





Anne Carpenter

BROAD IMAGING PLATFORM at Harvard and MIT 6.9994 83.333 14.113 1.5567

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# Images contain a wealth of information



### Case study: Tuberculosis

Estimated TB incidence rates, by country, 2006



9.2 million new cases of tuberculosis in 2006



1.7 million deaths in 2006

WHO Report, Global Tuberculosis Control 2008 3

# Traditional approach to find antibiotics

#### Put bacteria in individual wells of multi-well plates



Alternate approach to find antibiotics (effective but non-ideal)



### Search for tuberculosis treatments

#### Without drug

### With drug





### blue = human cells green = tuberculosis bacteria



Collaboration with Sarah Stanley in Deb Hung's lab, Broad/MGH



### Search for tuberculosis treatments

#### Put bacteria and cells in individual wells of multi-well plates



### Automated image analysis



Find human cells

# Find tuberculosis \_\_\_\_\_ Count the number of bacteria per cell



### Automated image analysis

Find

cells



### Find bacteria



# Count the number of bacteria per cell





Martha Vokes Image Assay Developer

# www.cellprofiler.org





Figure 5: IdentifyPrimAutomatic Display, cycle #3

File Edit View Insert Tools Desktor Window Help CellProfiler Image To-

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# **CellProfiler** in action

#### Ray Jones Comput'l **Biologist**





#### **Abnormal cell division**





blue = DNA

red = actin

Riki Eggert's lab at Harvard Medical School (Adam Castoreno, postdoc), ICCB



#### **Cell growth**



blue = DNA green = p-S6 red = actin

David Sabatini's lab at the Whitehead Institute for Biomedical Research (Jason Moffat, postdoc) & The RNAi platform/TRC at the Broad Institute (Dave Root, et al.)





# Polyploidization of megakaryocytes (Acute megakaryocytic leukemia - AMKL)



John Crispino's lab at Northwestern University (Jeremy Wen) & The Chemical Biology Platform at the Broad Institute





DNA stain



#### DNA damage response (cancer radiation treatment)







Mike Yaffe's lab at MIT's Center for Cancer Research (Scott Floyd & Michael Pacold, postdocs) & The RNAi platform/TRC at the Broad Institute



### CellProfiler around the world

| Cour | ntry/Territory | <u>Visits</u> |            |
|------|----------------|---------------|------------|
| 1.   | United States  | 1,072         |            |
| 2.   | Germany        | 213           |            |
| 3.   | United Kingdom | 180           |            |
| 4.   | Canada         | 106           |            |
| 5.   | France         | 83            | 503 cities |
| 6.   | Australia      | 76            |            |
| 7.   | Switzerland    | 68            |            |
| 8.   | Netherlands    | 67            |            |
| 9.   | Italy          | 52            |            |
| 10.  | Singapore      | 34            | 13         |

# Image analysis can yield biological knowledge

Collaboration with Novartis

### Yeast patch growth:

Goal: identify chemicals or genetic knockouts

that enhance/ suppress growth of a yeast strain



Collaboration with Leah Cowen, Lindquist lab, Whitehead Institute: Eukaryotic Cell, 2006

# Yeast colony size:

Goal: to understand pathways leading to drug-resistant yeast



# Iterative machine learning

System presents ~500 cells to biologists for scoring



System defines rule based on cytoprofile of scored cells



Based on: - Boosting Image Retrieval (Tieu & Viola, 2000) - GentleBoosting classifier (Friedman, et al. 1998)



# Automatically scoring complex phenotypes

CellVisualizer - 2006\_06\_14\_NIRHT

Makes use of:

~50 features per cell, chosen from ~500
Features are weighted, no hard thresholds

• Automatic machine learning

• Biological expertise during training phase

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File Plot Classify Show Info Window

#### **Glioblastoma proliferation &** differentiation

**Neurospheres** 

Adherent





blue = Hoechstgreen = Tubulin









#### **Abnormal cell division**

Normal mitosis



Tim Mitchison's lab at Harvard Medical School (Tiao Xie, postdoc; Melody Tsui), ICCB

#### Abnormal mitosis



DNA stain



#### Leukemia stem cells

Cobblestones

Differentiated hematopoietic cells



Gary Gilliland's lab at the Brigham and Women's Hospital and Harvard Medical School(Kimberly Hartwell & Peter Miller), Stuart Schreiber's lab at the Broad Institute (Alison Stewart, Shrikanta Chattopadhyay, et al.), and David Scadden's lab at Massachusetts General Hospital (Siddhartha Mukherjee) & Broad Chemical Biology Platform





GFP



+ Growth factor



Eric Lander's lab at the Broad Institute (Piyush Gupta, postdoc) & The RNAi platform/TRC at the Broad Institute



# Beyond simple cells...

Neuron assays, Haggarty/Stanley Ctr, Sabatini, Gertler labs







Zebrafish speckles, Peterson & Lees labs



Yeast progeny tracking, Weizt & Samadani labs Adjacent Image, ciycle # 2 Tracked Objects 50 100 ☑ ✓ 150  $\checkmark$ 200 250 300 100 120 140 10 20 30 20 40 60 80

# Alternate approach to find antibiotics

Put bacteria and worms in individual wells of multi-well plates















Add 53,000 test chemicals, each chemical in a different worm



# Automated microscope

# \$3,000+ images















# Search for E. faecalis treatments

Looking for chemical compounds that rescue C. elegans from death by E. faecalis infection





#### Brightfield

IMAGING

PLATFORM

#### Image processing result: Live/Dead



Fred Ausubel Terry Moy



### Fat accumulation (Nile Red)



Brightfield

Nile Red

**Brightfield + Nile Red** 



Gary Ruvkun Eyleen O'Rourke 21



# Gratitude

IMAGING





BROAD

Vebjørn Ljoså David Logan Kate Madden Björn Nilsson Martha Vokes



free, at www.cellprofiler.org

Contact: anne@broad.mit.edu

Many thanks to our many biology collaborators who provide images, and to Polina Golland, our computer science collaborator at MIT's Computer Science/Artificial Intelligence Laboratory (CSAIL)

#### This work has been supported by:

- The Broad Institute of Harvard and MIT
- Society for Biomolecular Screening Small Grant Award
- •L'Oreal for Women in Science fellowship
- •DOD Tuberous Sclerosis Complex Grant
- •Novartis fellowship from the Life Sciences Research Foundation
- Merck/MIT Computational & Systems Biology postdoc fellowship
- •MIT EECS/Whitehead/Broad Training Program in Computational Biology

S.D.G.