 2011

Hypothesis

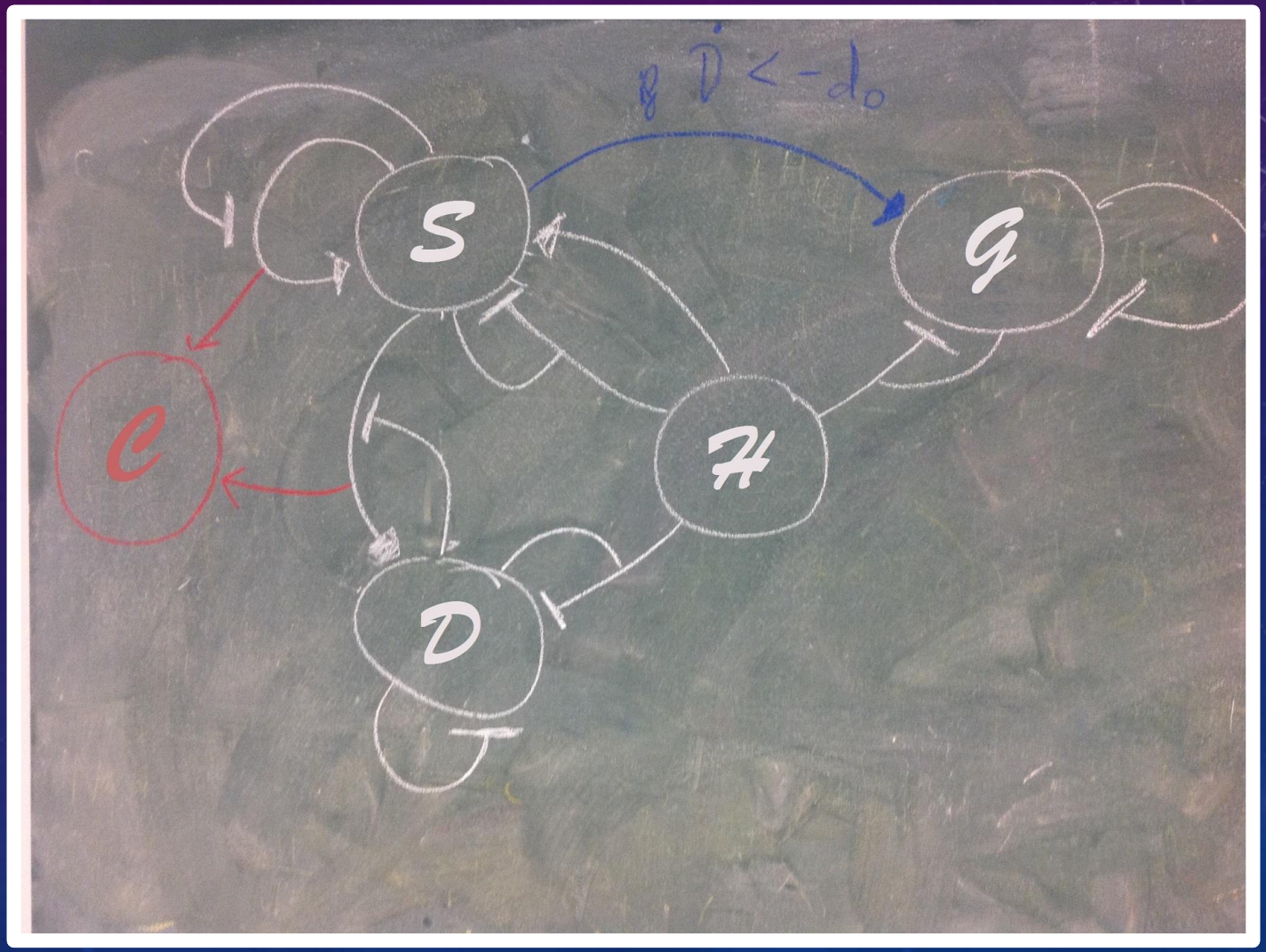
Stem cells play a pivotal role in the progression from normal to metaplasia, dysplasia, and carcinoma.

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.

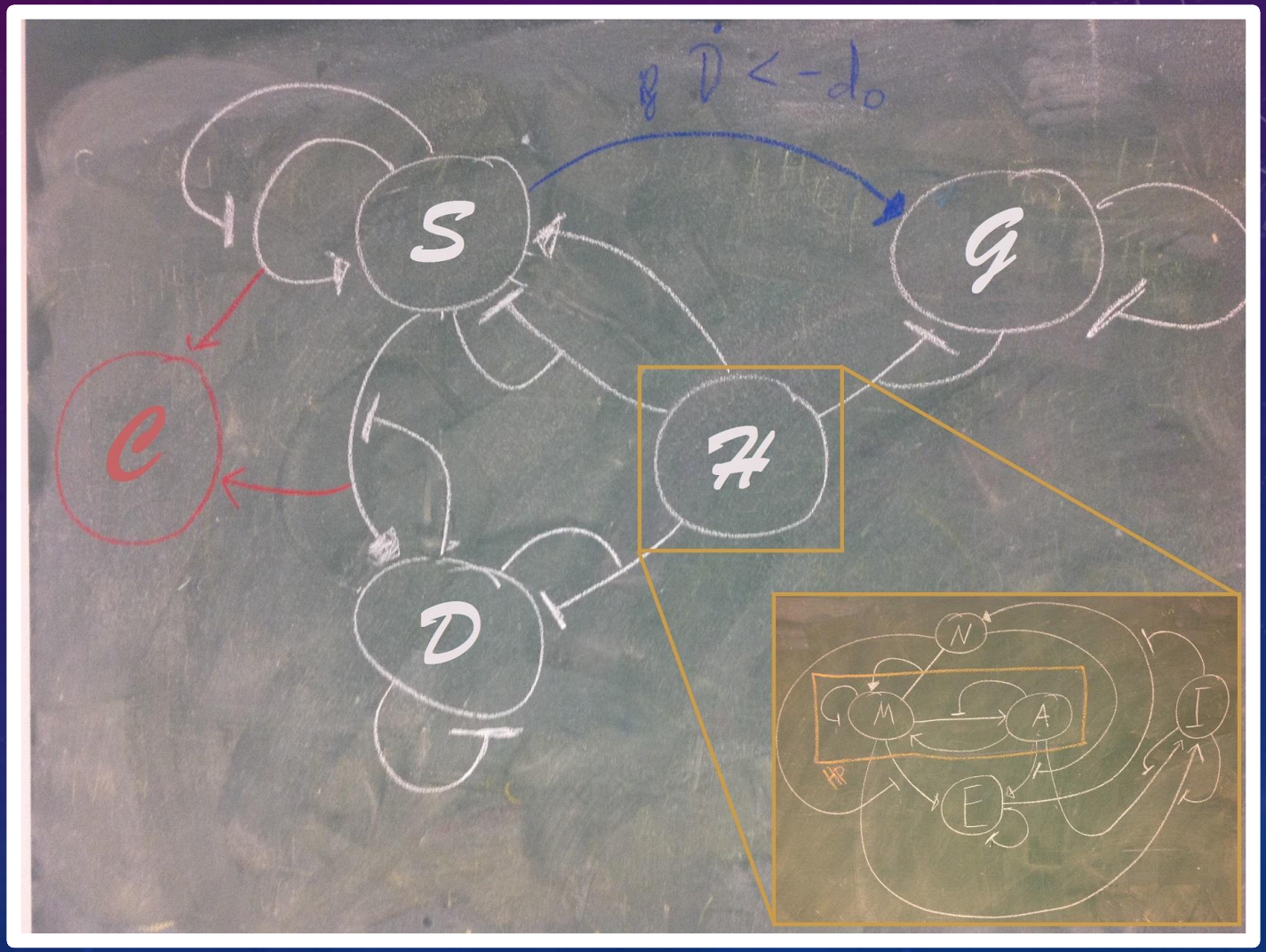
Quest: Develop a mathematical model of H. Pylori-associated Carcinogenesis



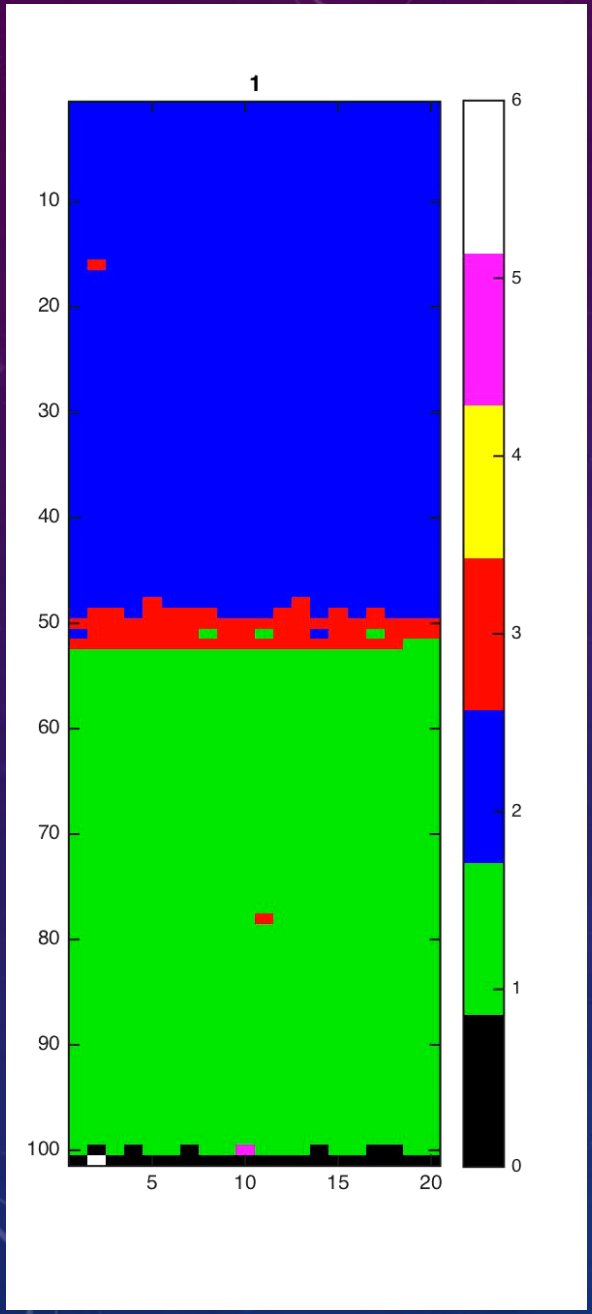
Quest: Develop a mathematical model of H. Pylori-associated Carcinogenesis



Quest: Develop a mathematical model of H. Pylori-associated Carcinogenesis



Agent Based Model



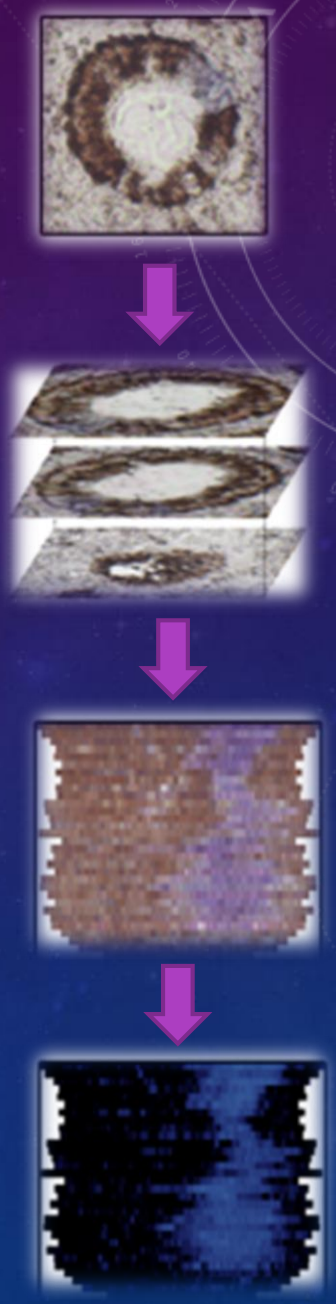
Dysplasia/Cancer

Goblet Cells

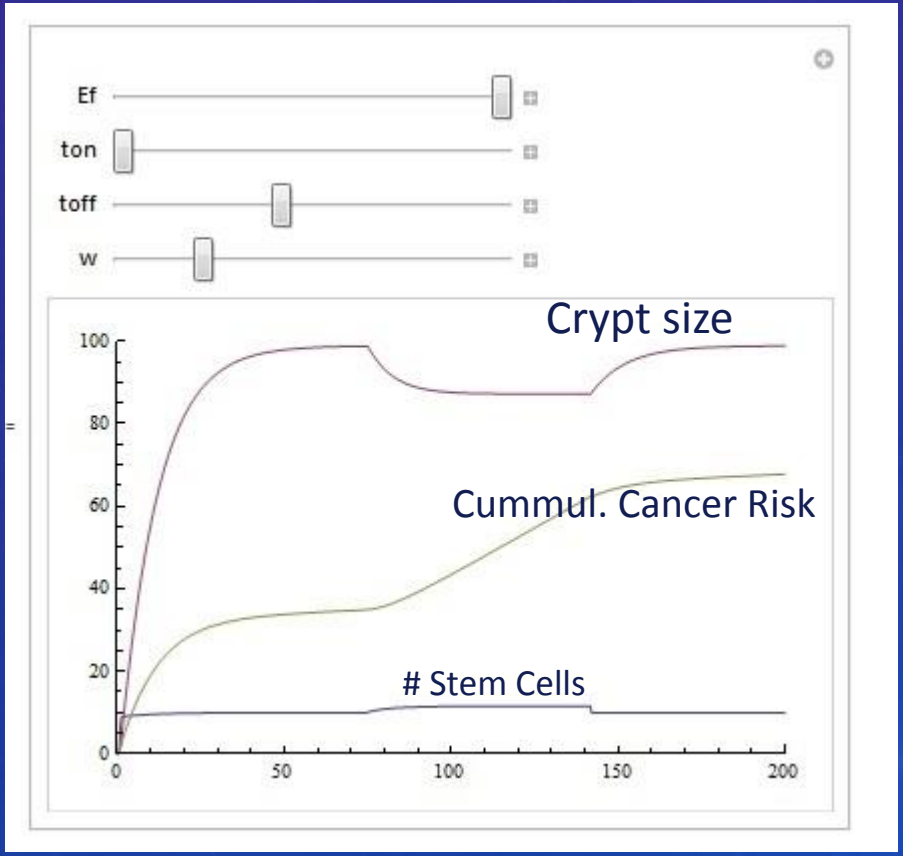
Gastric Stem Cells

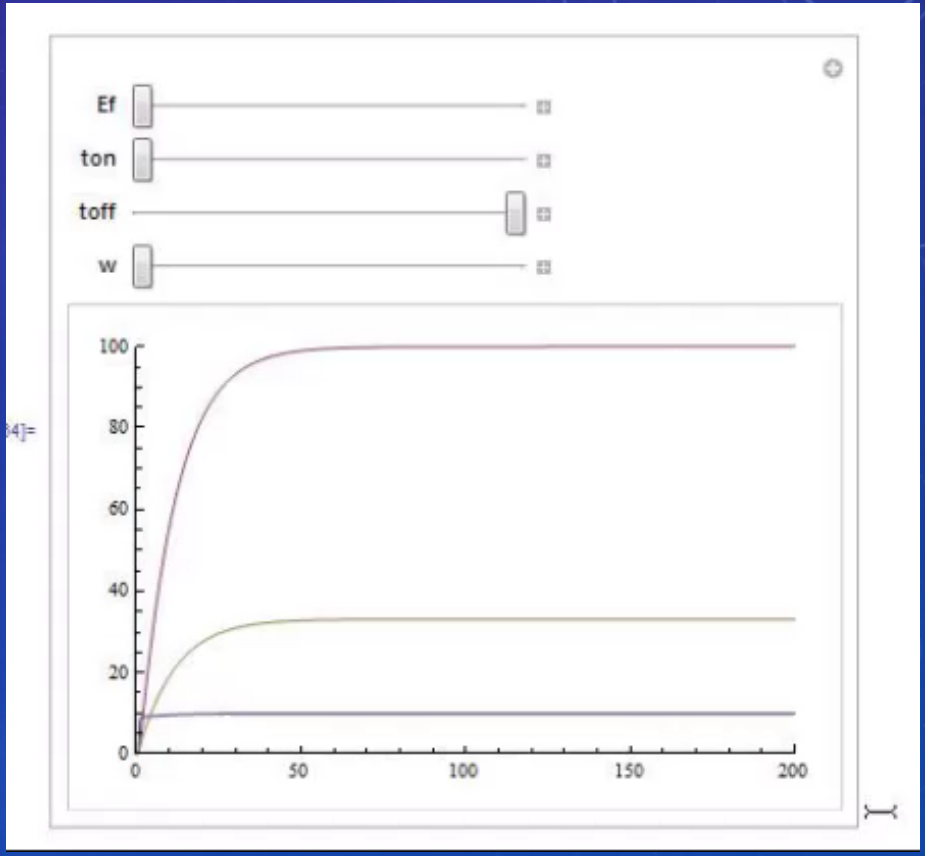
Mucosal Cells

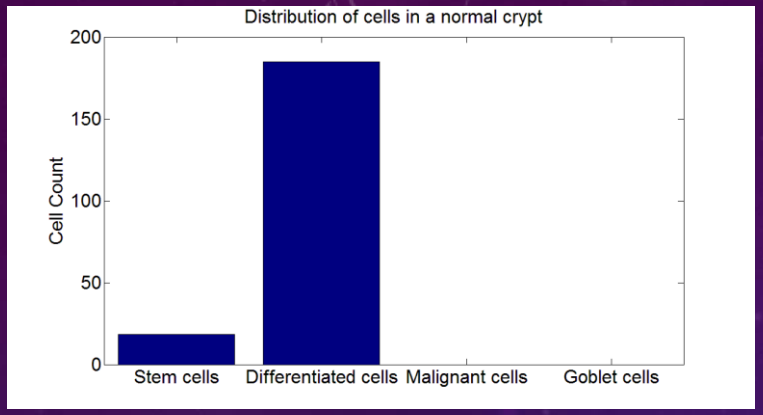
Secretory Cells
(Chief, Parietal, G Cells)

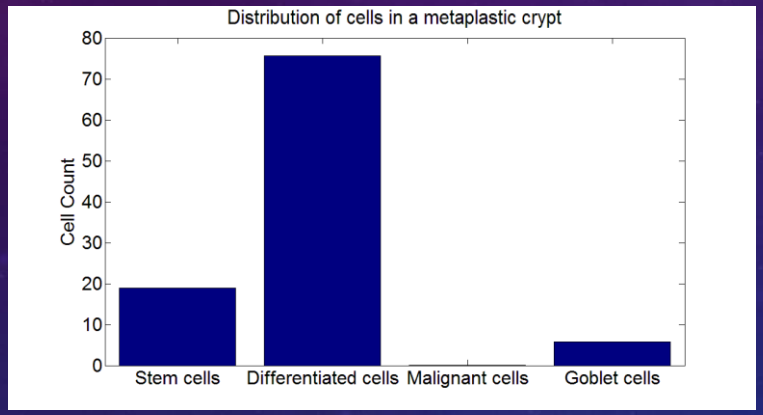


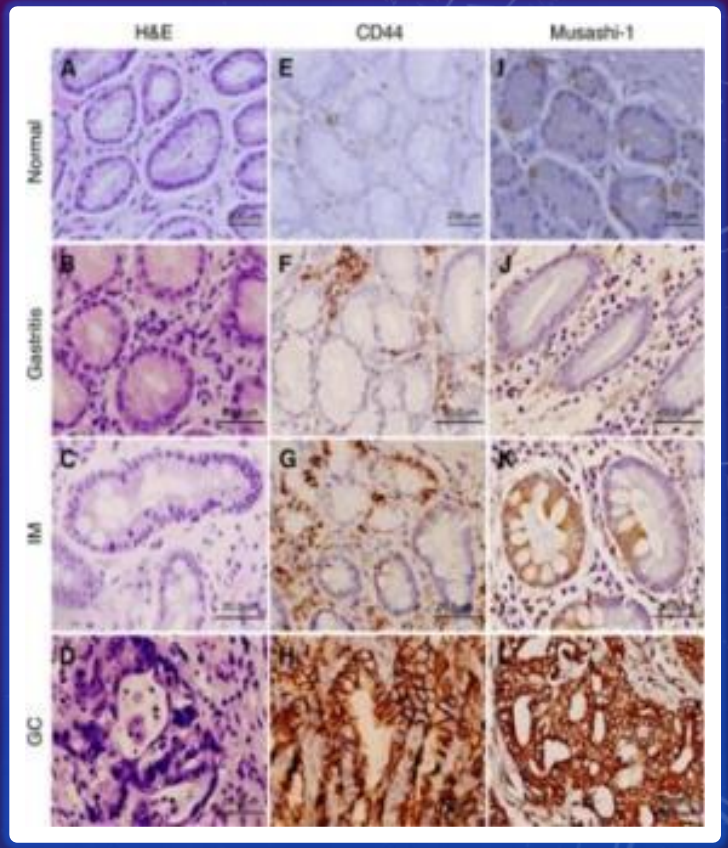
Crypt Dynamics

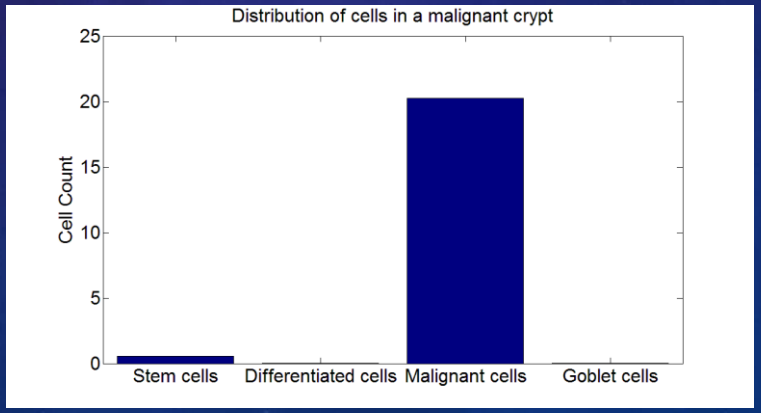





Distribution of cells in a normal crypt
Cell Count
200
150
100
50
0
Stem cells
Differentiated cells
Malignant cells
Goblet cells


Distribution of cells in a metaplastic crypt
Cell Count
80
70
60
50
40
30
20
10
0
Stem cells
Differentiated cells
Malignant cells
Goblet cells


H&E
CD44
Musashi-1
Normal
Gastritis
IM
GC
A
E
I
B
F
J
C
G
K
D
H
L


Distribution of cells in a malignant crypt
Cell Count
25
20
15
10
5
0
Stem cells
Differentiated cells
Malignant cells
Goblet 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.

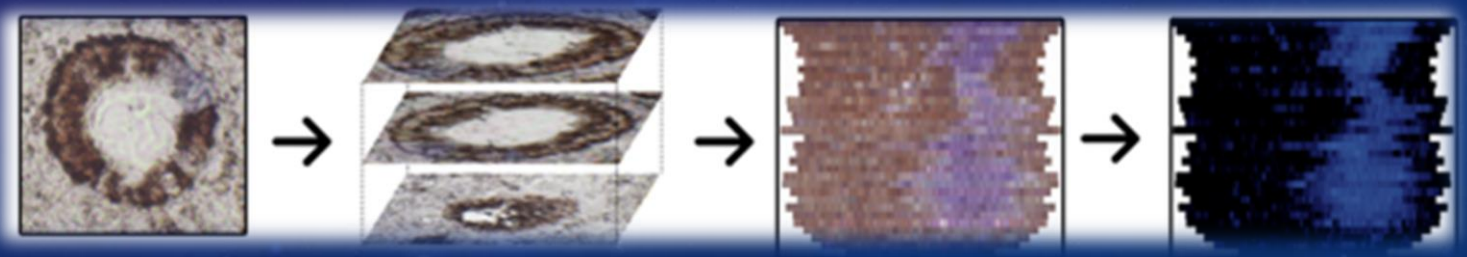
AVAILABLE DATA

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

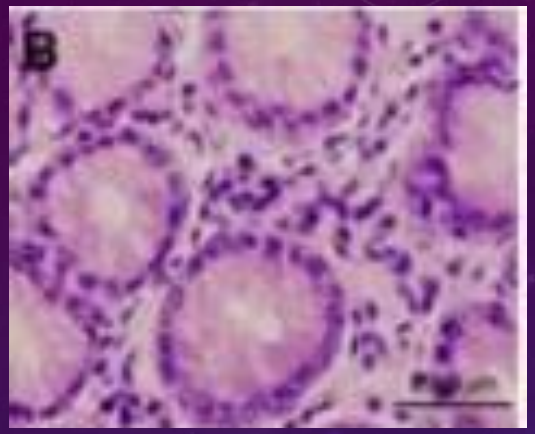
Single patient (n=10) gastric biopsy tissue samples from different disease stages (normal, hyperplasia, metaplasia, cancer)

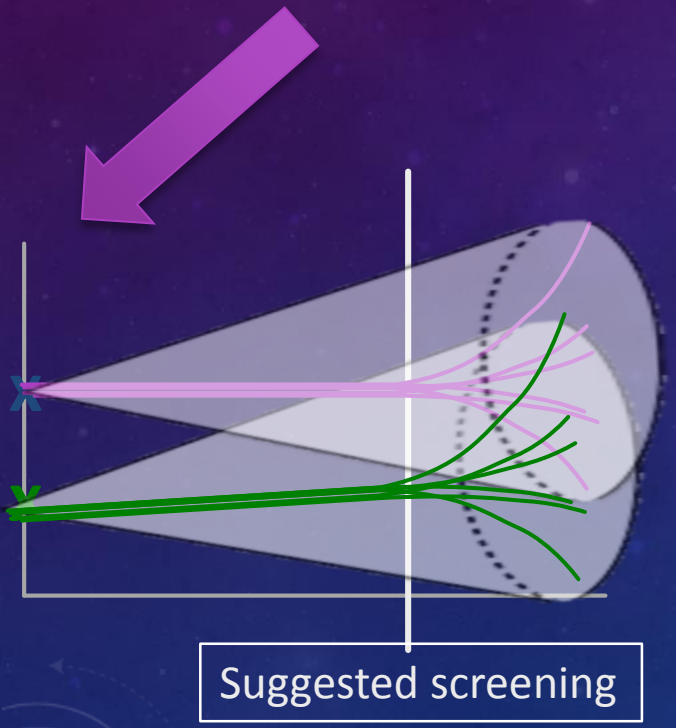
To be done: staining for GSC: CD44, **Musashi-1**

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’

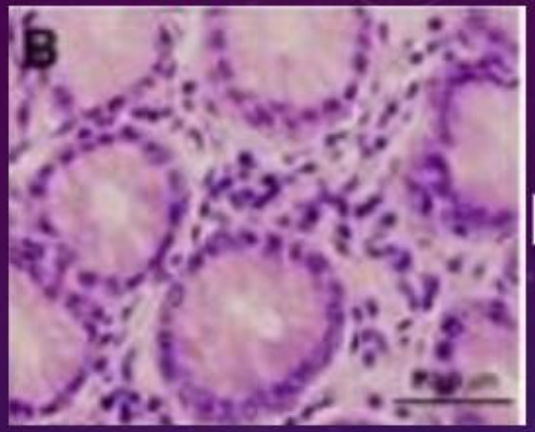
Normal



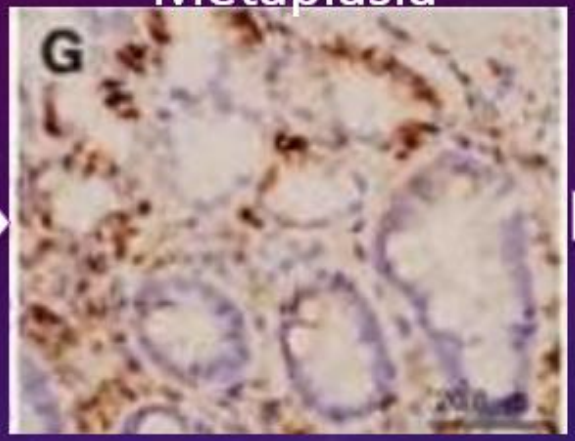


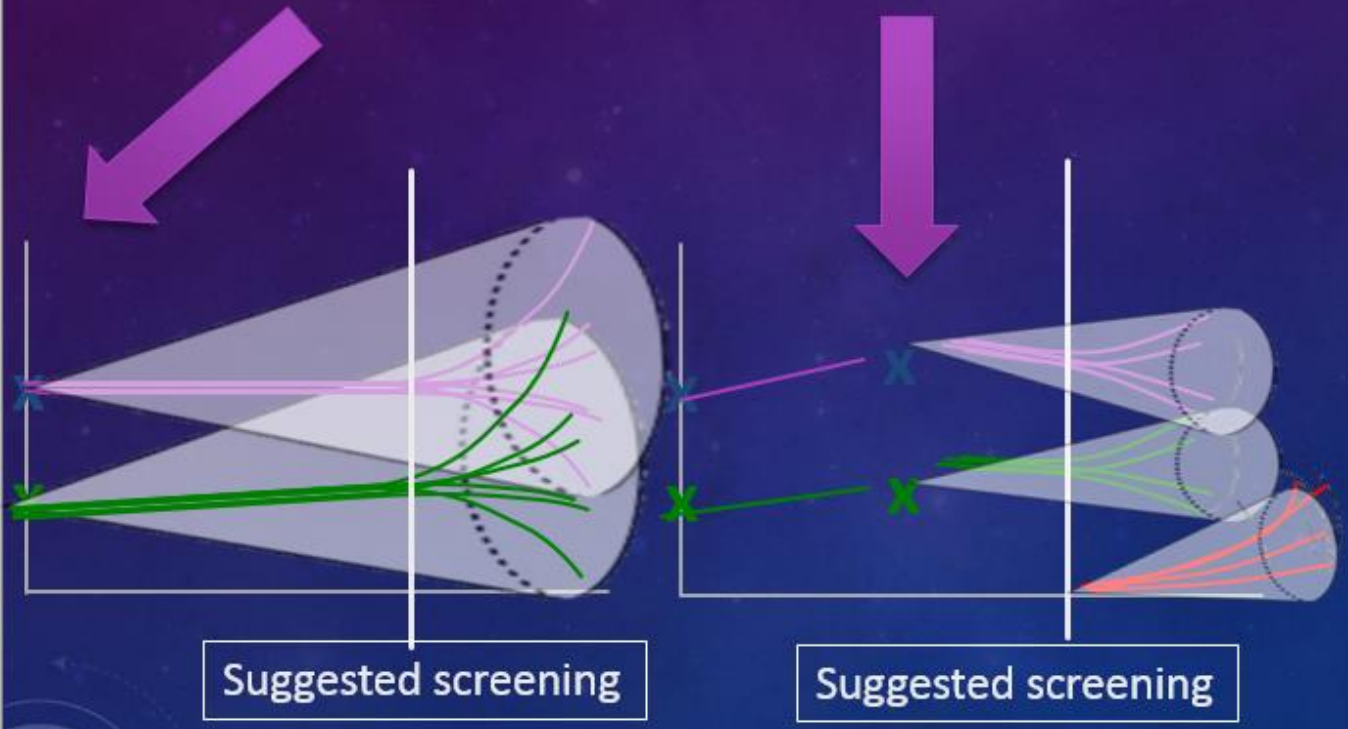
Suggested screening

Normal



Metaplasia

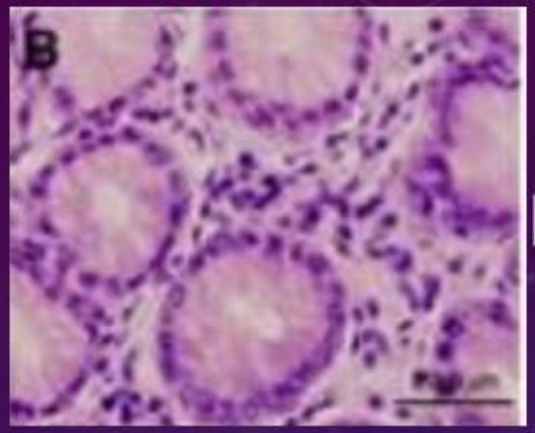




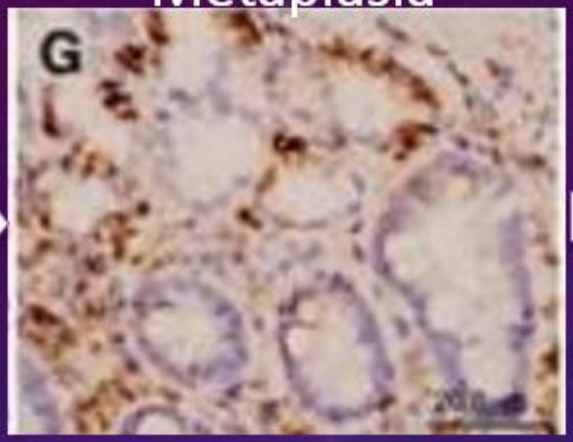
Suggested screening

Suggested screening

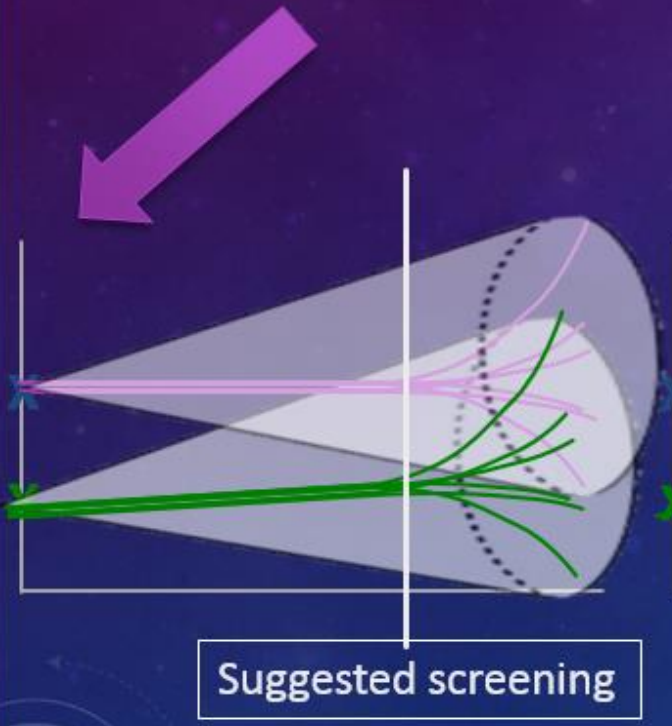
Normal



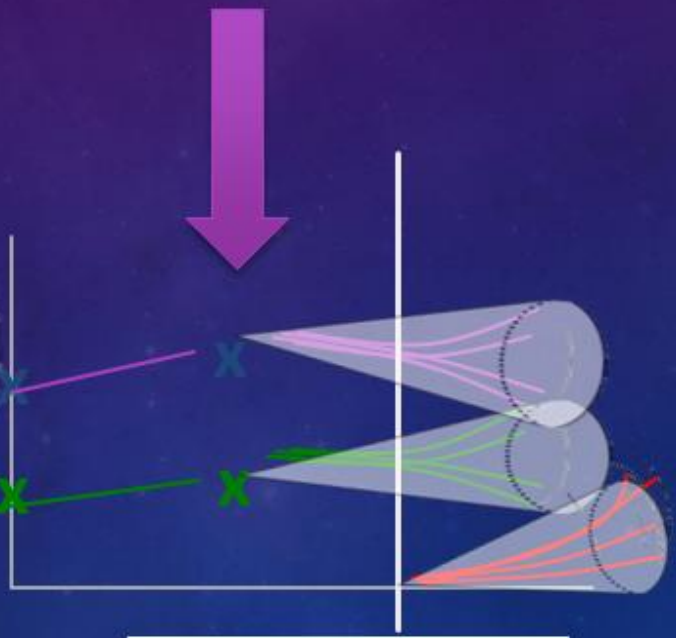
Metaplasia



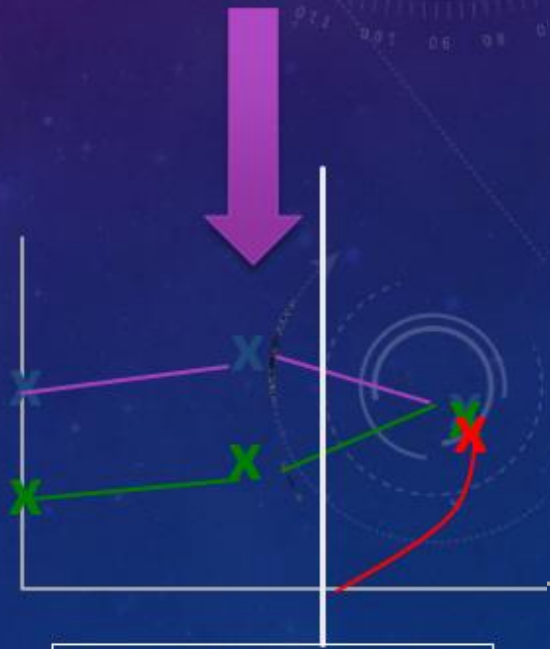
Low Grade Dysplasia



Suggested screening



Suggested screening



Suggested screening

SUMMARY

- 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

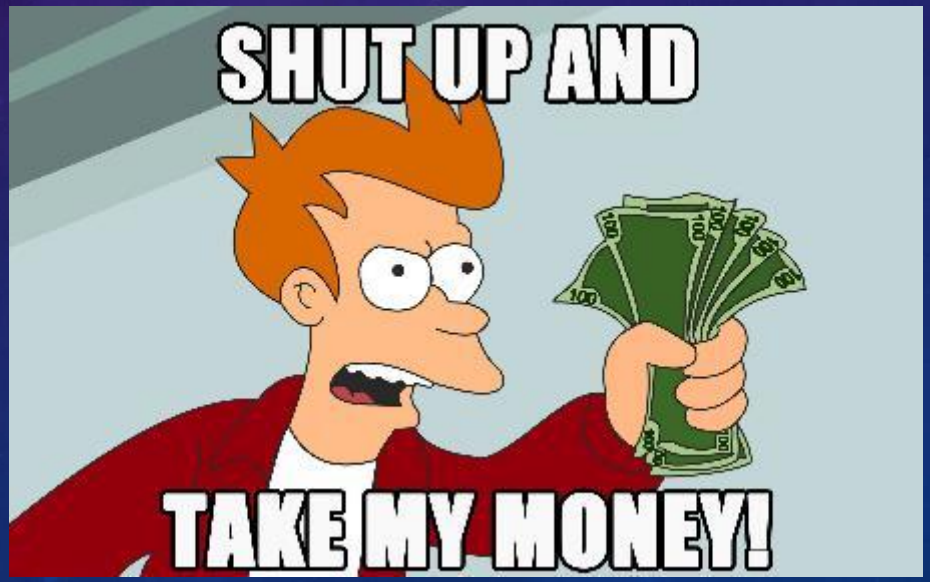
BUDGET

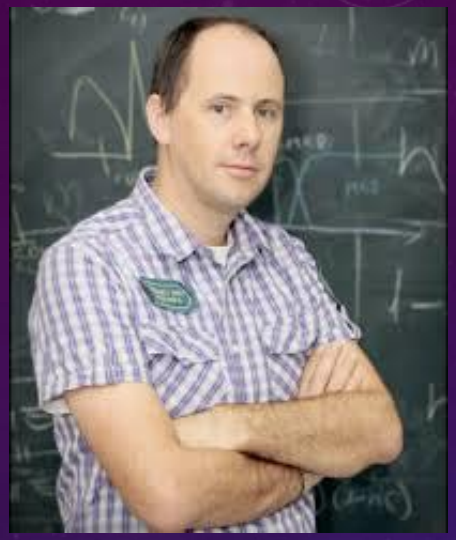
- IHC on available retrospective data

  $20,000

- 50% effort Postdoc for model calibration and validation

  $30,000





THANK YOU.

MOFFITT CANCER CENTER