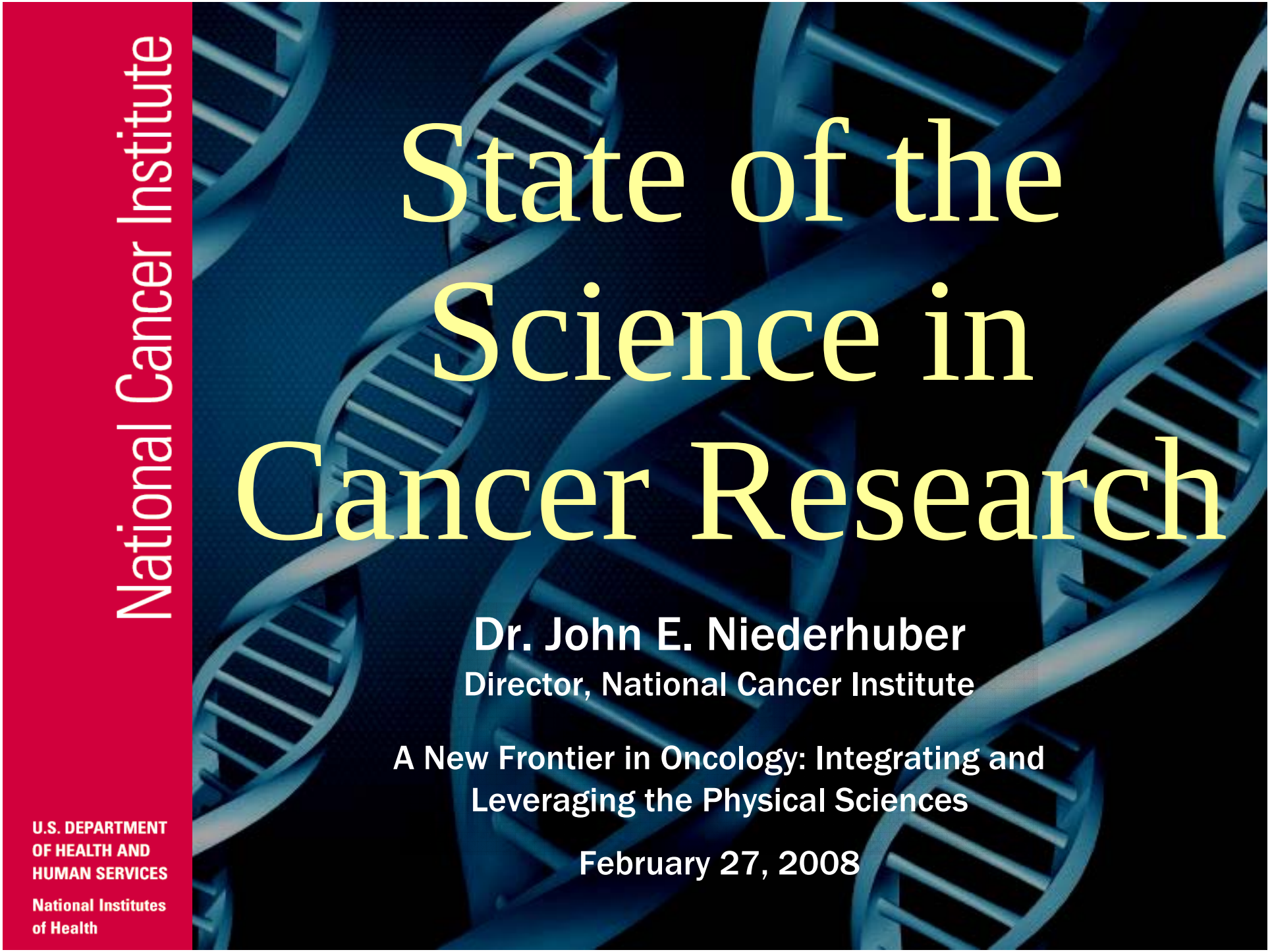
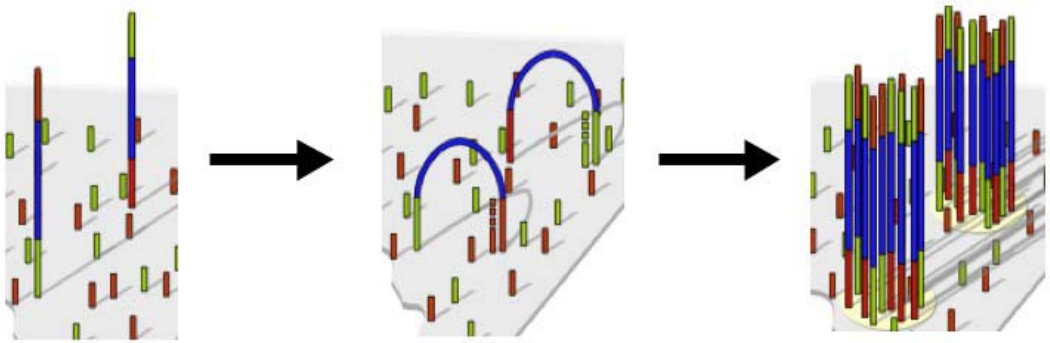
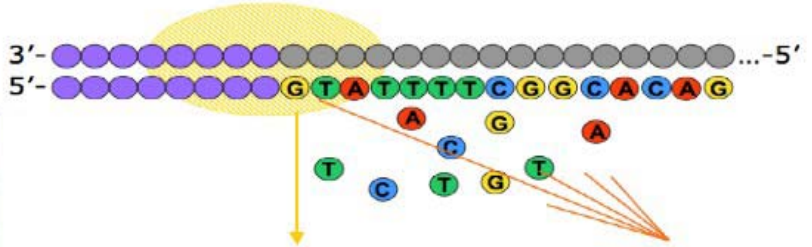

National Cancer Institute
State of the Science in Cancer Research
Dr. John E. Niederhuber
Director, National Cancer Institute
A New Frontier in Oncology: Integrating and Leveraging the Physical Sciences
February 27, 2008
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

What can physics, physical chemistry, and applied mathematics bring to cancer biology?





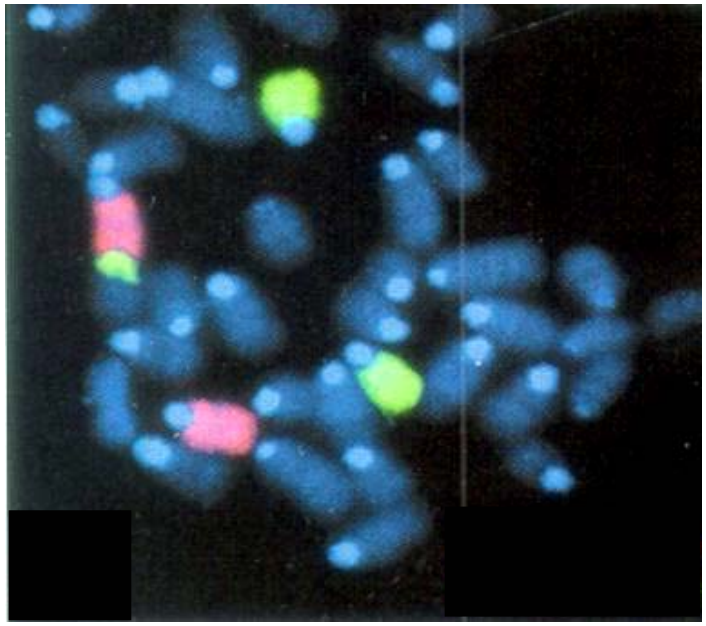
An Unprecedented Era of Discovery

A transformation in medicine

Cancer is a Disease of the Genome

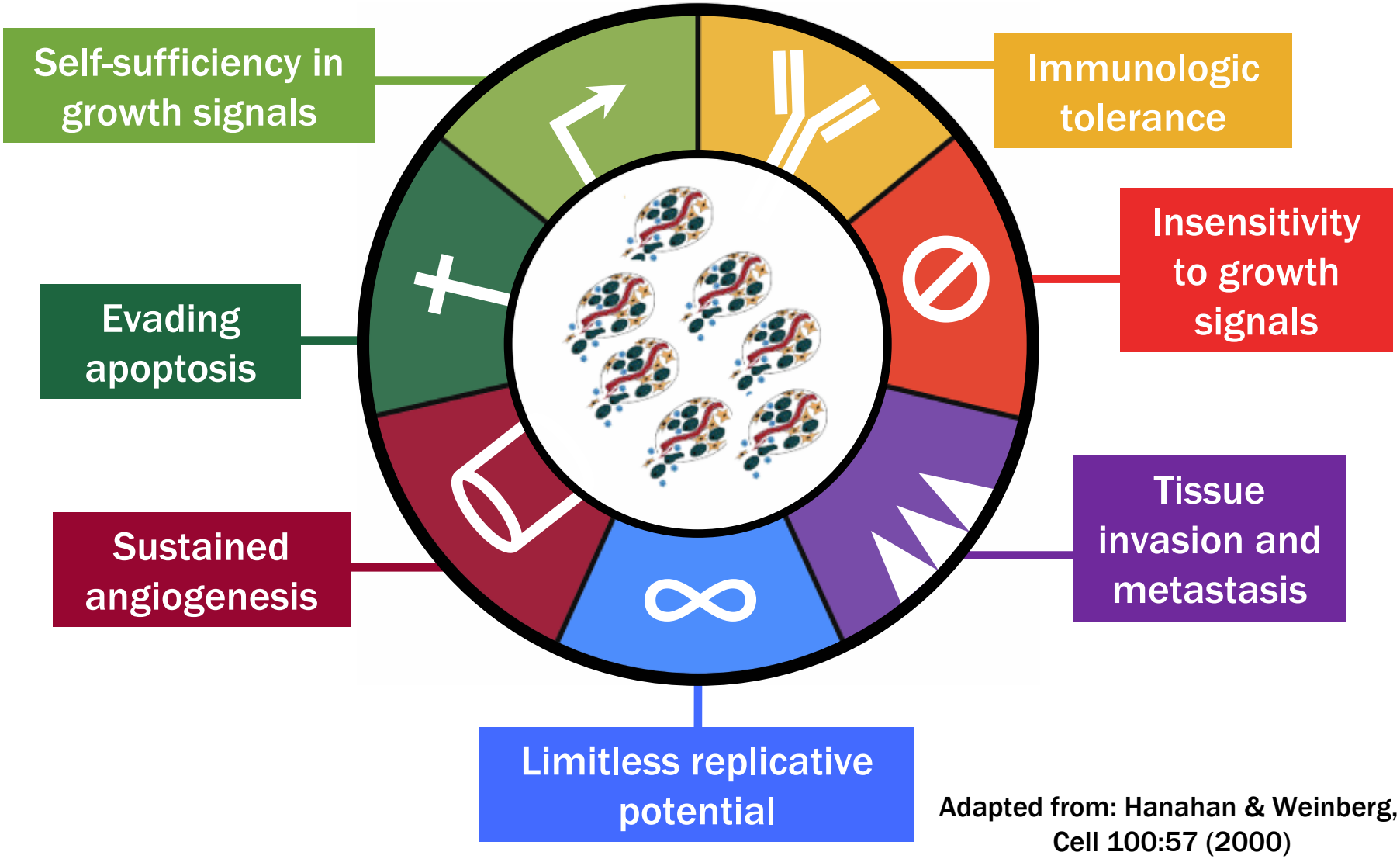
It arises from changes within the DNA of our cells during their lifespan

- Deletions
- Amplifications
- Mutations
- Translocations
- Epigenetic changes



A Complex Foe

The essential aberrations of cancer

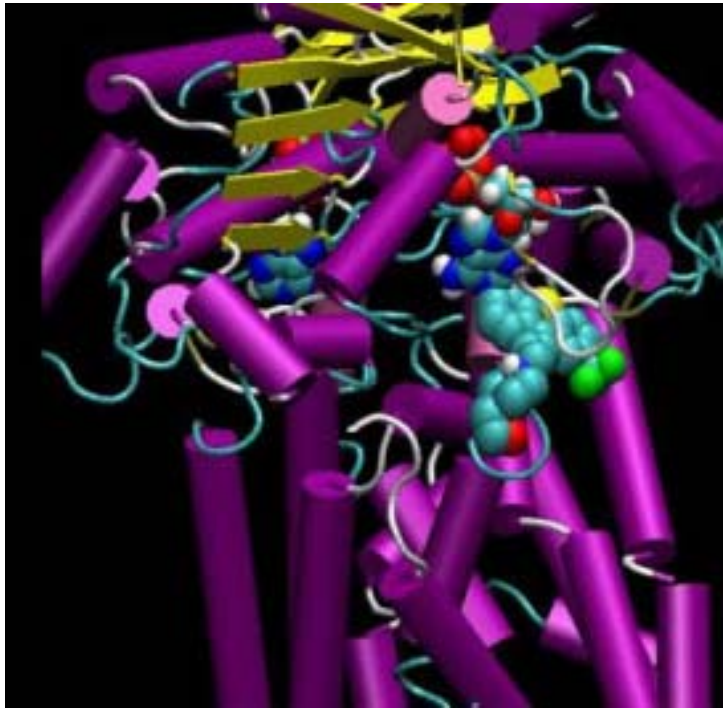


Adapted from: Hanahan & Weinberg, Cell 100:57 (2000)

The Complexity of the "Interactome"

Molecular interaction networks

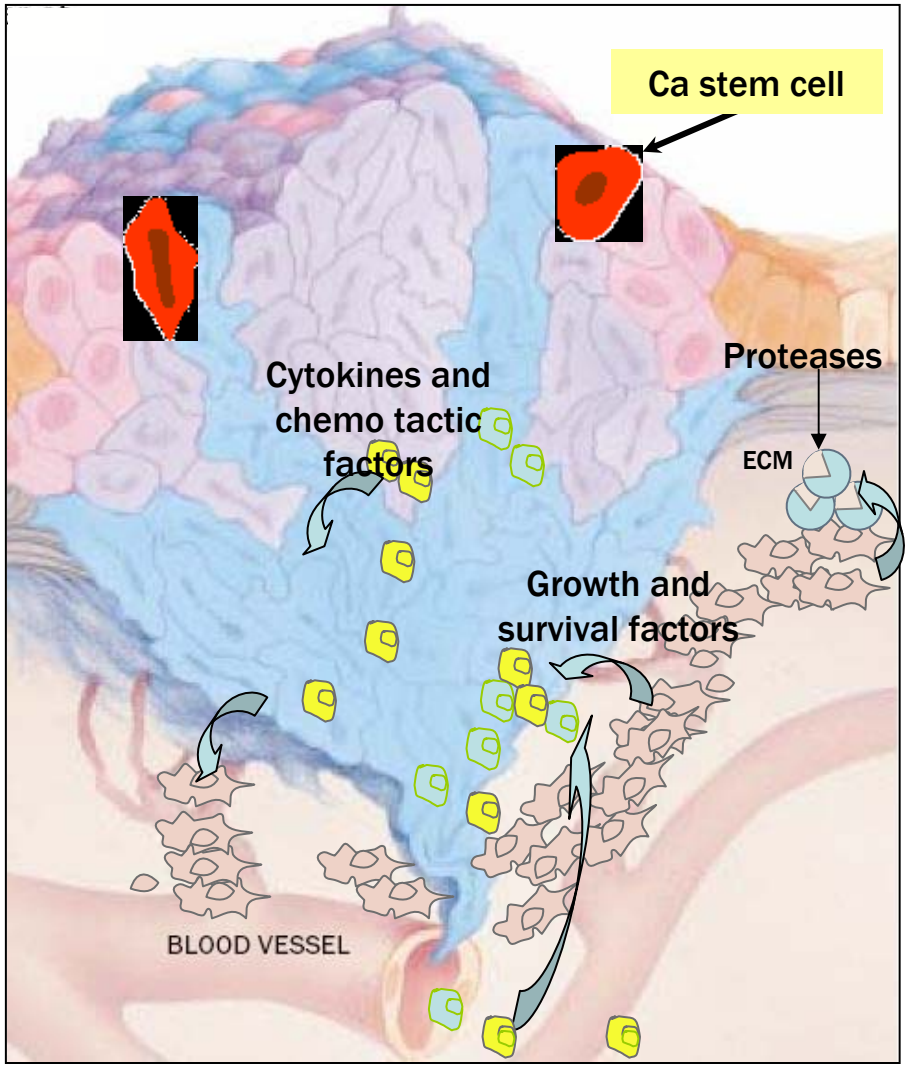
- **Protein-protein interactions**
- **Protein-DNA interactions**
- **MicroRNA-mRNA interactions**



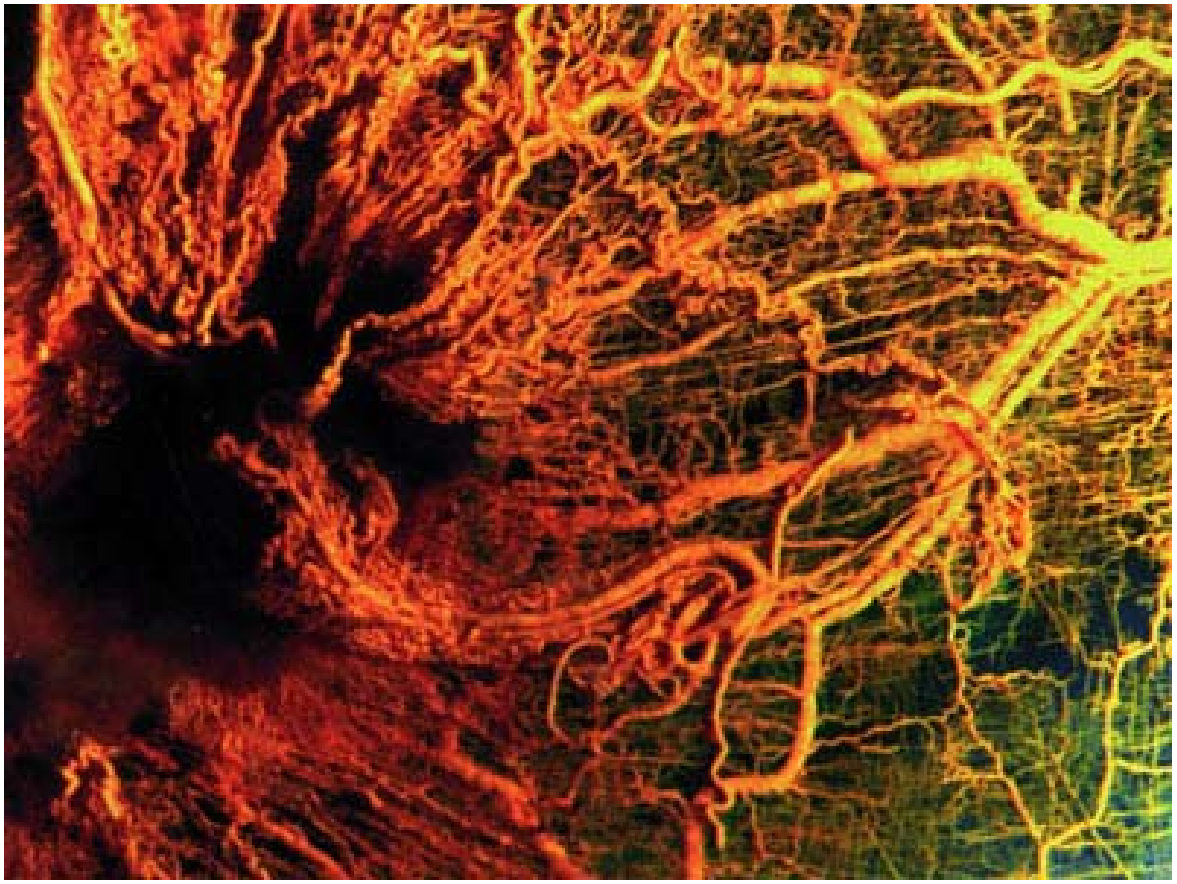
Tumors are “organs” composed of many interdependent cell types

Factors produced in cells within the tumor microenvironment can alter aspects of tumor cell behavior

- Growth factors **produced in adjacent cells** promote **cell proliferation and survival**
- Cytokines and chemo tactic factors **produced by inflammatory cells and other stroma promote cell** migration and invasion
- Proteases **produced by the mE** break down basement membrane, **altering the architecture of tissue structures and migration/invasion of tumor cells**



New Blood Vessel Growth Into Tumor

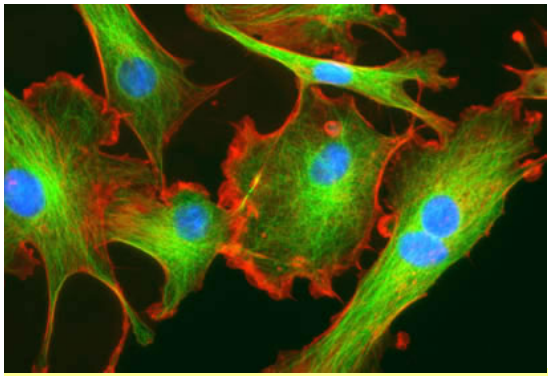


MicroRNA profiling results

Name	P-Value	Average Consistent Fold Change
hsa-miR-503	0.0072	-1.88
hsa-miR-424	0.0015	-1.81
hsa-miR-146a	0.0015	-1.80
hsa-miR-181b	0.0072	-1.80
hsa-miR-542-3p	0.0072	-1.57
hsa-miR-638	0.0072	-1.54
hsa-miR-29b	0.0266	-1.50
hsa-miR-127	0.0266	1.53
hsa-miR-148a	0.0266	1.57
hsa-miR-224	0.0002	1.61
hsa-miR-31	0.0072	3.66

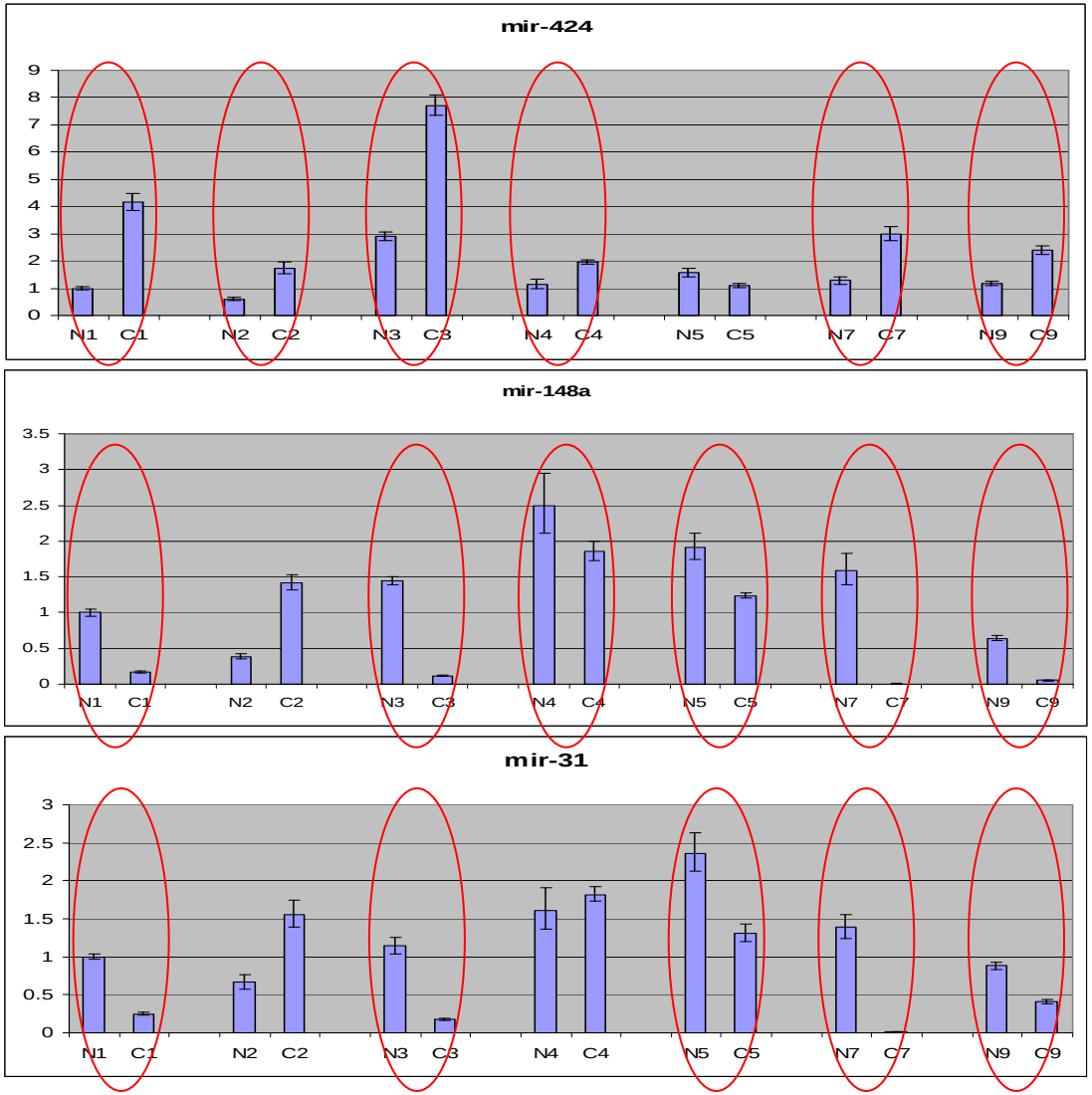
Higher in cancer fibroblasts

Higher in normal fibroblasts



Out of 553 human microRNA spotted on the chip, 11 showed more than a 1.5-fold difference between normal and cancer fibroblasts with the P-value < 0.027

Real-time PCR validation of microRNA profiling data

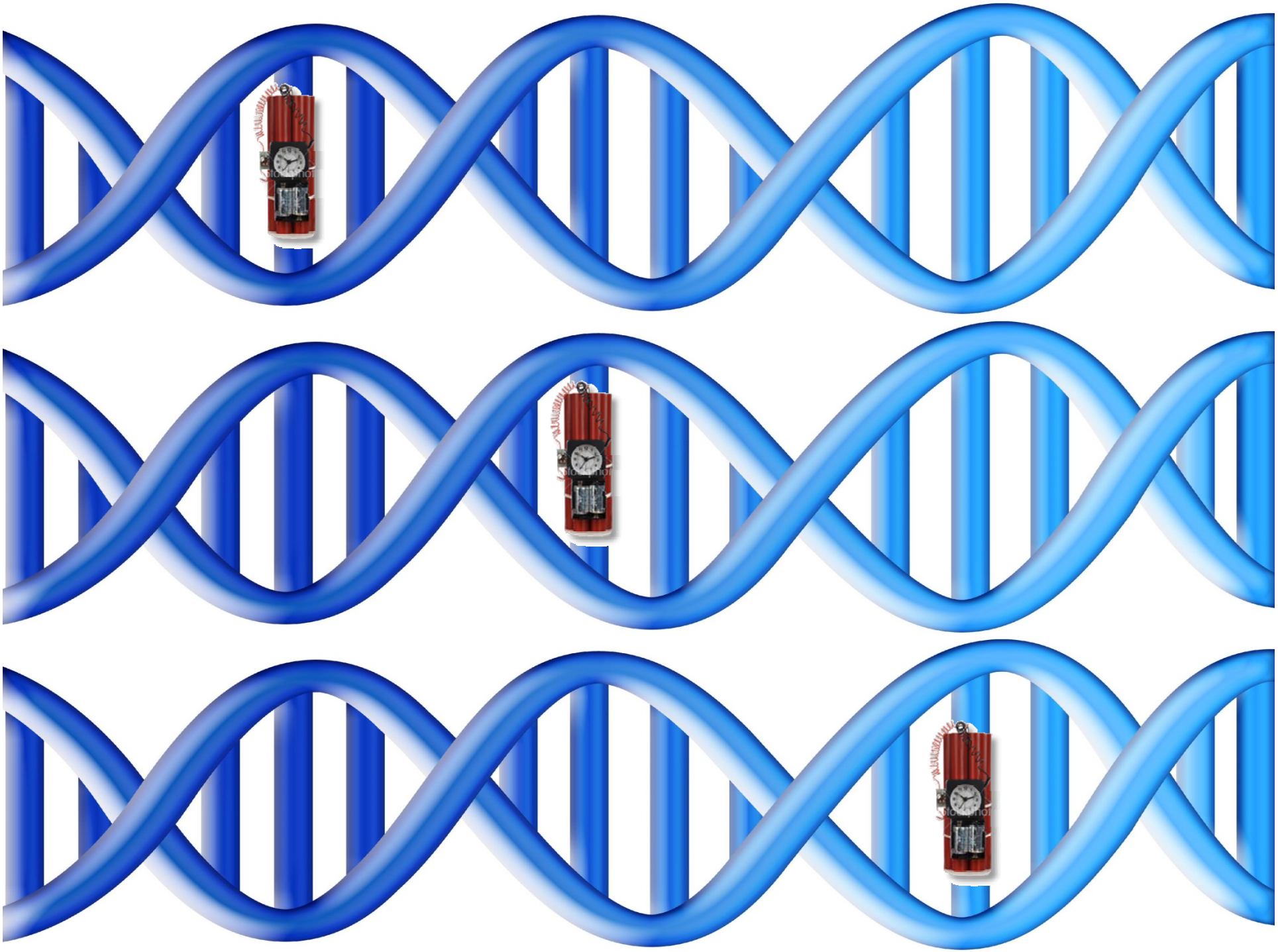


Upregulated in cancer fibroblasts

Down regulated in cancer fibroblasts

Down regulated in cancer fibroblasts


27 October 2005 | www.nature.com/nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
nature
THE HAPMAP PROJECT
Chapter and verse on human genetic variation



Identifying Genetic Markers for Prostate & Breast Cancer

Initial Study
1,150 cases/1,150 controls

→ 540,000 Tag SNPs

Follow-up Study #1
4,600 cases/ 4,600 controls

→ >28,000 SNPs

Follow-up Study #2
5,500 cases/ 5,500 controls

→ *at least* 7,600 SNPs

Fine Mapping →

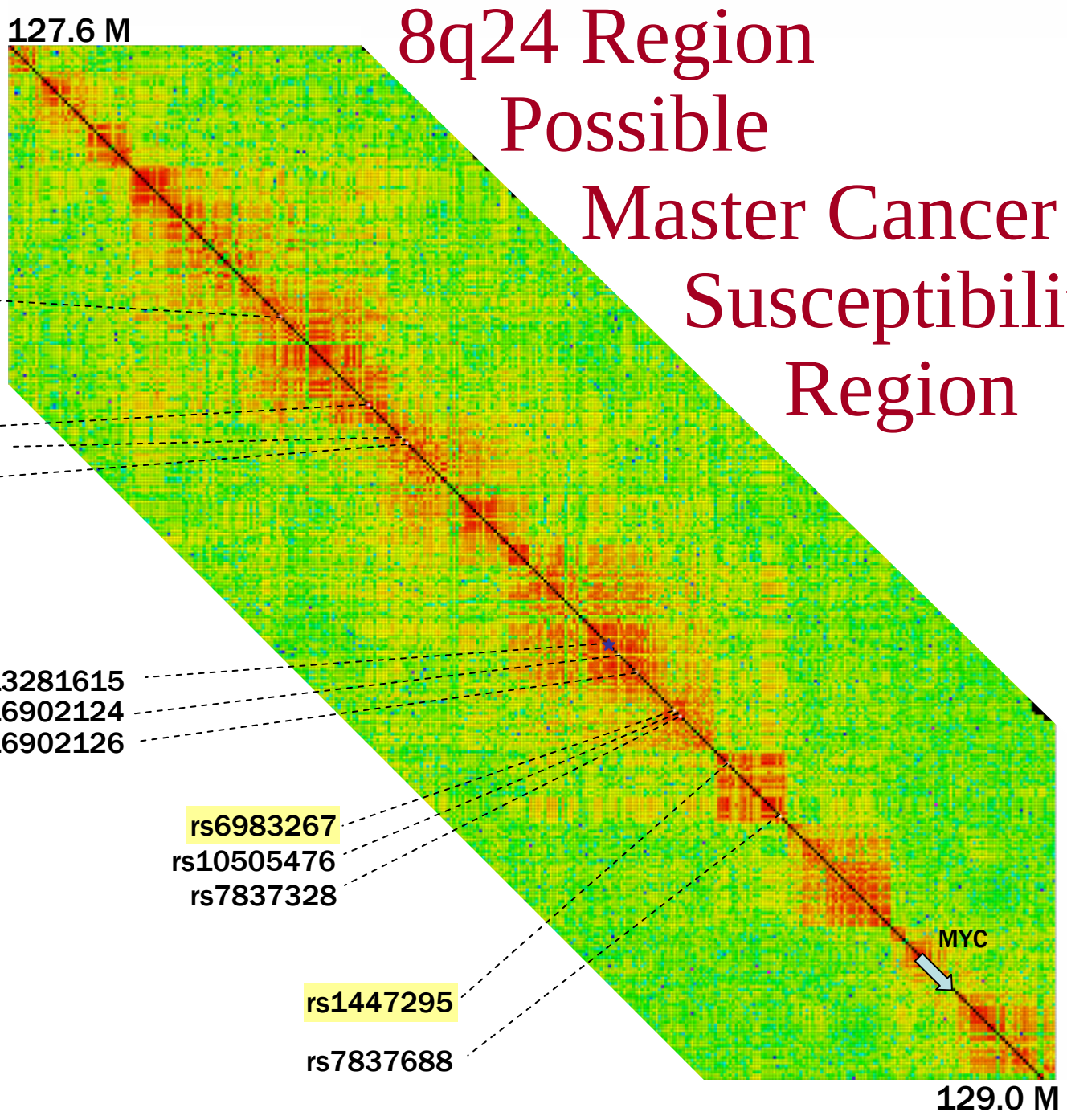
15 ±5 loci

Genotype, Haplotype, Sequence

Determine Causal Variant(s)

Stephen Chanock, M.D.
Cancer Genome Anatomy Project

8q24 Region Possible Master Cancer Susceptibility Region



Region 2
Prostate only

Breast only

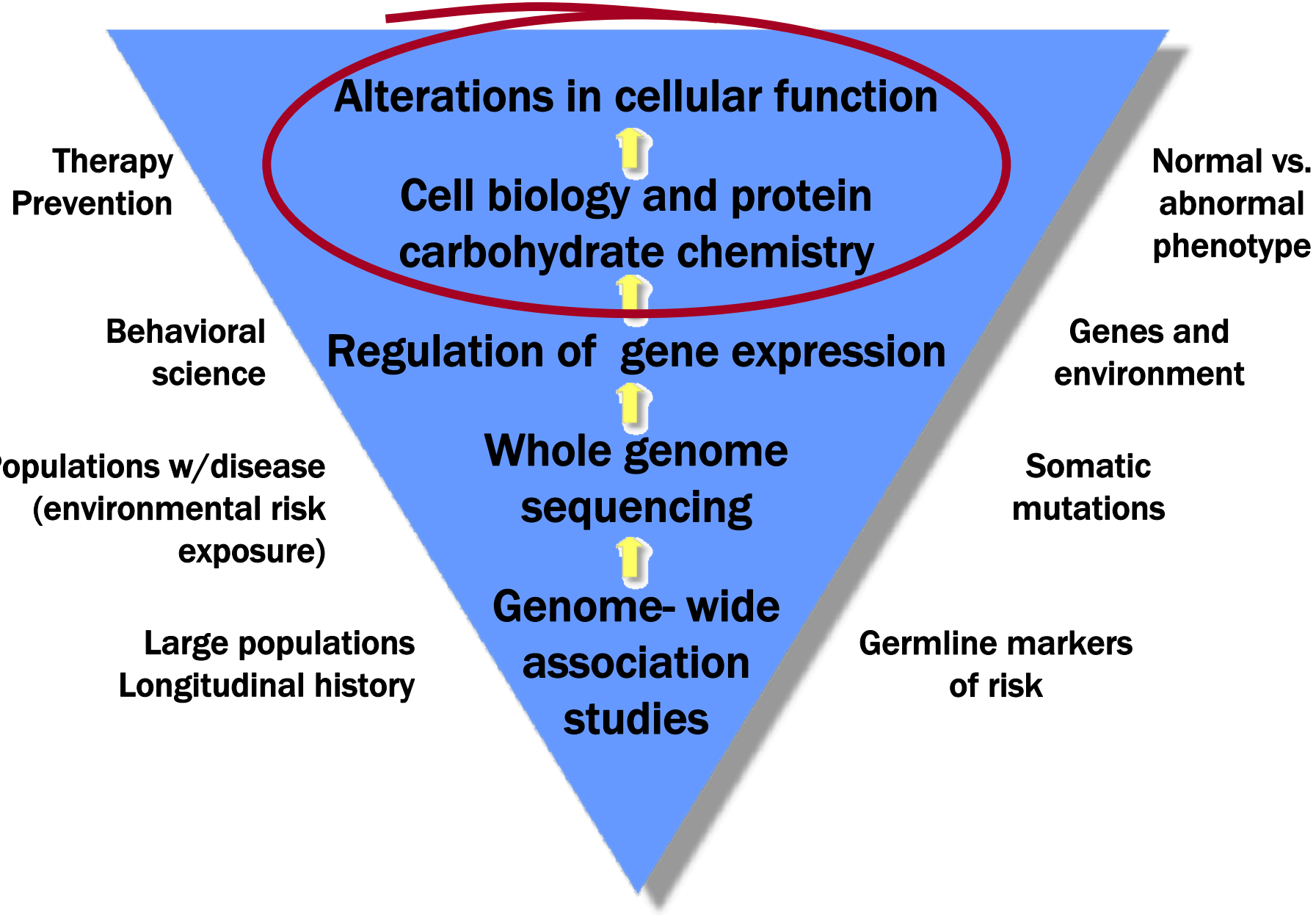
Region 3
Prostate & Colon

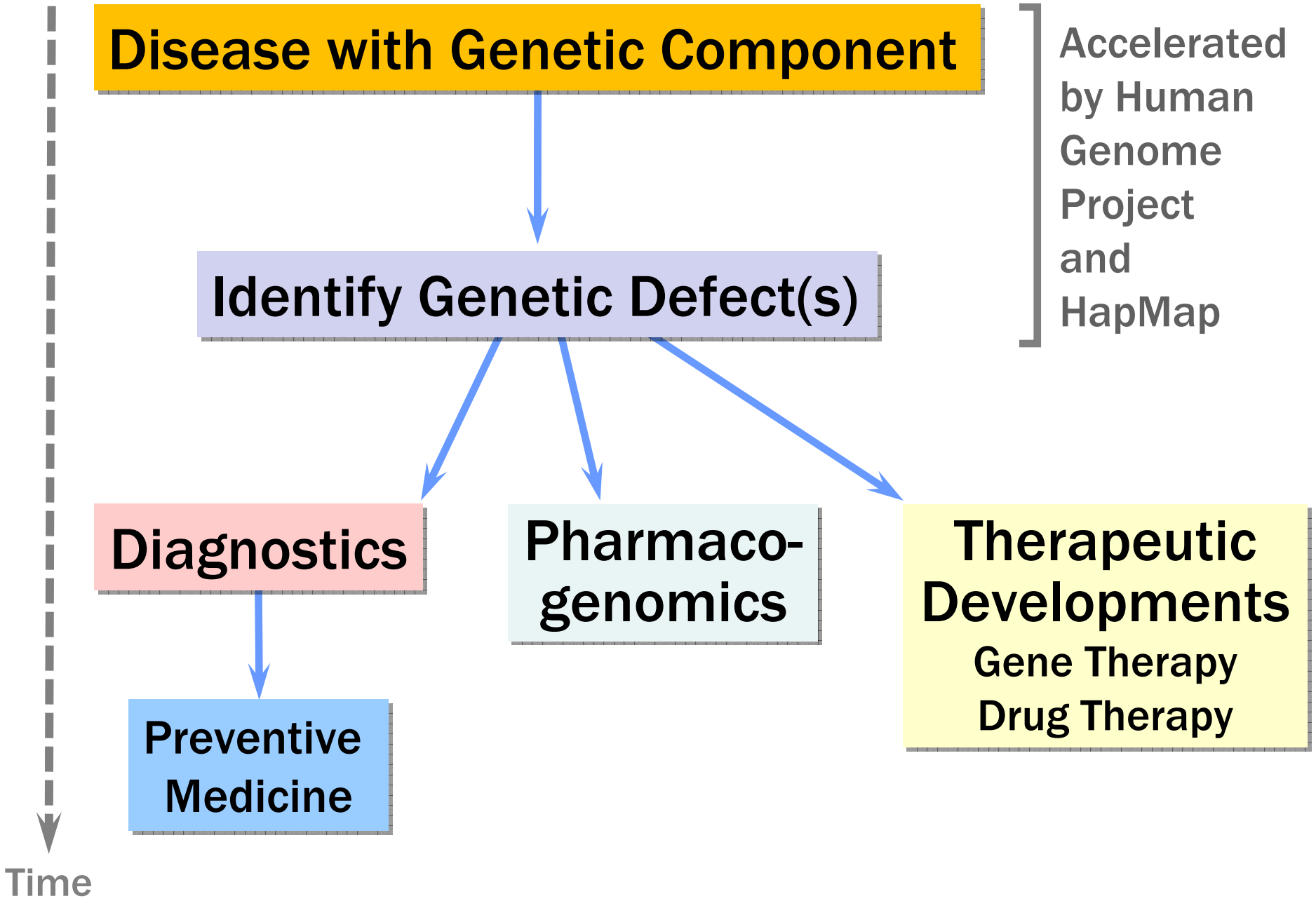
Region 1
Prostate only

The Cancer Genome Atlas

- **Pilot Project of NCI-NHGRI**
  - **Cancers:** Brain, Lung and Ovarian
- **Components**
  - **Human Cancer** Biospecimen **Core Resource**
  - **Genome** Sequencing Centers
    - **Targeting sequence in phase 1**
  - **Cancer Genome** Characterization Centers
  - Data Management**, Bioinformatics and Computational Analysis**
- **Data Access-Registered**

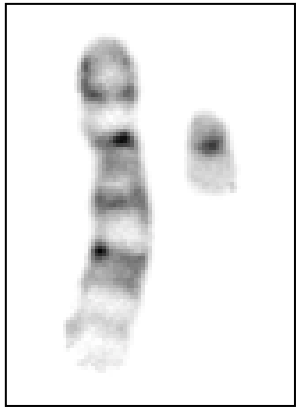
Functional Genomics

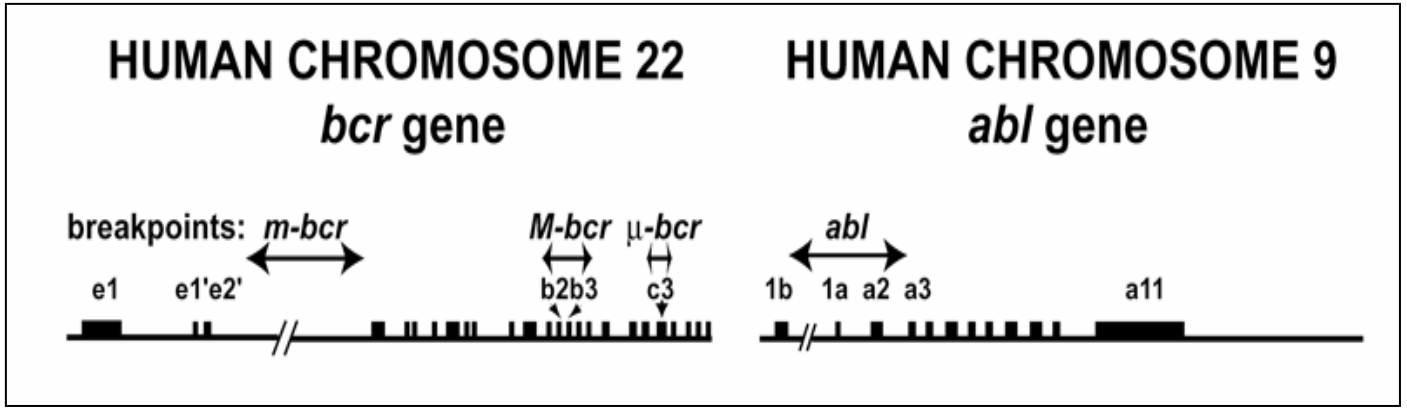


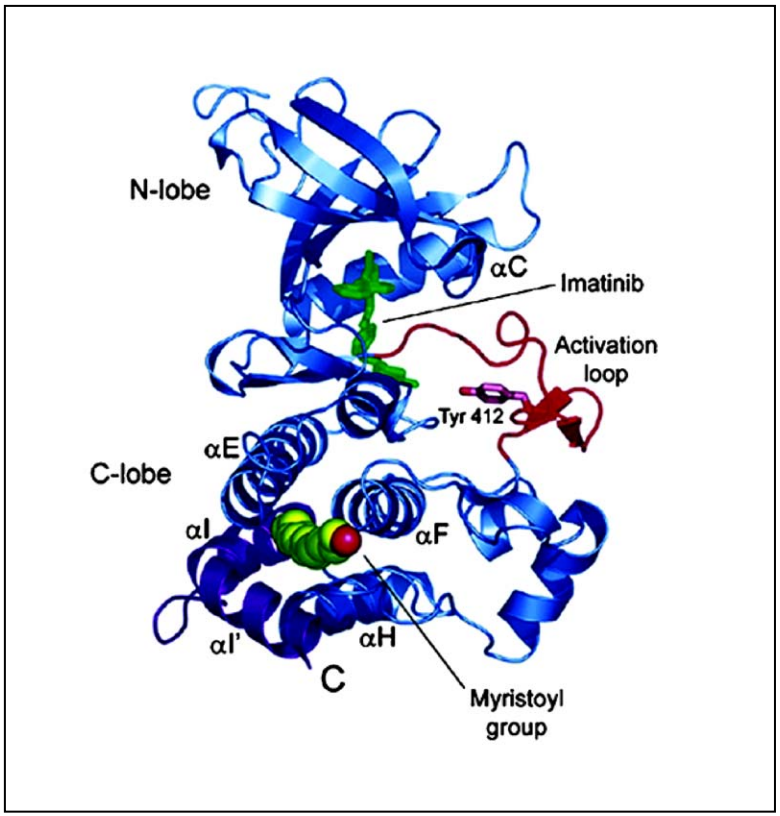


Courtesy Francis Collins, NHGRI

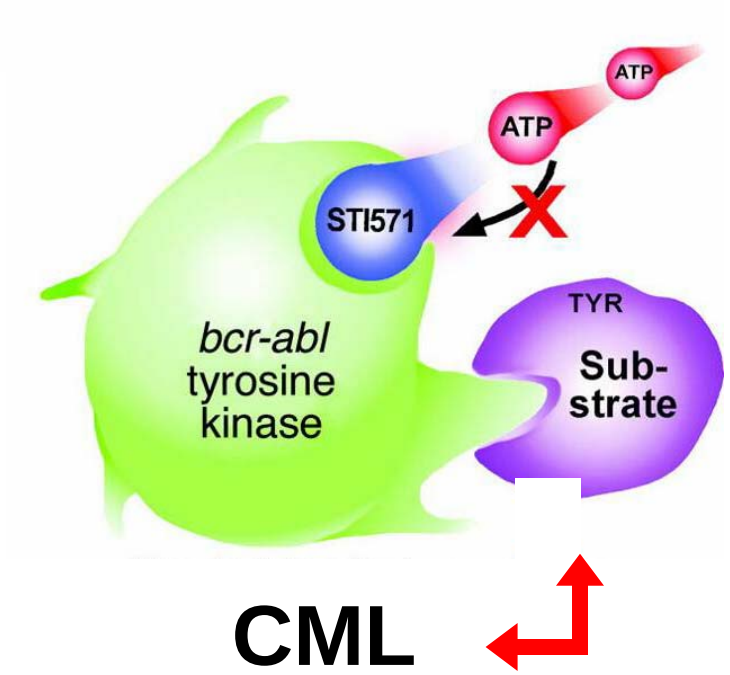
CML t(9;22)



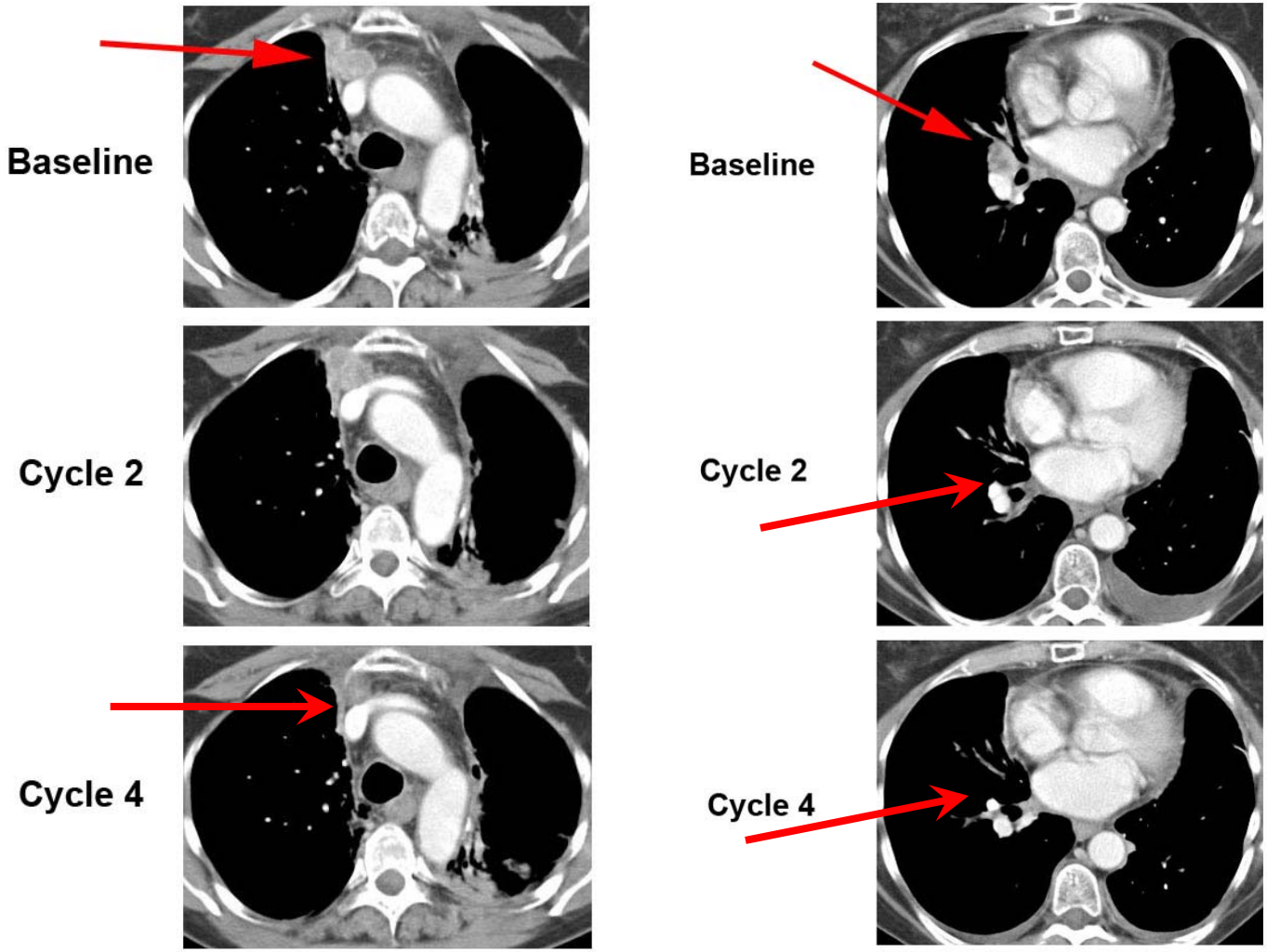




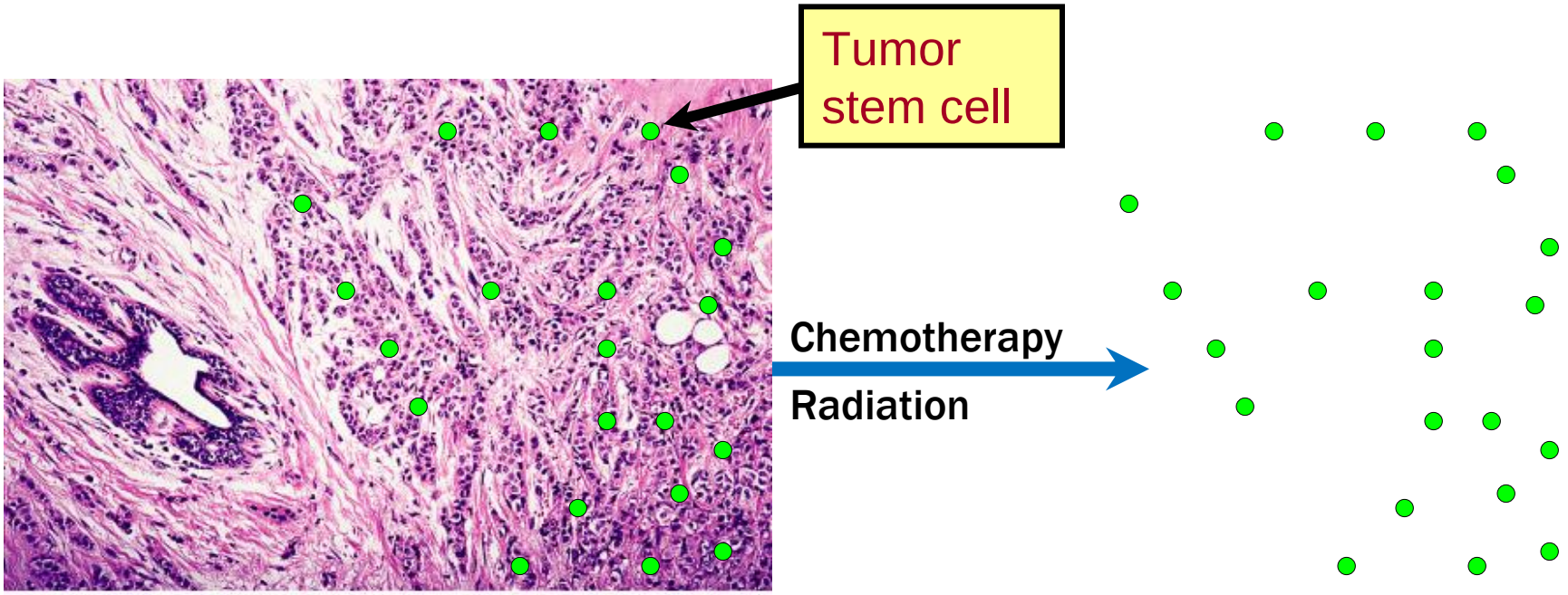
Imatinib (Gleevec)



Response in Patient with Metastatic NSCLC to Epigenetic Therapy



Cancer Stem Cells



Tumor **“Remission”**

Cancer Stem Cells

- Have ability to travel to other tissues; do not need to acquire this characteristic
- Drug resistance not acquired but present
  - High levels of ABC (ATP Binding Cassette) transporters actively efflux drugs (ABCG2, ABCB1, ABCD1)
- Molecular pathways uniquely present in HSCs and CSCs (Notch, Hedgehog (Hh), Wnt, Bmi-1)

Breast Cancer Stem Cells

	2000*	500*	200*	100*
Stem-like cells (1%) $CD44^+ CD24^- ESA^+$	10/10	4/4	4/4	1/6
Non stem cells (99%) $CD44^+ CD24^- ESA^-$	0/10	0/4	0/4	0/6

* Number of cells injected into mammary fat pads in NOD/SCID mice.

The stem cell-like cells out of a breast tumor are tumorigenic; the rest of the cells are not.

Source: Dontu, Genes Dev 17:1253 (2003)

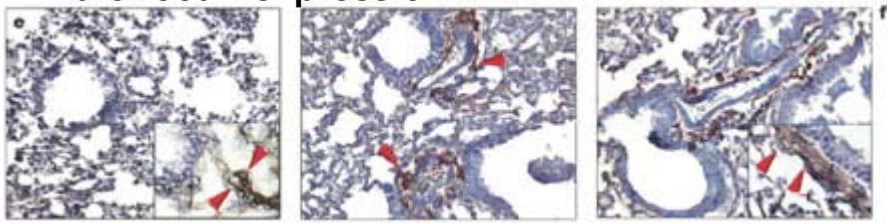
- What role do tissue stem cells play in the process of metastasis?
- What is the role of cancer stem cells/tumor initiator cells in the development of a metastatic lesion?

Chemokines & Role in the Premetastatic Niche

1. Fibronectin recruitment

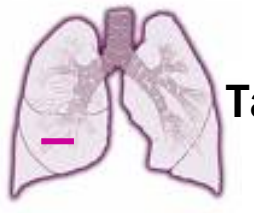
Tumor

Fibronectin expression



Baseline Day 3 Day 14

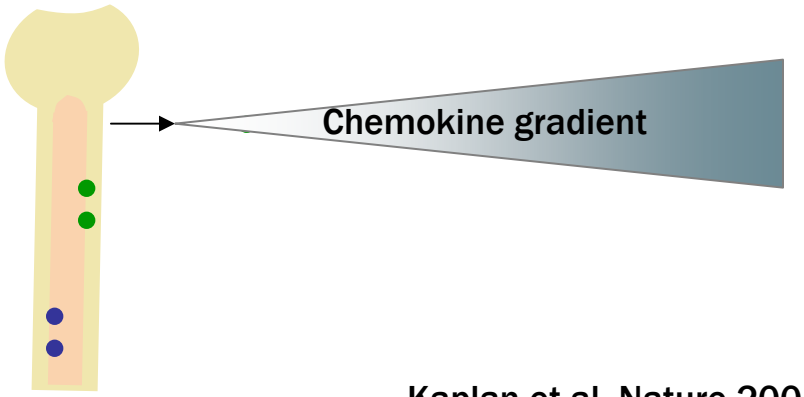
VEGF & other chemokines



Target Organ

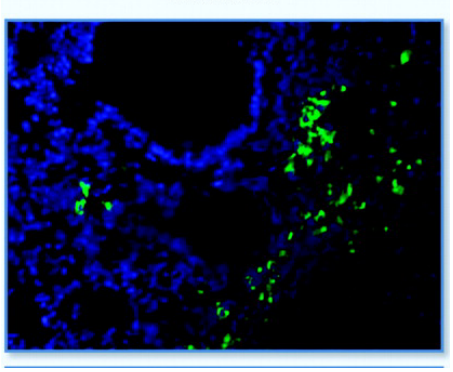
- VLA 4$^+$ VEGF R1$^+$ HPCs
- VEGF R2$^+$ EPCs
- Fibronectin fibers

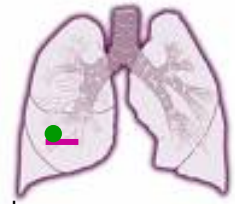
2. Premetastatic niche



Chemokine gradient

Bone marrow



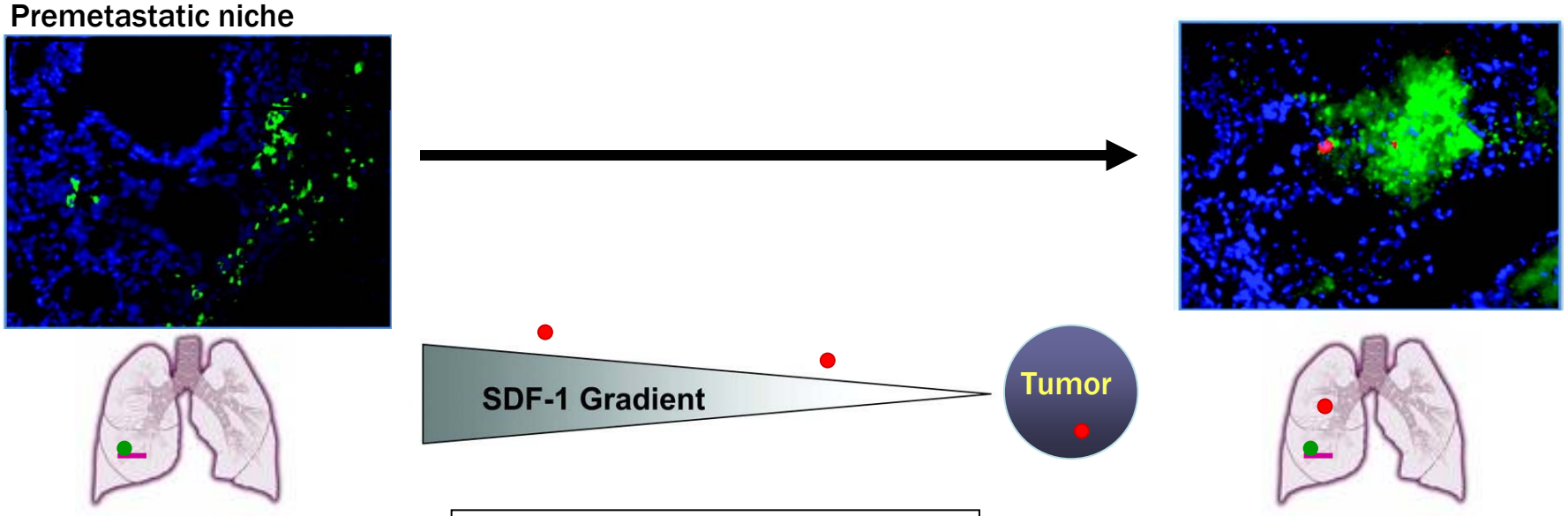


VLA 4$^+$ cells preferentially bind to fibronectin

Kaplan et al. Nature 2005;438(8): 820 -7

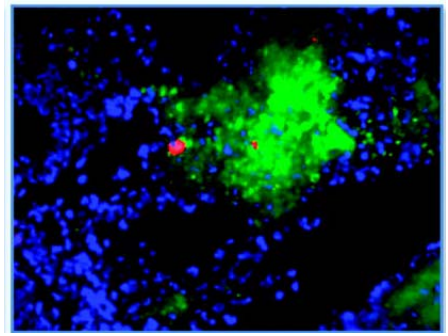
Kaplan et al. Cancer Res 2006; 66(23):11089-93

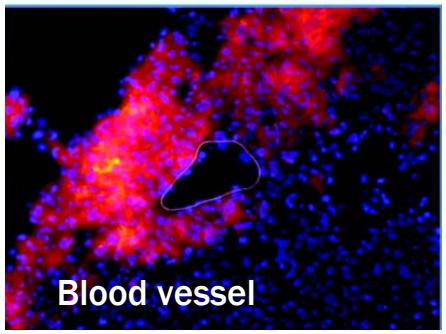
Possible Mechanism for Recruitment of Tumor Stem Cells to Premetastatic Niche

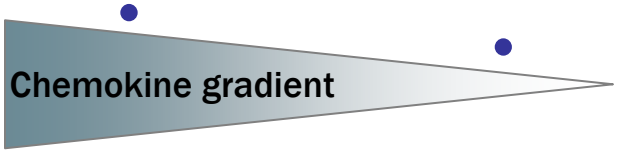


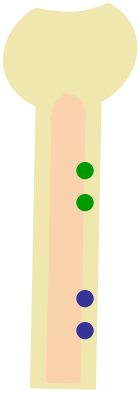
Kaplan et al. Cancer Res 2006; 66(23):11089-93

Vascular Organization of Metastasis









Bone marrow

- VLA 4^+ VEGF $R1^+$ HPCs
- VEGF $R2^+$ EPCs
- Fibronectin fibers
- CRX4 R^+ tumor cell

Kaplan et al. Cancer Res 2006; 66(23):11089-93

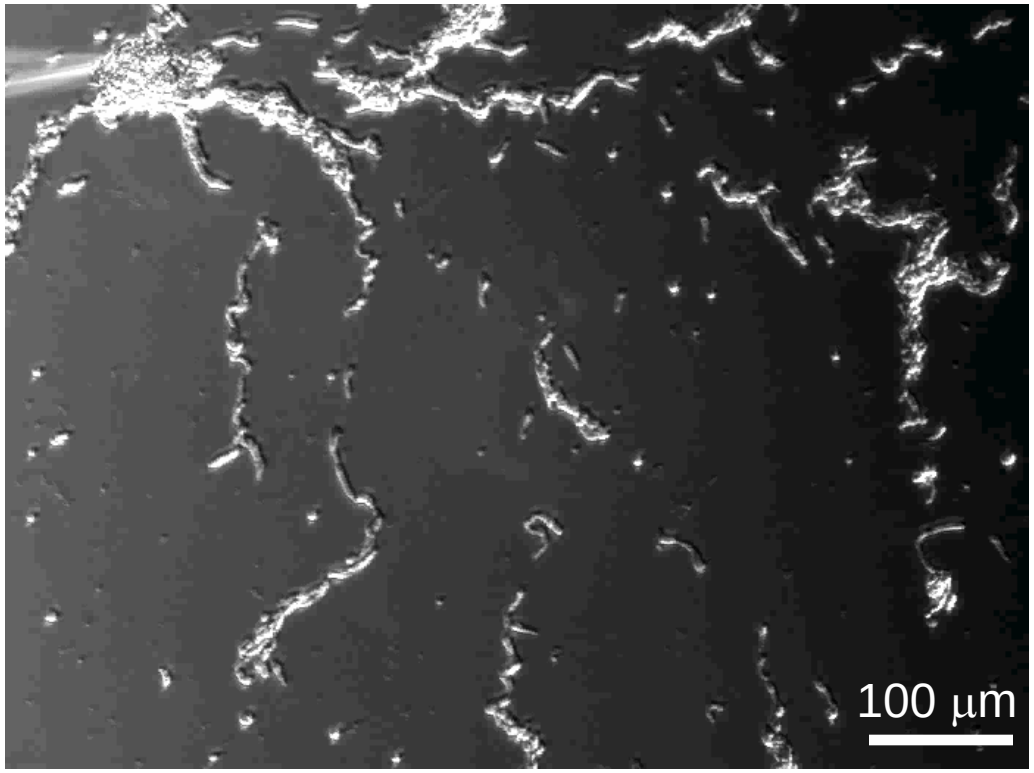
Neutrophils in a Chemoattractant (fMLP) Gradient

Carole A. Parent, Ph.D.

One frame every 10 sec.

Dictyostelium cells Migrating in a Chemical Gradient

- Cells migrate in a chemical gradient to form aggregates
- **Single-cell migration is heavily studied and well characterized**
- **In contrast, group cell dynamics are not well understood**

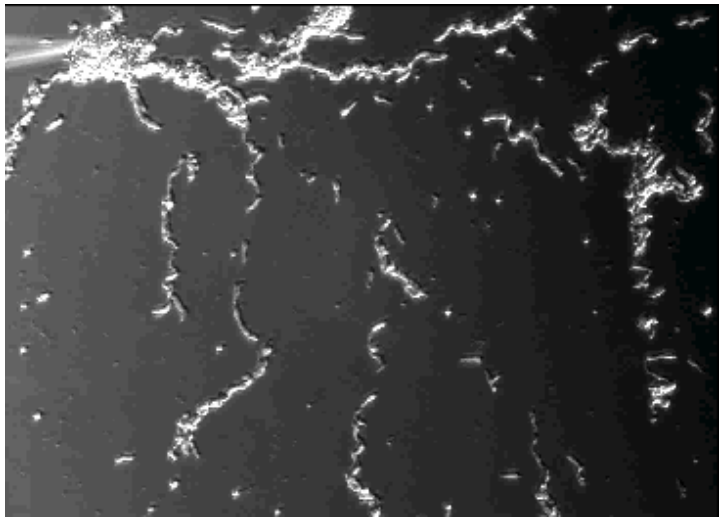


Dictyostelium **cells migrating towards a signal-releasing pipette (upper left) over the course of 2 hrs**

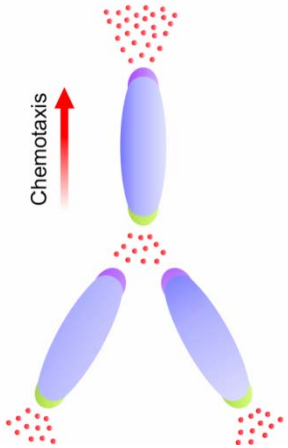
Group Cell Migration

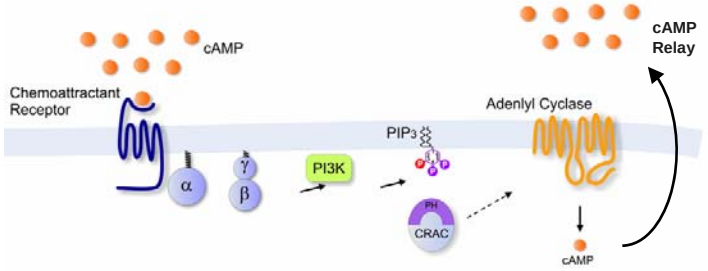
- Group cell migration is crucial to many cellular processes, including metastasis
  - How do cells migrate in groups?
  - How do cells behave inside and outside groups?
  - Which cells migrate together?
- Physical analyses and techniques can help provide answers and – when coupled to cell biological, genetic, and biochemical analyses – they can give rise to a global understanding of the molecular mechanisms at play during group migration

How do cells migrate in groups?

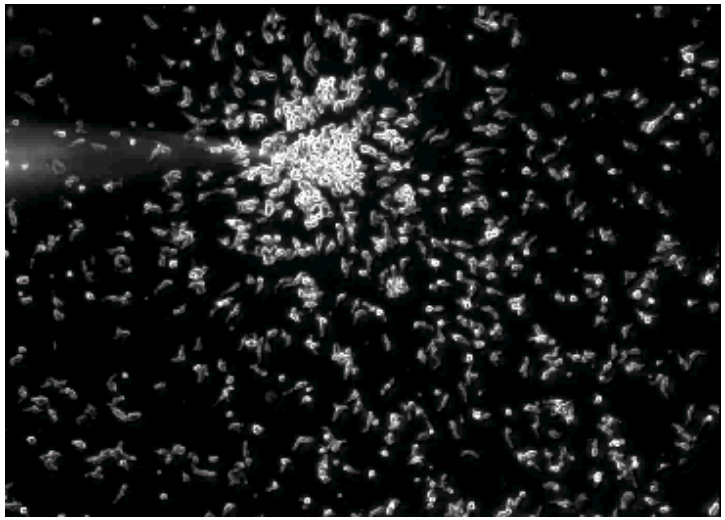


Chemical Signal

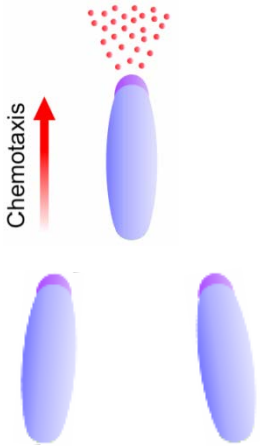


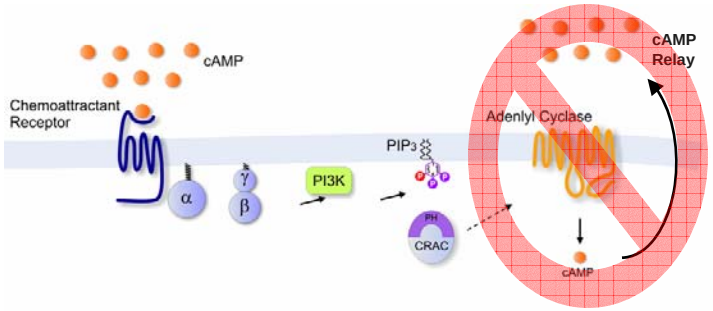


Dictyostelium **cells migrating towards a signal-releasing pipette form groups by** relaying chemical signals



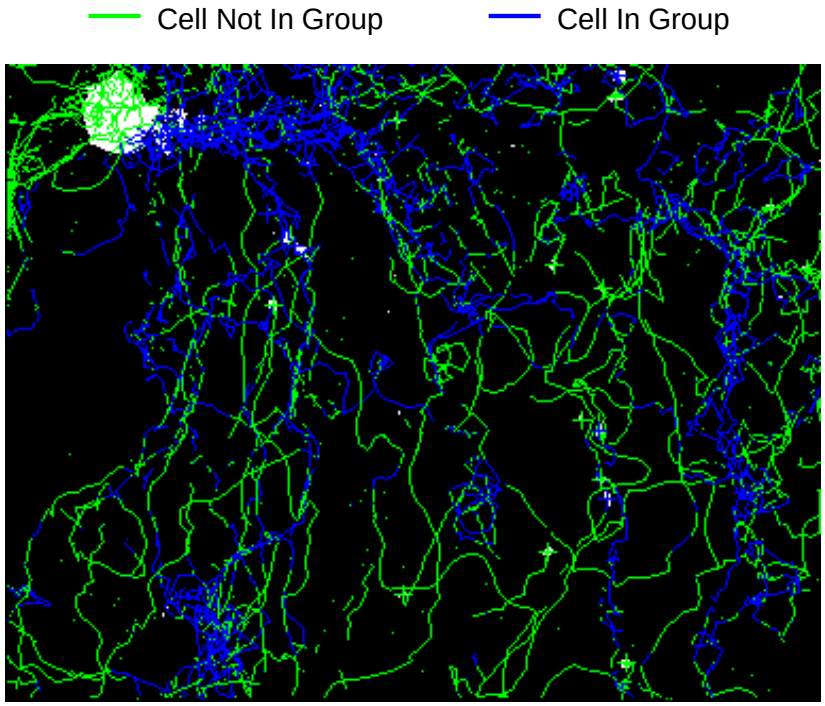
Chemical Signal



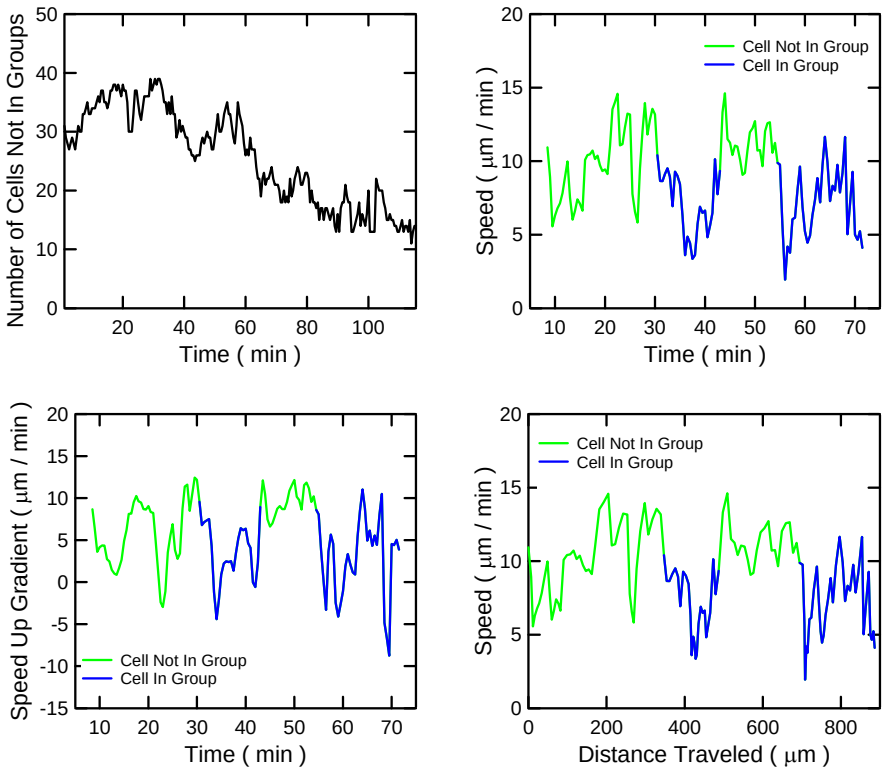


Dictyostelium **cells** defective in signal relay **do not form groups and instead migrate independently**

Computational Tools for Statistical Analysis of Complex Biological Behaviors



Automated software tracks the migration of cells from the previous movie



Various statistics for a representative cell from the movie on the left

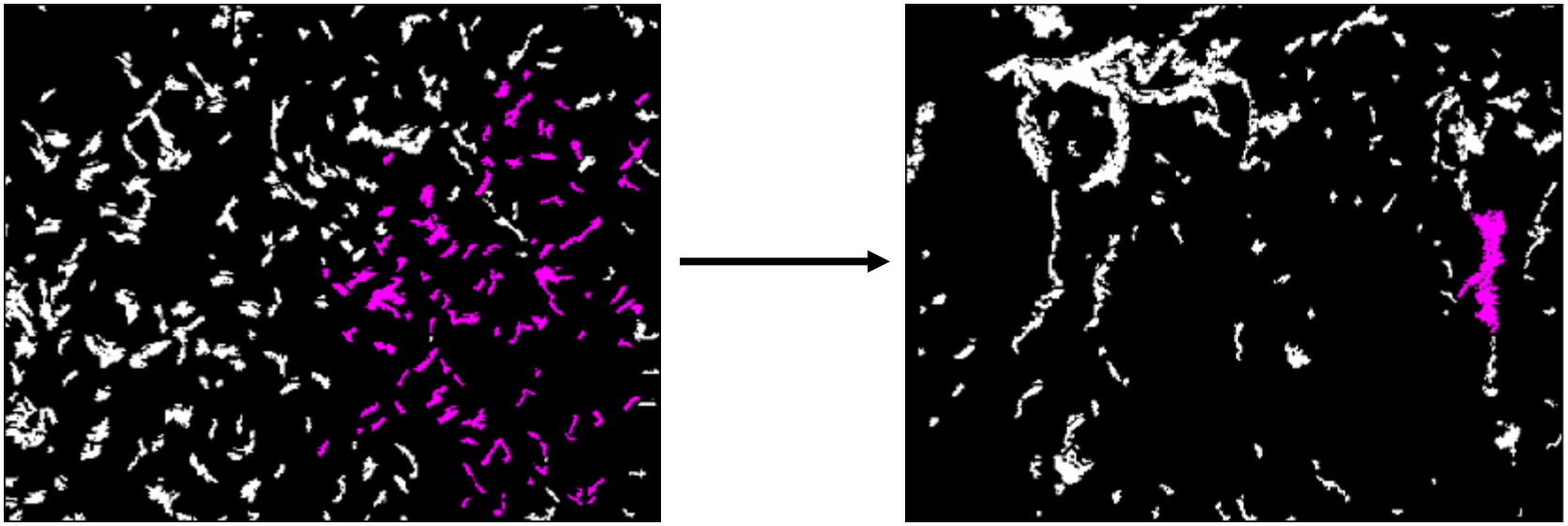
How are cellular aggregates formed?

- **Tracking software analyzes image stacks and provides statistics, such as velocity, velocity correlations, directionality, and shape**
- **By comparing the motility characteristics of wild type cells to mutants cell lines that have specific signal transduction defects, we can identify key components affecting group behavior and** build pathways that control group cell migration

Which cells decide to migrate together?

Initial Cell Positions

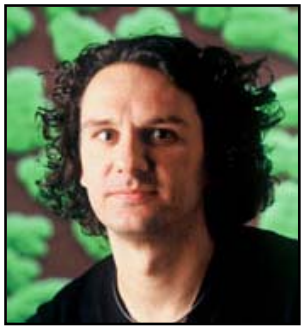
Final Cell Positions



Dictyostelium cells at 0 and 90 minutes. In the right panel a group of cells is highlighted in pink. In the left panel cells that entered this group are highlighted in the same color.

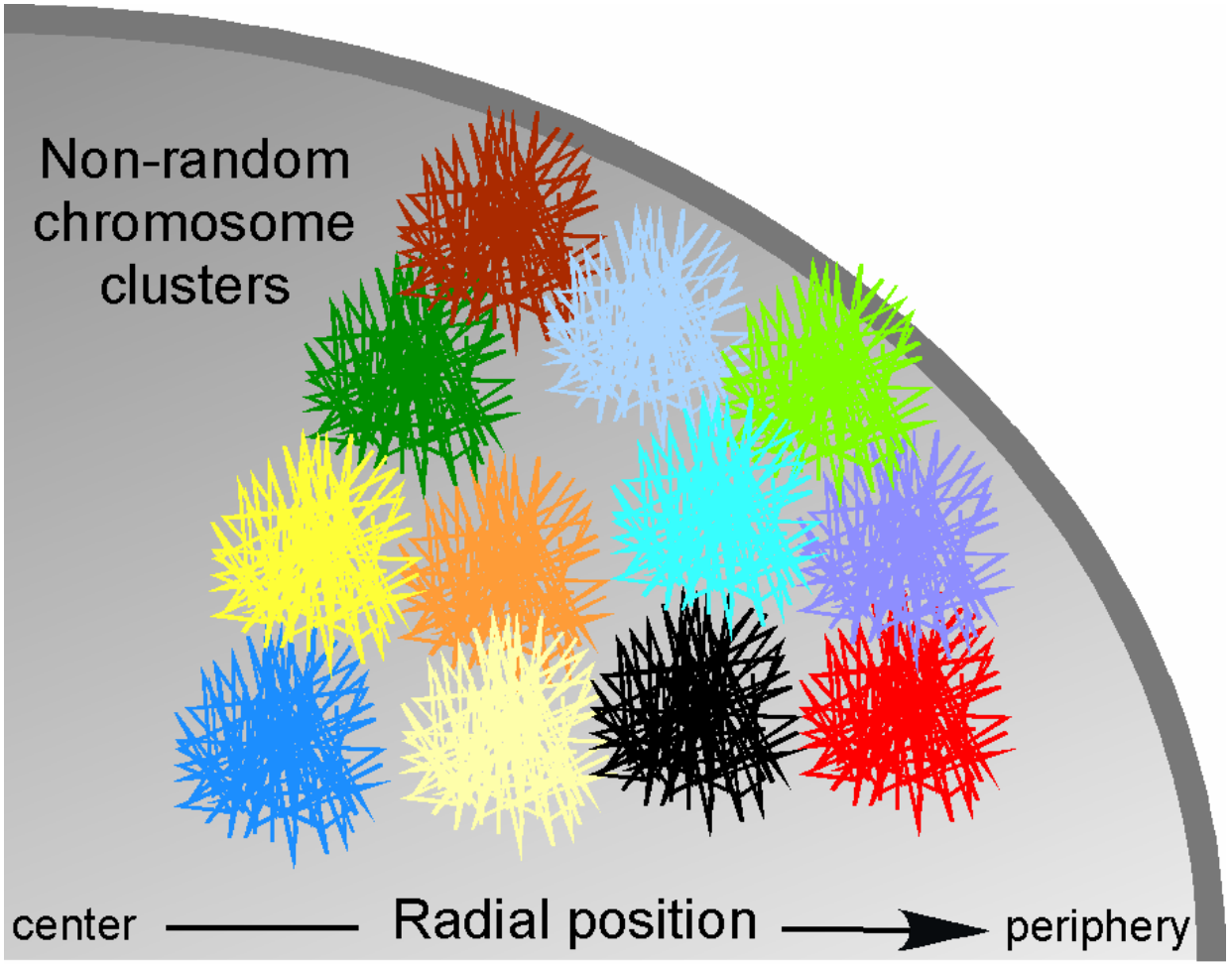
Software automatically determines which cells join which communities and allows quantitative analyses with respect to cell density, strength of chemical gradient, and mutant behavior

Organization of the Genome in 3D Space



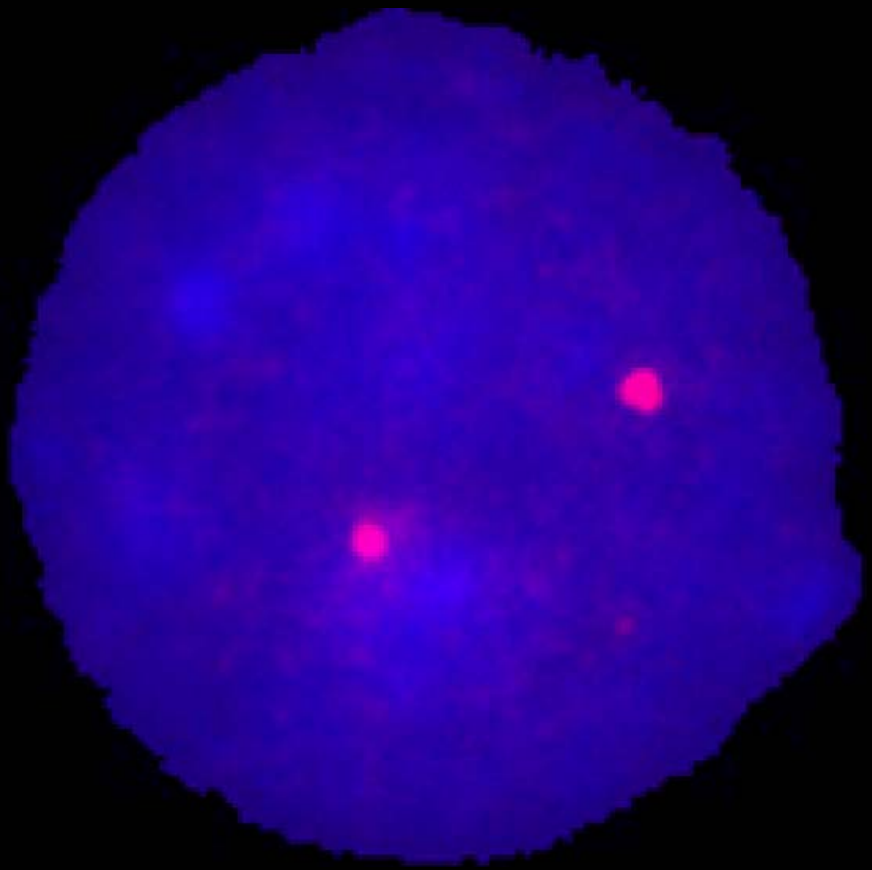
Tom Misteli, Ph.D., NCI

Karen Meaburn, Ph.D., NCI

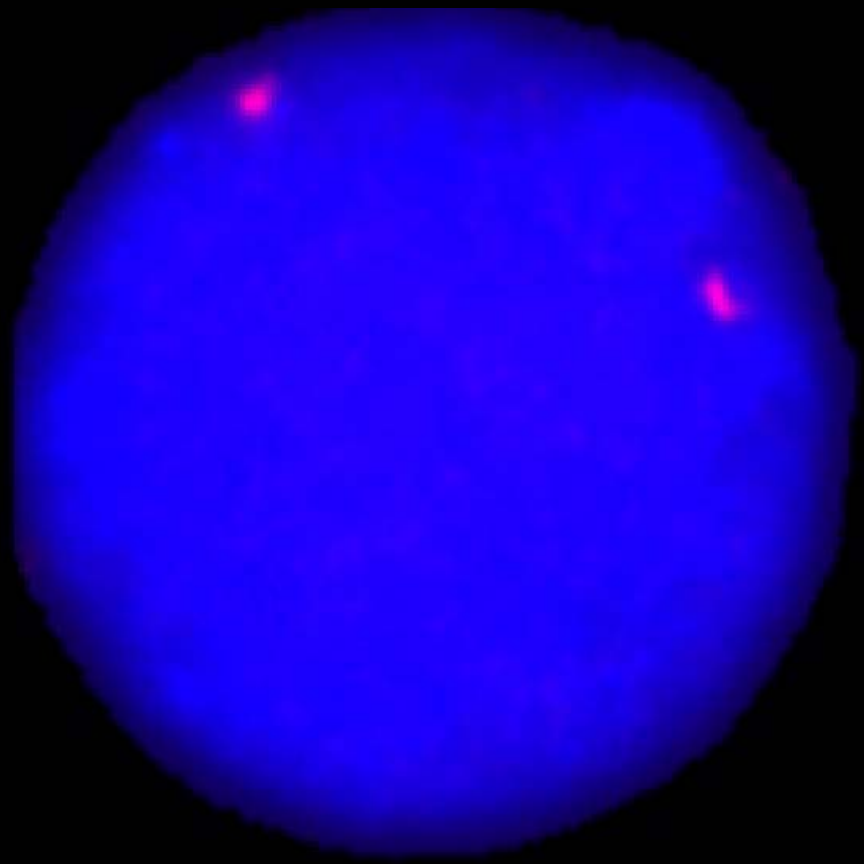


Meaburn & Misteli, Nature, 2007

Diagnostic applications

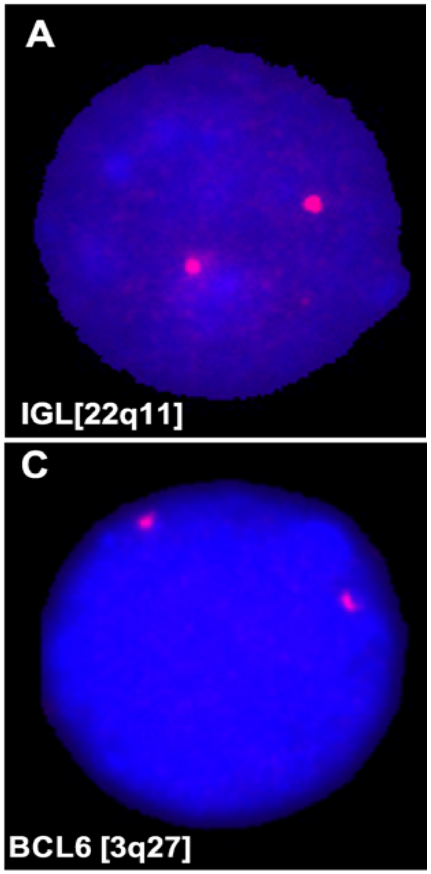


Normal



Breast tumor

Non-Random Genome Organization



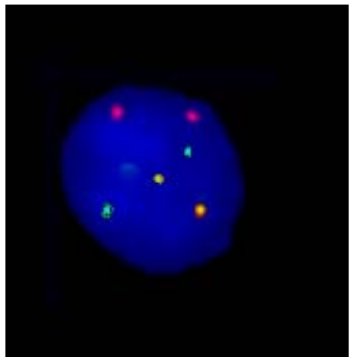
- Non-random chromosome position
- Non-random gene position
  - Cell-type
  - Tissue-specific
  - Evolutionarily conserved
  - Differentiation
  - Development

Roix & Misteli, Nature Gen., 2003
Meaburn & Misteli, Nature, 2007

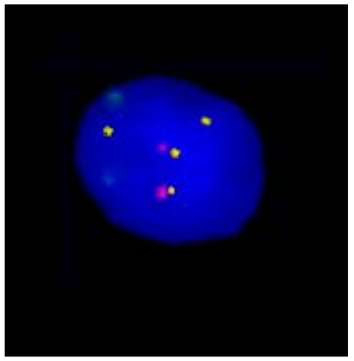
Spatial positioning as a potential diagnostic tool

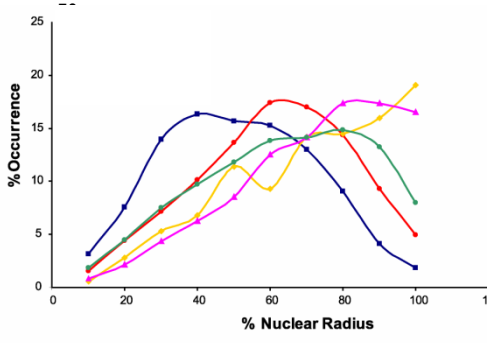
Interphase Cytogenetics

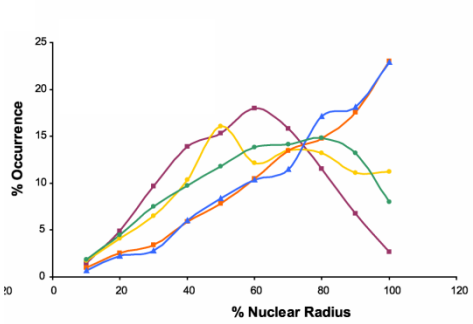
normal



(pre-) malignant

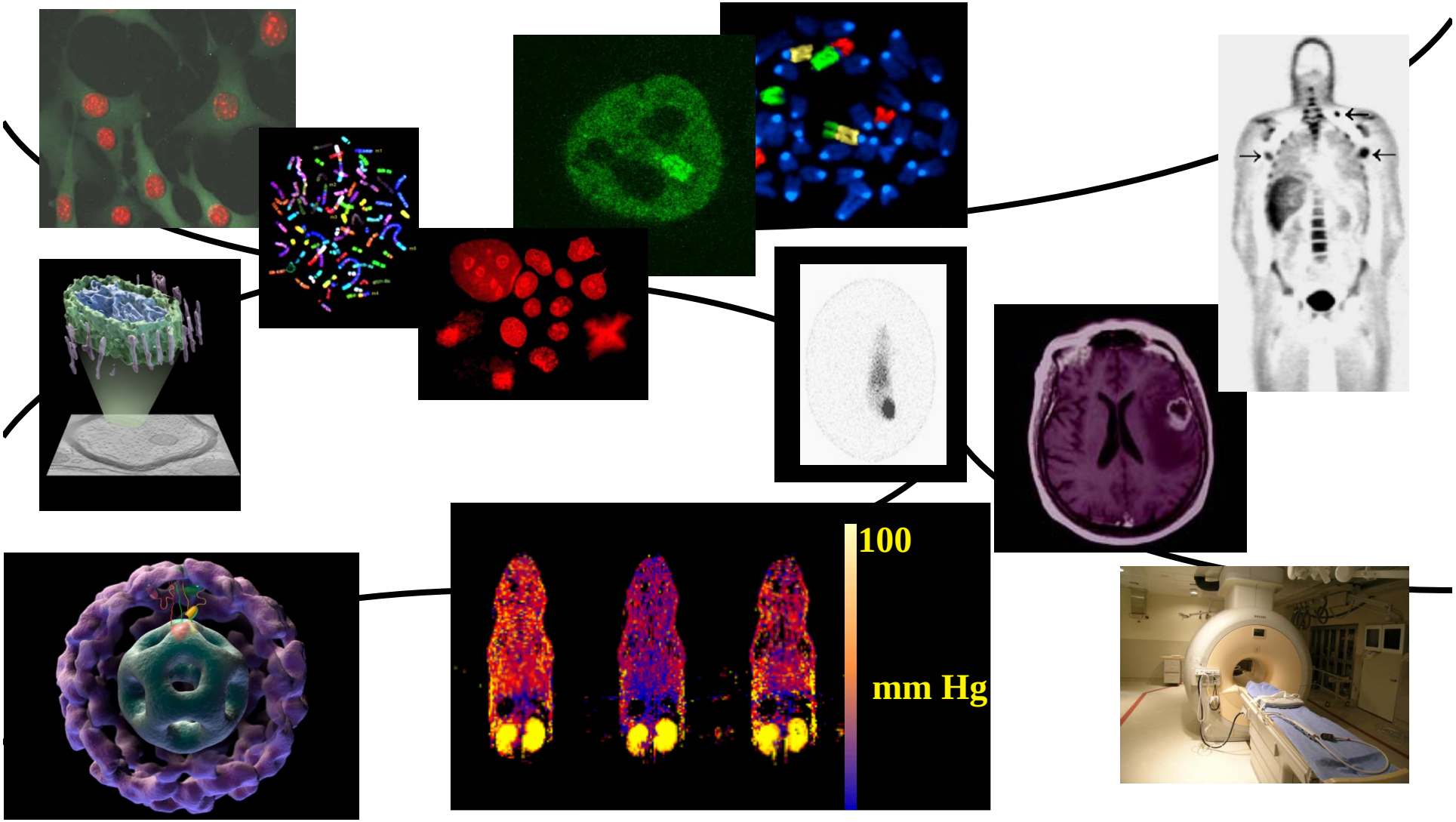




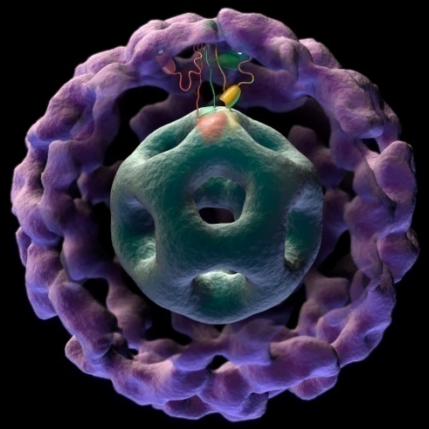


- Normal vs. malignant
- Metastatic cells
- Pre-malignant
- Metastatic potential
- Tumor type

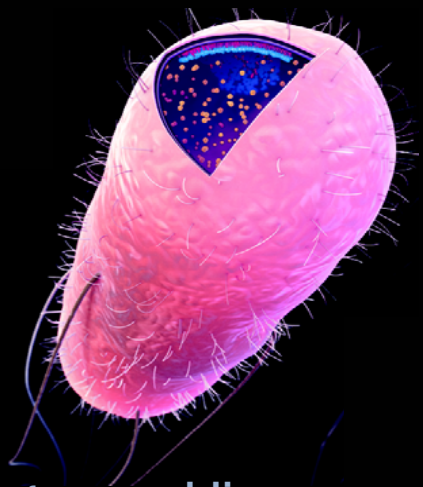
From Molecules to Man



Bridging the imaging gap



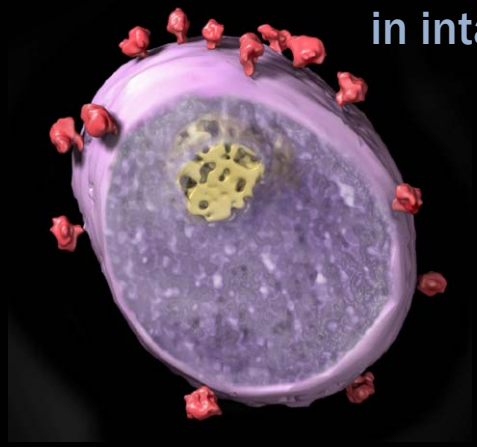
~50 nm



~2000 nm

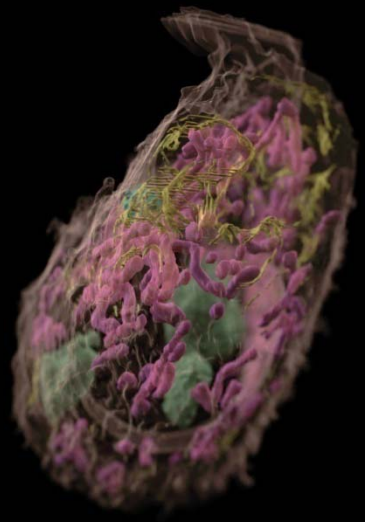
Dynamic multiprotein complexes

Signaling assemblies in intact cells



~150 nm

~30,000 nm

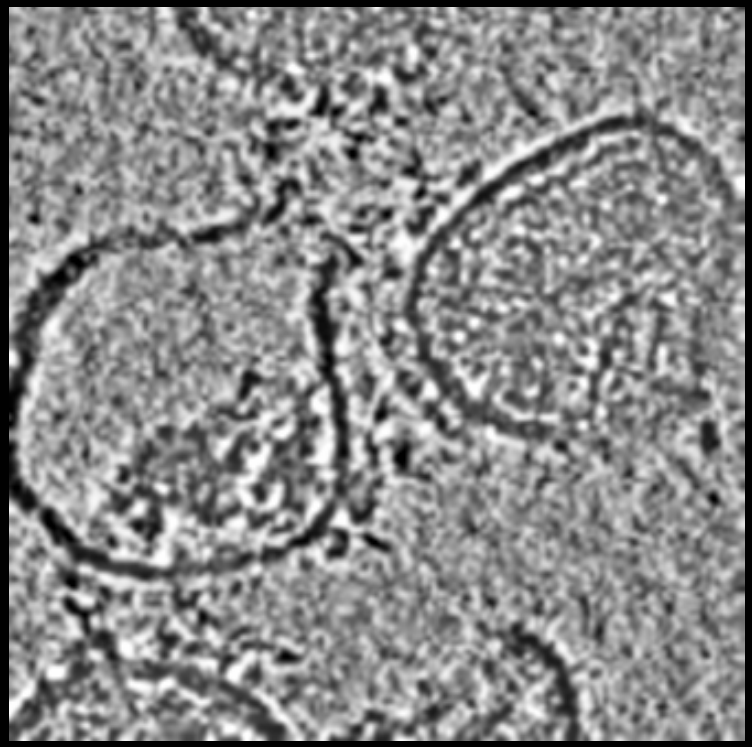


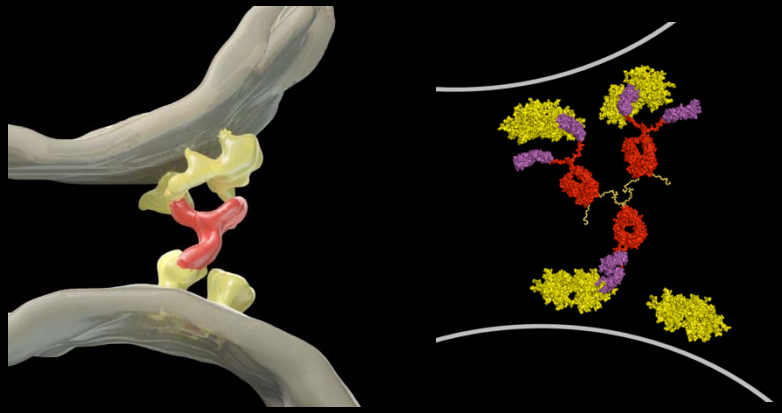
HIV structure and cell entry mechanisms

Subcellular architecture of melanoma cells

Sriram Subramaniam, Ph.D.

Molecular footprint of AIDS virus neutralization





Cryo-electron tomography of complex between viral gp120 and D1D2-IgP, a potent neutralizing antibody

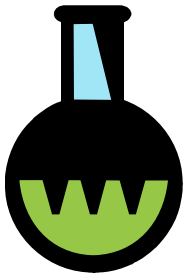
Conceptual approaches to complex problems of biology

Increasing the dimensions of biological science

- Protein-protein interactions
- Chemical gradients in vivo
- Energy and time as critical dimensions of interactions at the target
- Imaging the target reaction

Cancer Modeling Spectrum

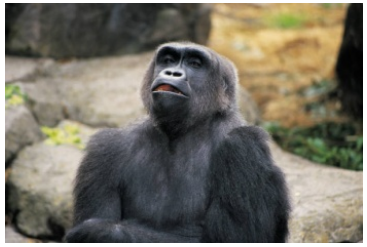
All models are problematic but some are more useful than others.



In vitro

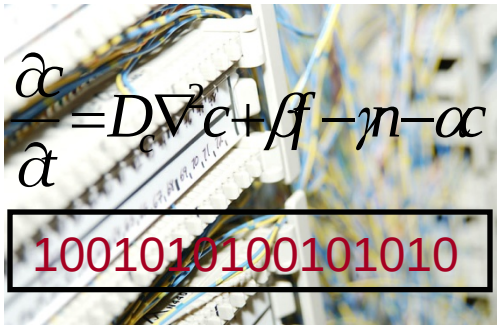
Cell Lines

Mammalian



Primates

- Simple
- Adaptable
- Modular
- Personal
- Economical



Mathematical/Computational

NATIONAL CANCER INSTITUTE ICBP

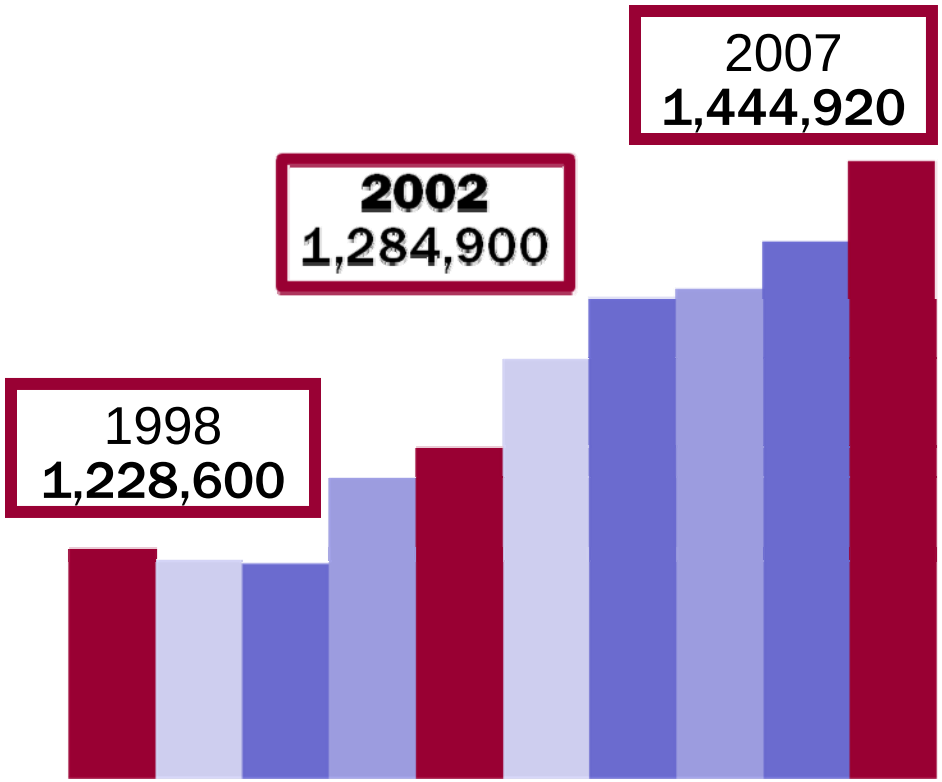
Thoughts in Conclusion

- **Never a more exciting time to work in science**
- **Rapidly advancing technology that drives complex research**
- More and more a team approach


Patients & Families
www.cancer.gov

Why What We Are Doing is So Important

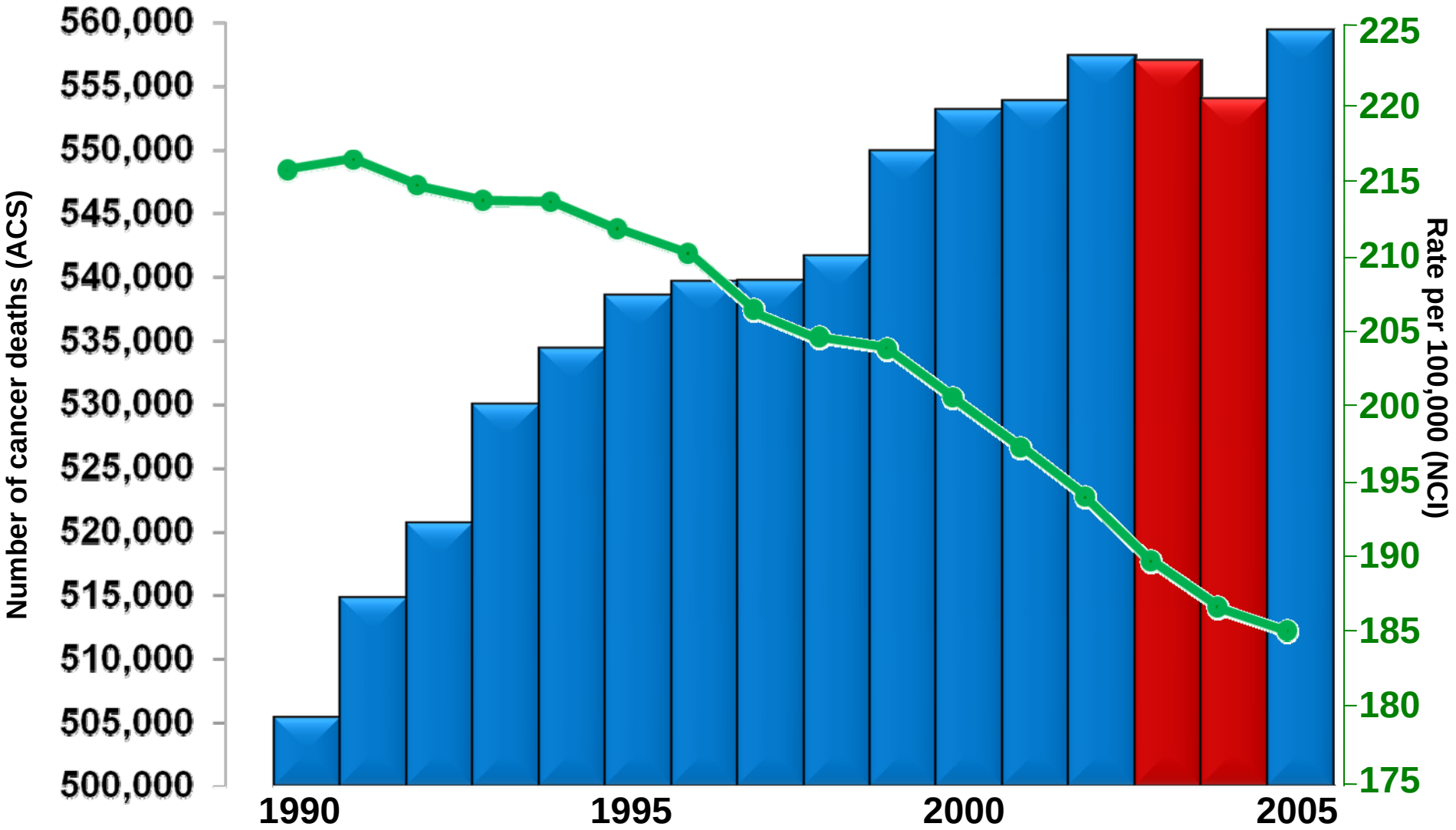
Human and Economic Burden of Cancer



Estimated # of New U.S. Cancer Cases

- **1,444,920 Americans were diagnosed in 2007**
- An estimated 559,650 died of cancer in 2007
- **$206.3 billion spent on healthcare costs for cancer in 2006**
- **47 million Americans lack health insurance**

Cancer Death Rates



A Physicist's Insight into Biology

"It is not that the subject (biology) was simple enough to be explained by mathematics, but rather that it was much too involved to be fully accessible to mathematics."

1944

$$\hat{H}|\psi\rangle = i\hbar\frac{d}{dt}|\psi\rangle$$

Erwin Schrödinger

"Biology is more like history than it is like physics. You have to know the past to understand the present; there is no predictive theory of biology just as there is no predictive theory of history. The reason is the same; both subjects are too complicated for us."

Carl Sagan