Our National Commitment to Biomedical Research: Return on Investment

Presentation to the Congressional
Biomedical Research Caucus
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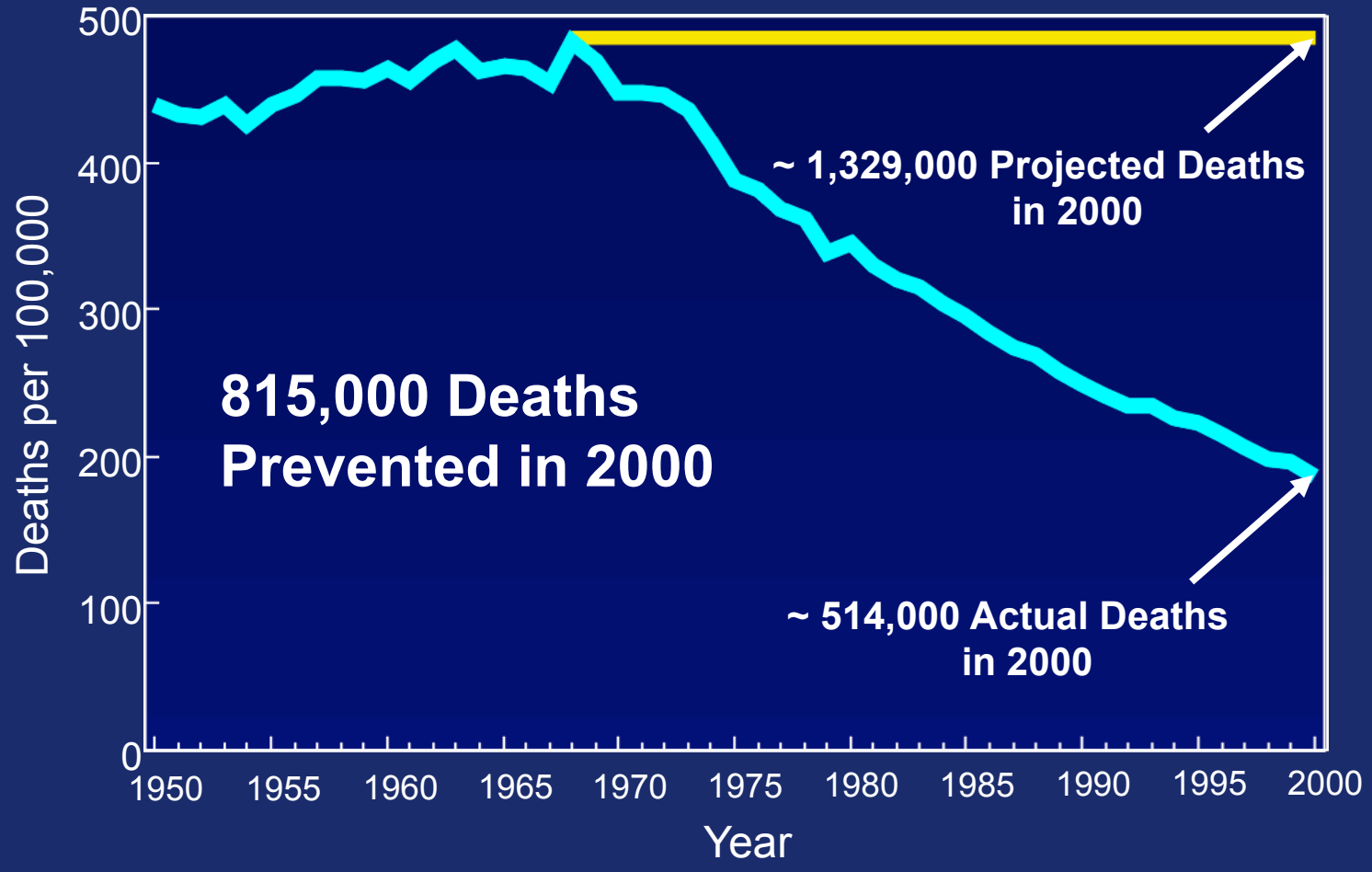
What is the Yield from NIH Funding?

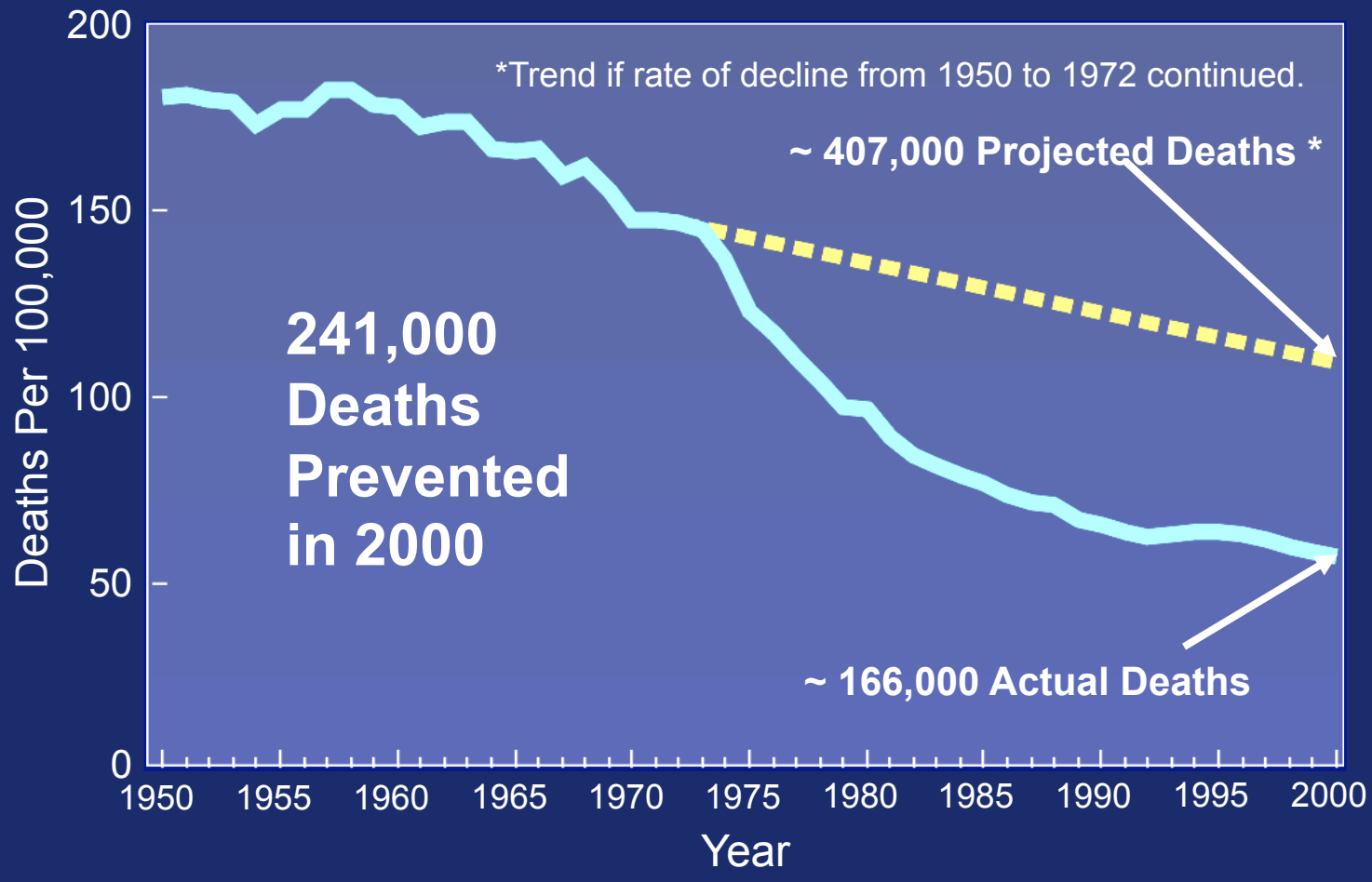
- Improvements in our Nation's health
- Development of a whole new biotechnology industry
- Greatly improved ability to tackle new and ongoing biomedical challenges
  - the continuing scourge of cancer
  - the alarming increase in obesity and type II diabetes
  - diseases of aging - Parkinson's, Alzheimer's, Macular degeneration (blindness)
  - emerging infectious diseases (AIDS, SARS etc)
  - the threat of bioterrorism

Coronary Heart Disease
Age-Adjusted Death Rates: Actual and Expected
United States, 1950-2000



Source: NIH/E.Zerhouni

Stroke Age-Adjusted Death Rates: Actual and Expected



Source: NIH/E.Zerhouni

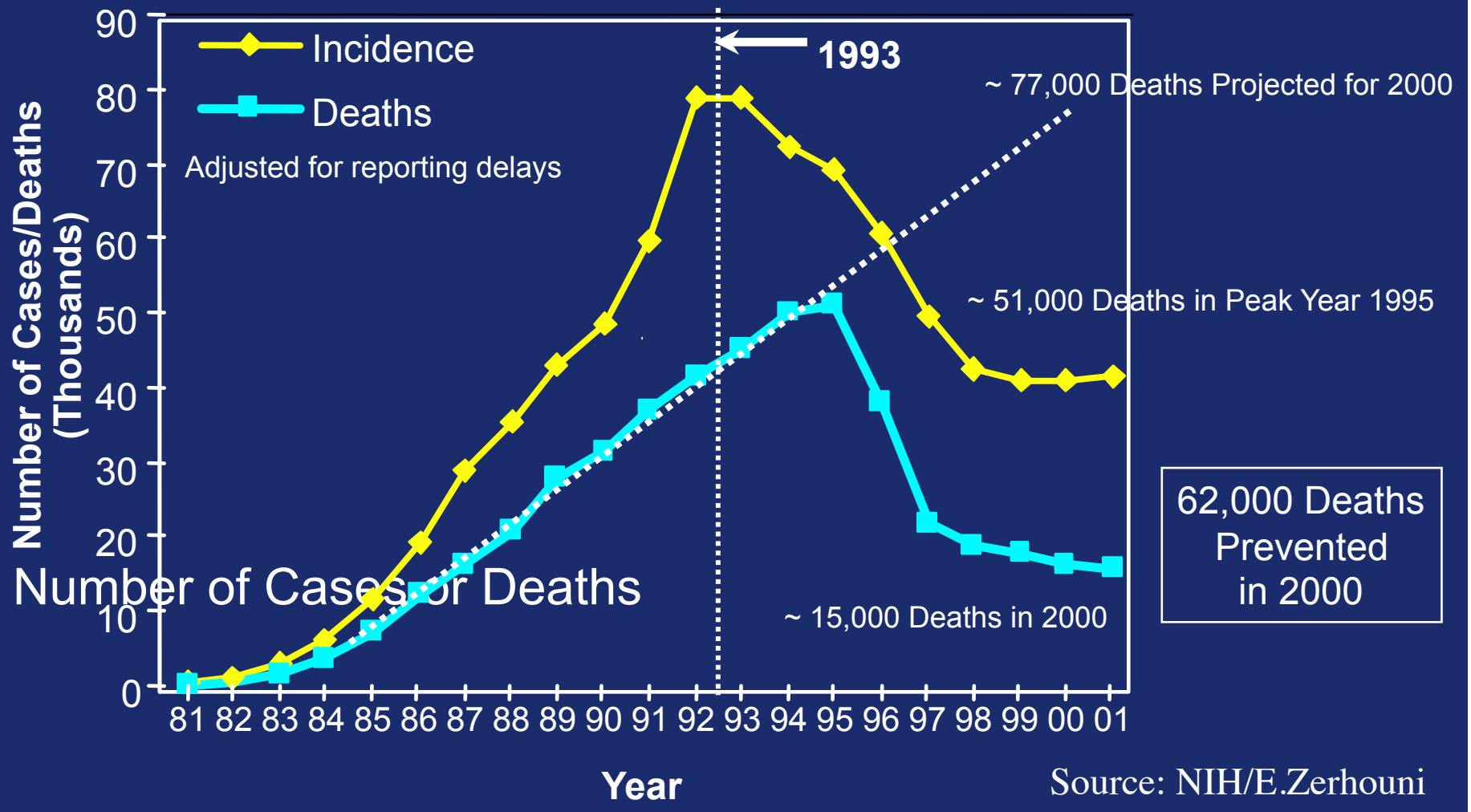
Reasons for these Decreases in Mortality From Heart Disease and Stroke

- Statins to lower blood cholesterol
- t-PA as a "clot buster" - agent to dissolve thromboses
- These drugs were firmly based on NIH-funded basic research into cholesterol metabolism and blood coagulation

Estimated U.S. Incidence of and Mortality from AIDS 1981-2001

More than 80 new drugs in development

Nearly 3 times the number of vaccines in Phase I since 2001



Source: NIH/E.Zerhouni

Reasons for the Decreased Mortality from HIV/AIDS

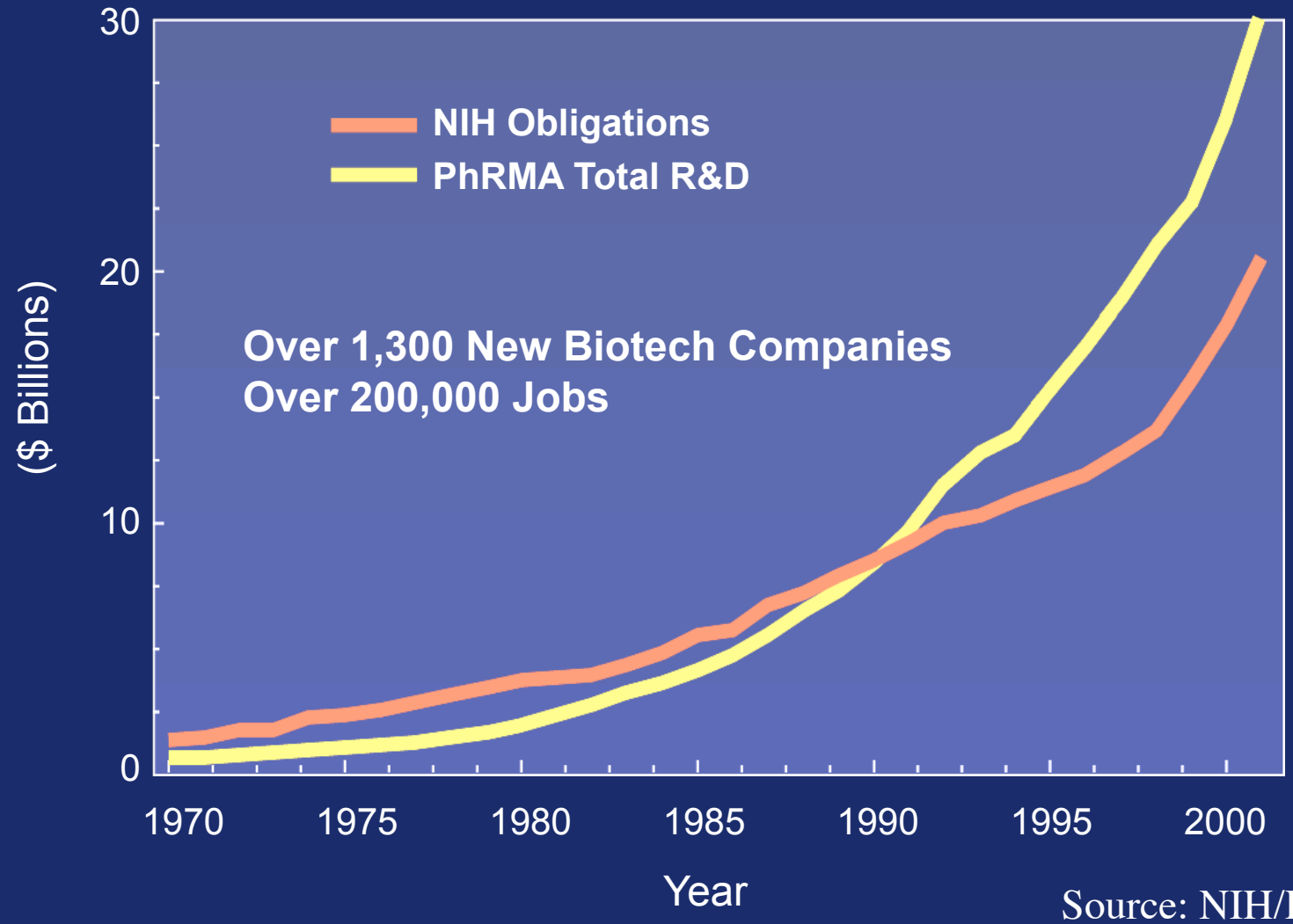
- Drugs targeting the HIV Viral Enzyme - Reverse Transcriptase
- Drugs targeting the ability of the HIV virus to process its own proteins
- These drugs were firmly based on NIH-funded basic research into other viruses - long before HIV emerged as a threat

The 2003 SARS outbreak and the doubling of the NIH budget

- Increased investments in the Human Genome
- Better DNA sequencing technology
- Finished the Human Genome faster
- Allowed powerful ways to identify Microbes and Viruses through their genomes
- Cause of SARS identified in record time !

- Similarly, the source of the anthrax in 2001 was rapidly identified by DNA sequencing !

PhRMA Member Companies' R&D Expenditures and NIH Obligations



Source: NIH/E.Zerhouni

Biotechnology Growth in the US

Major Swiss Pharmaceutical Company Relocates to Cambridge MA

Examples of the Direct Impact of the Doubling

- **Acceleration of Genomic Research Capacity**
  - Completion of Human Genome ahead of schedule
  - Ability to complete genome of over 60 other organisms.
    - Most recent: malaria parasite and the carrier mosquito
- **Accelerated Vaccine Development**
  - NIH Vaccine Research Center
  - 50 vaccines in development (15 near or in clinical trials)
  - West Nile Virus vaccine to be tested by 2003 in record time
- **Major Investments in Basic Research Infrastructure**
  - Synchrotron facilities for Structural Biology research
  - NIH repository of human stem cells
- **Expansion of Research Centers Focused on Major Diseases**
  - e.g.: Cancer SPOREs from 3 types of cancer to 13 and from 10 centers to 30
- **Expansion of Clinical Trials to Accelerate Translation of Knowledge**
  - Over 4500 with 2500 currently recruiting patients
- **New Investments in Minority Health and Health Disparities Research**

Healthcare Challenges

- **Continuing Health Issues**
  - **Cancer remains a leading cause of death and illness (around 1 in 3 people)**
  - **Infectious diseases such as tuberculosis and malaria**

- **Emerging Health Issues**
  - **Obesity (4.6 to 15% of children and adolescents)**
  - **Diabetes (Incidence of type II diabetes has doubled)**
  - **Age-related Diseases, e.g., Alzheimer's, Parkinson's, Macular Degeneration**

- **New Threats**
  - **New Health Threats (West Nile, SARS, Others)**
  - **BIODEFENSE**

- **The opportunites for tackling these problems have never been better**

- **Given adequate support we can provide solutions to these problems.**

NEW CHALLENGES

- **NIH's Strategic Roadmap**
  - **Creating Revolutionary Methods of Research**
  - **Mastering Complex Biological Systems**
  - **Re-engineering Clinical Research**
  - **Developing the Multidisciplinary Scientific Team of the Future**
- **Exploiting the Human Genome sequence - making the most of the "goldmine"**

The Human Genome

An Encyclopedia in 23 volumes (chromosomes) - total number of letters is 3 billion

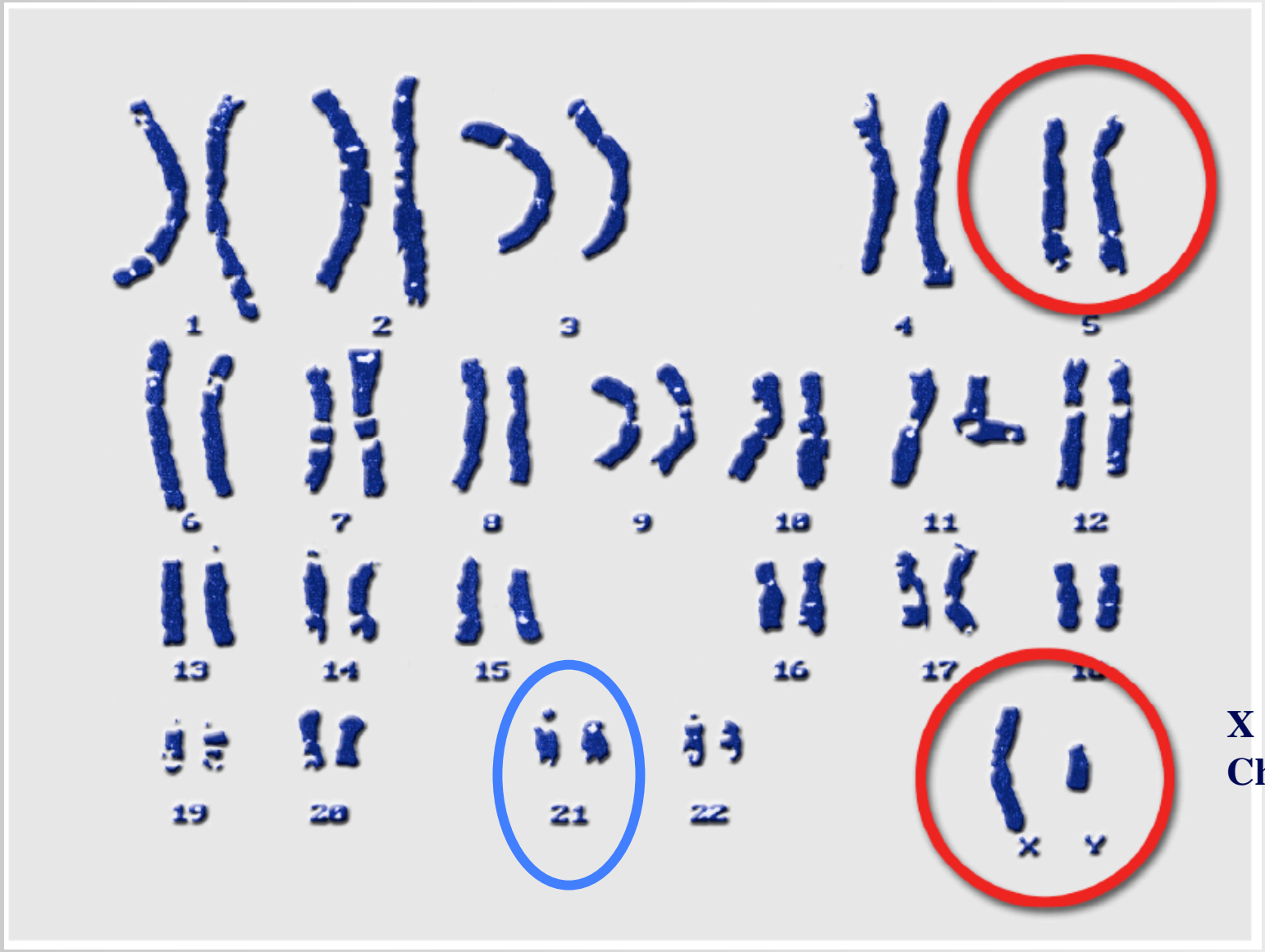
Each of us has two Editions with minor differences between them

Each volume (chromosome) has many different chapters (genes)
- there are about 30,000 chapters (genes) in total

Each chapter/gene carries a meaning/consequence - we need to understand those meanings/consequences - and the significance of “typos”

We have methods to detect the minor differences between editions
- we need to find out what they mean

Human Chromosomes



Typical Autosomes

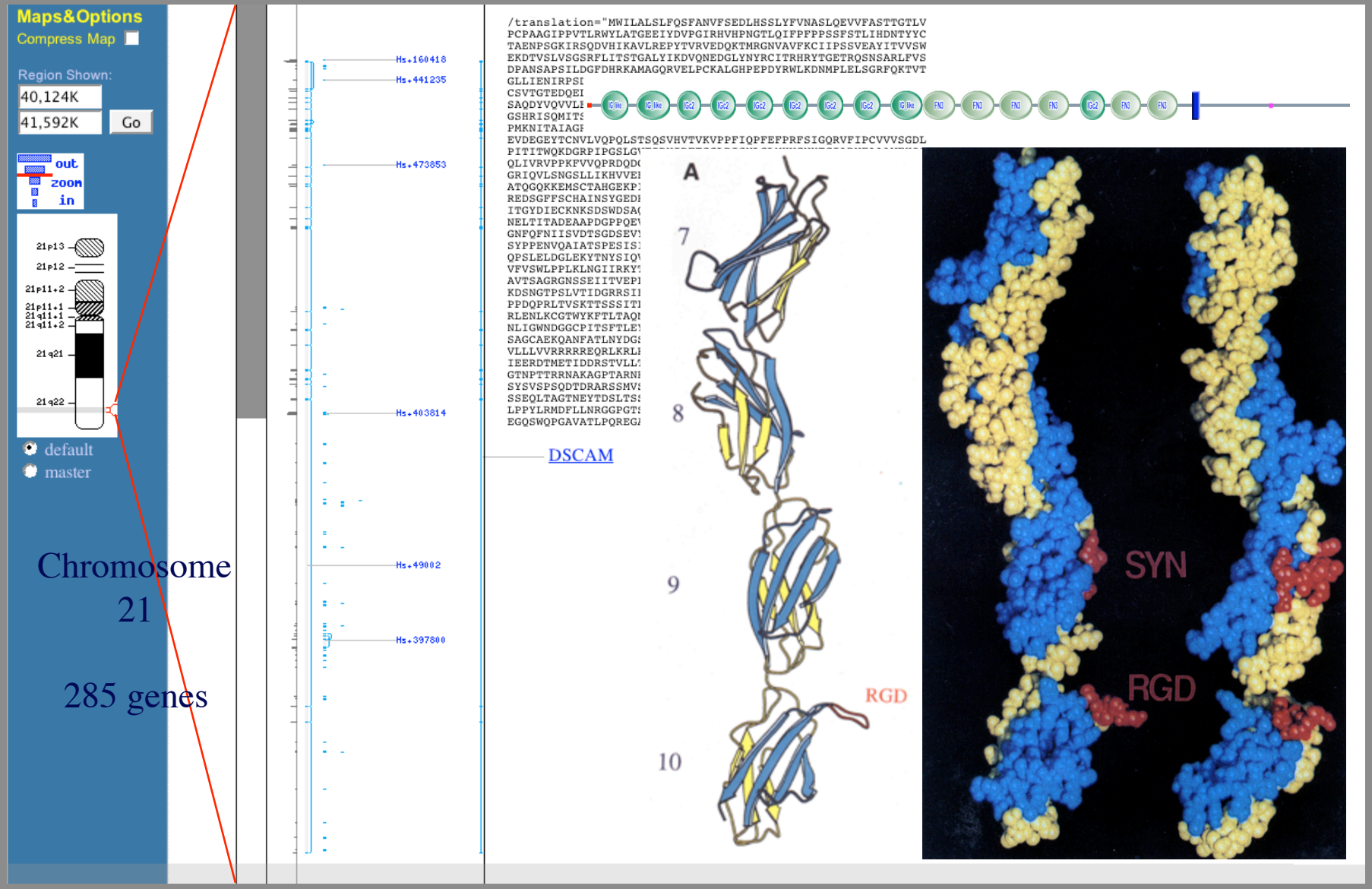
X and Y Sex Chromosomes

Bioinformatics - Decoding the Genome

Chromosome 21

285 genes

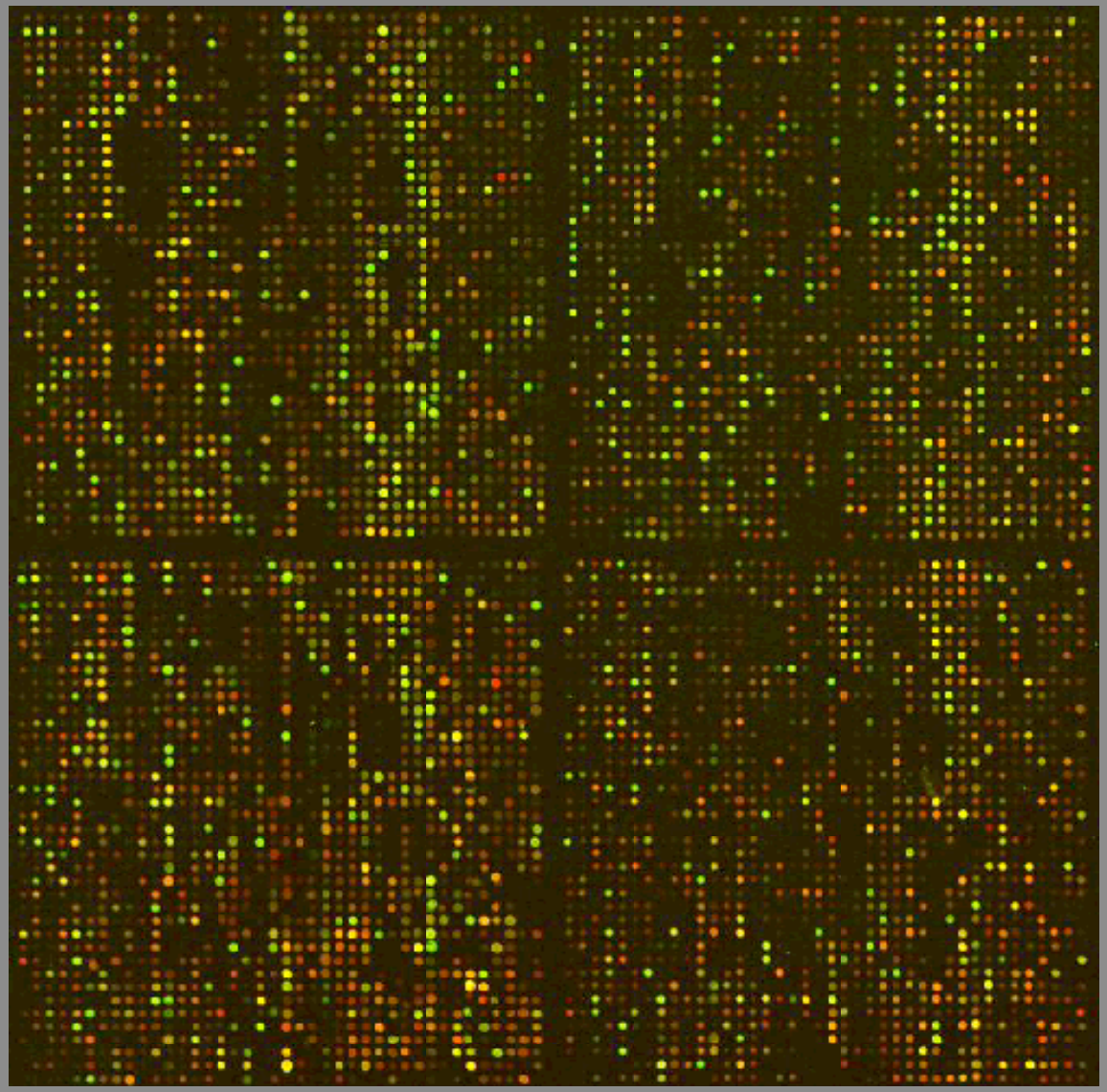
Bioinformatics - Decoding the Genome



Chromosome 21

285 genes

DNA Arrays - Using the Genome



Thousands of genes are arrayed on a glass slide.

One can then test any sample for which genes are expressed (ON) and how much they are expressed.

Two samples - red and green can be compared - a gene that is expressed equally in both samples gives a yellow signal

Improvements in Breast Cancer Diagnosis

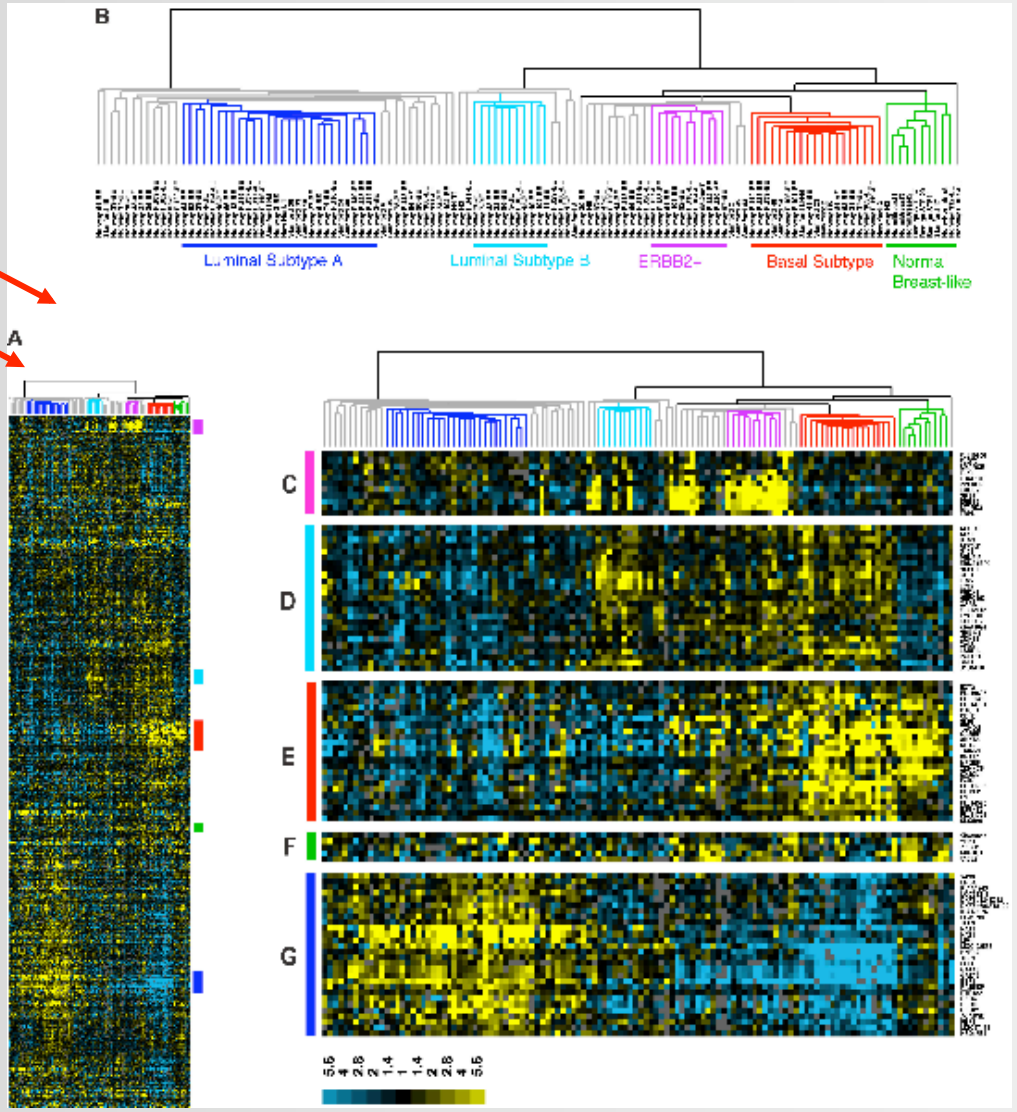
Tumor samples tested for expression of a set of diagnostic genes

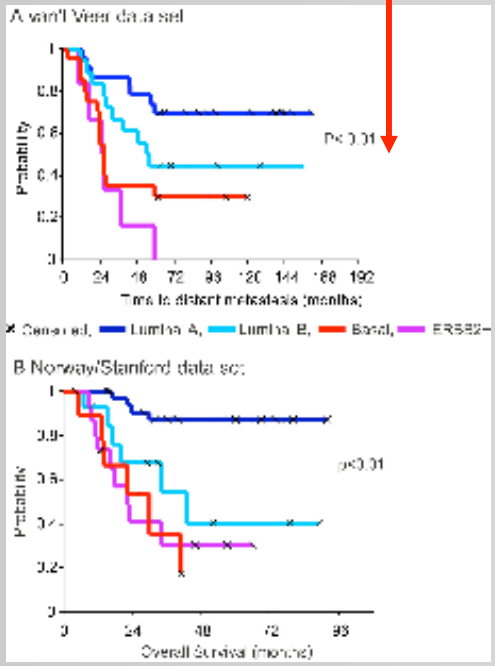
Each line represents a gene

Each column represents a tumor

Tumors fall into subgroups that predict clinical outcomes

Sorlie, Brown, Botstein et al PNAS 2003





Metastasis-free survival

Overall survival

Rationally Designed Anti-Cancer Drugs

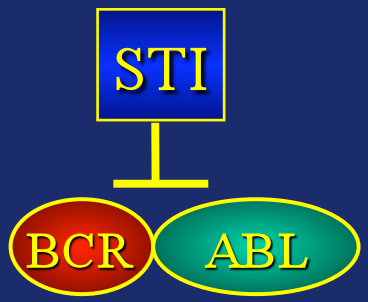
- We now know many of the initiating events in cancer
- We can study the relevant molecules in detail
- That information informs drug design
  - no longer blind screening for toxic drugs
  - designed drugs are more specific
  - fewer side effects
- Recent years have yielded several such drugs
- Given adequate research support, the next few years will yield many more

Recent Novel Anti-Cancer Drugs

- Herceptin - a humanised monoclonal antibody against a breast cancer oncogene
- Rituxan - a monoclonal antibody that targets lymphoma cells
  - also showing promise against autoimmune diseases
- Gleevec / Imatinib - a drug targeting a leukemia oncogene
  - also effective against some other cancers
- Avastin - an antibody that blocks tumor angiogenesis
- Current drugs target only a small number of genes/proteins
- There are ~30,000 genes out there to target !

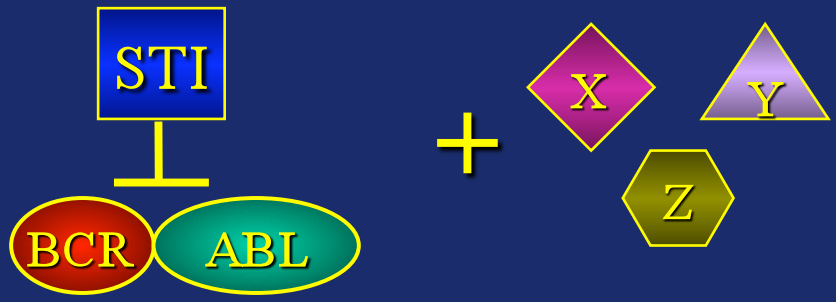
Response to Imatinib/Gleevec/STI571 in Chronic Myelogenous Leukemia (CML)

CHRONIC PHASE



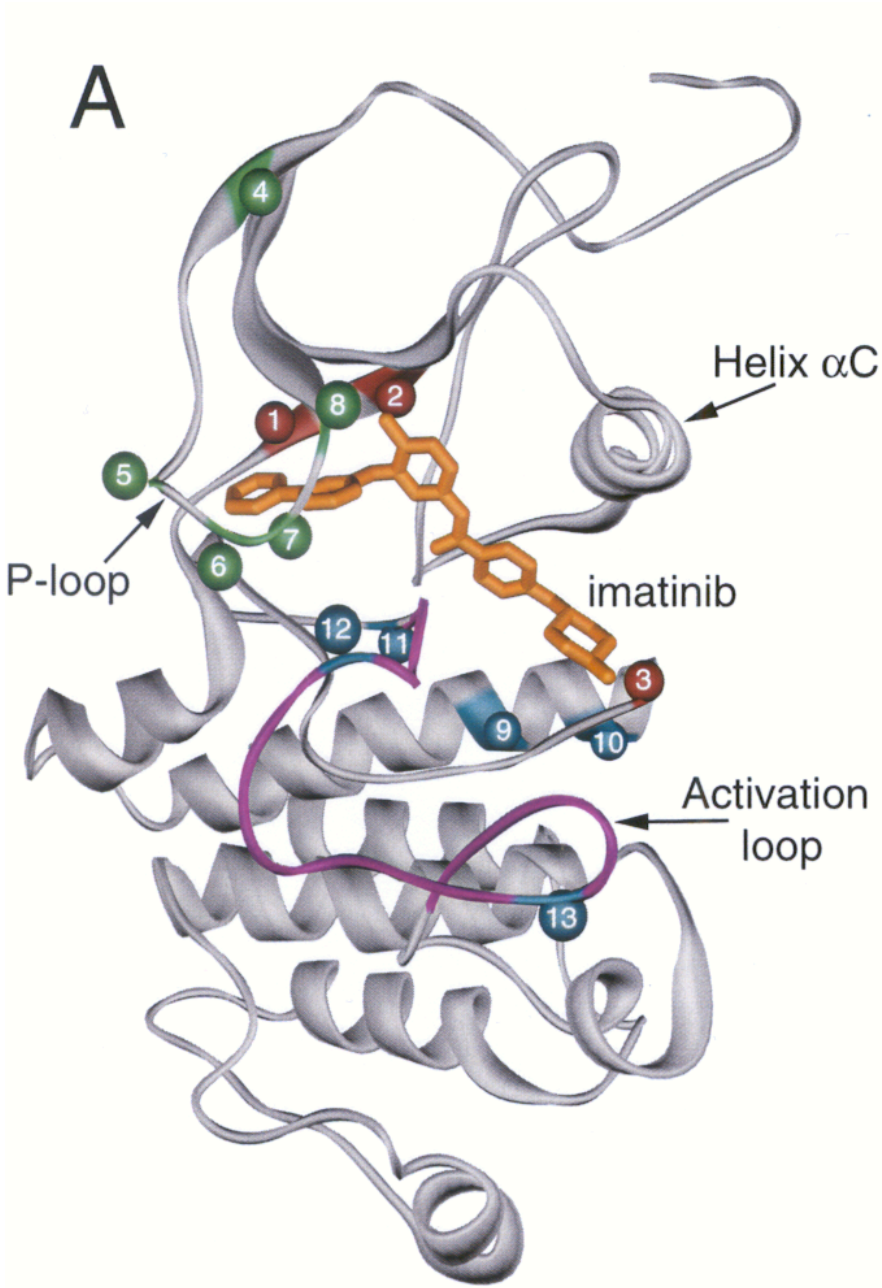
95% of patients respond, remissions last for years

BLAST CRISIS



70% of patients respond, remissions last for weeks to months

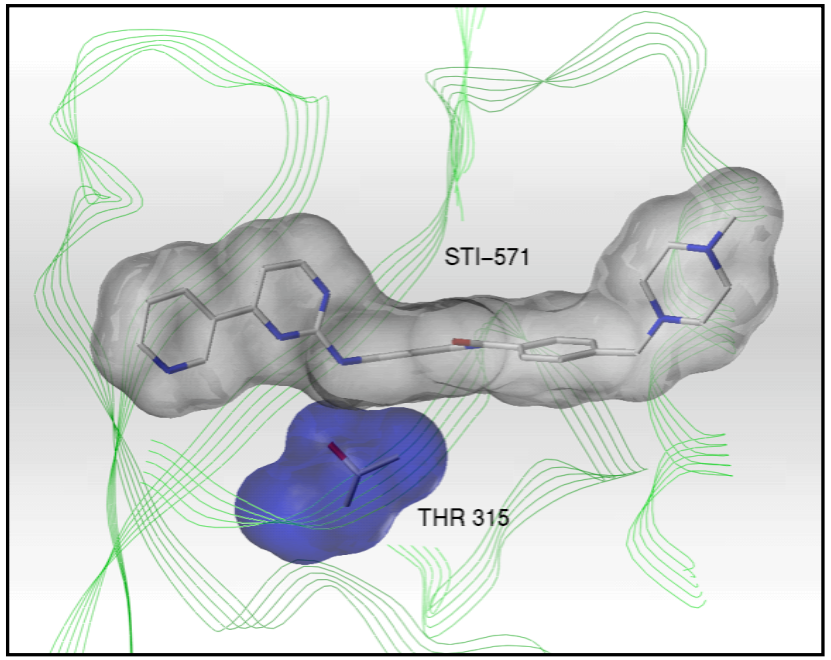
Why does resistance develop and what can we do about it?

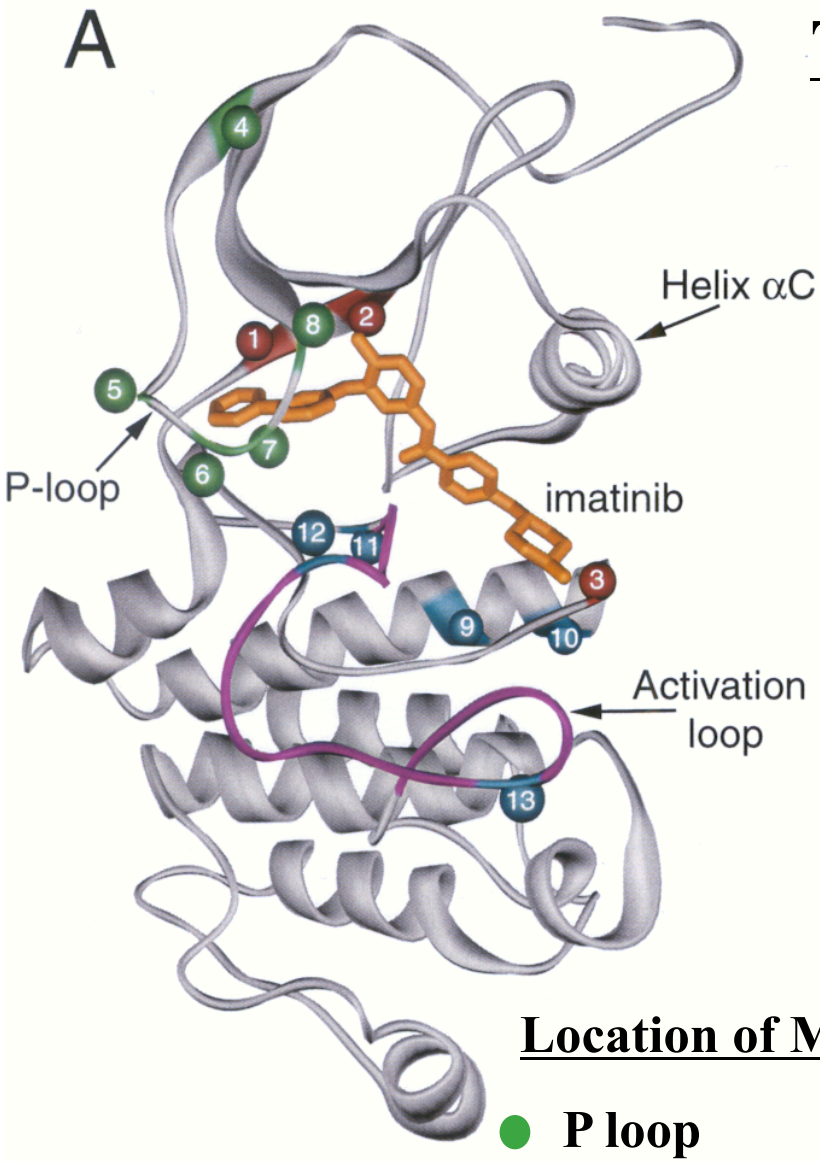


Imatinib bound to Abl kinase domain

B. Nagar, J. Kuriyan,
C. Sawyer et al

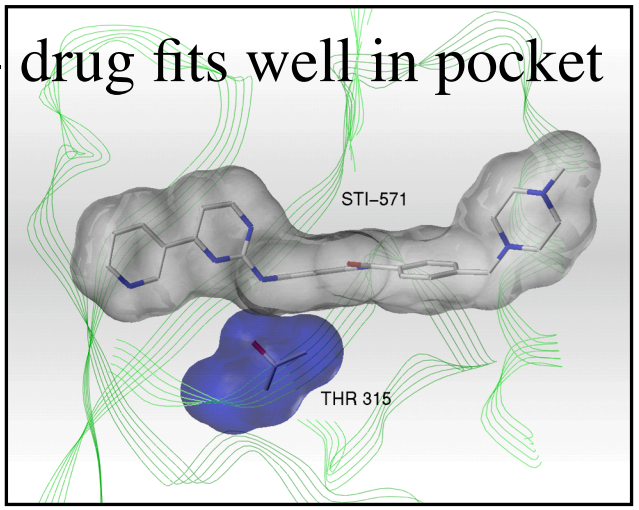
Cancer Cell
Cancer Research
(2002)



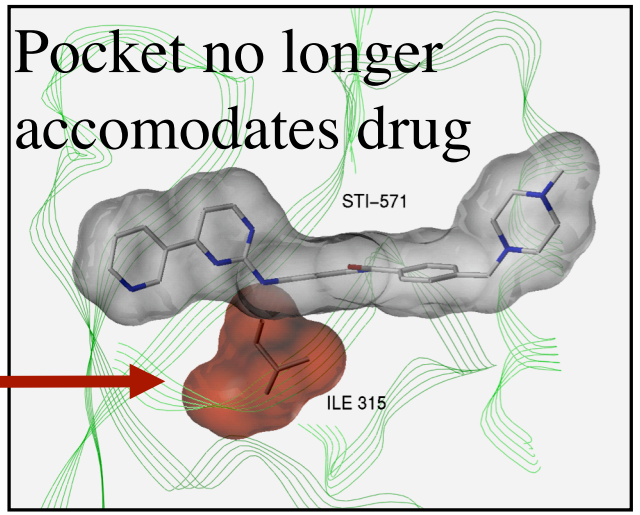


The Problem

Normal - drug fits well in pocket

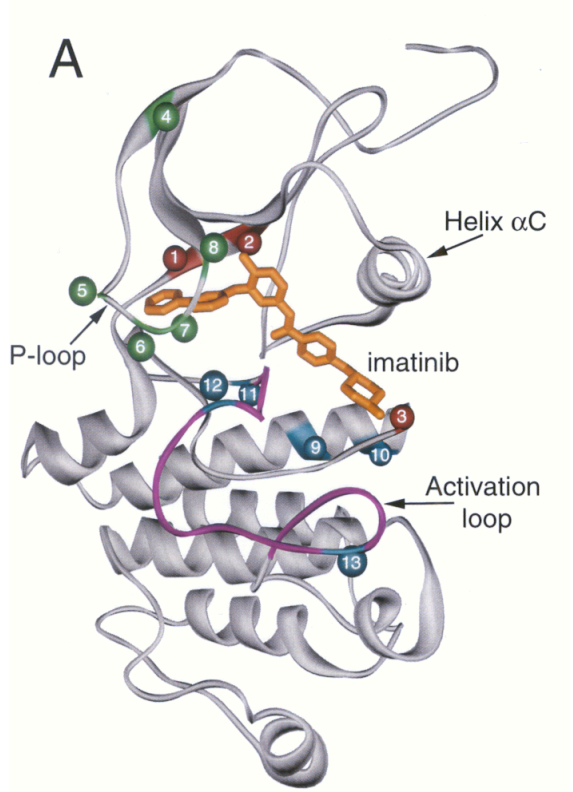


Resistant mutant develops



Location of Mutations

- **P loop**
- **Direct contact with drug**
- **hinge**



A Solution

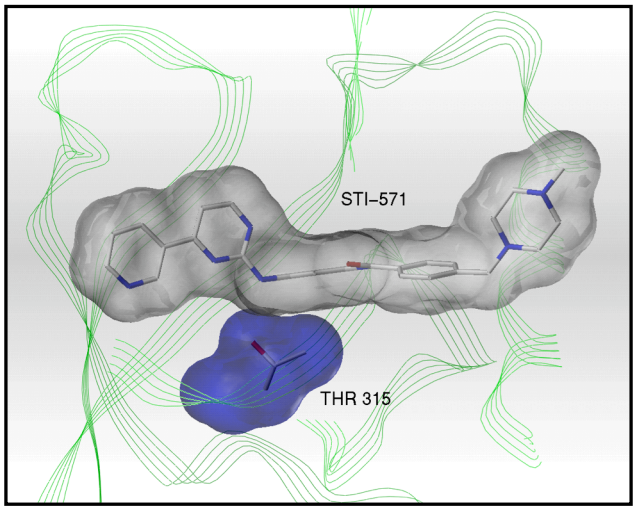
Design new variants of the drug

that can bind the mutant pockets.

Such drugs work in mouse models.

Now in clinical trials.

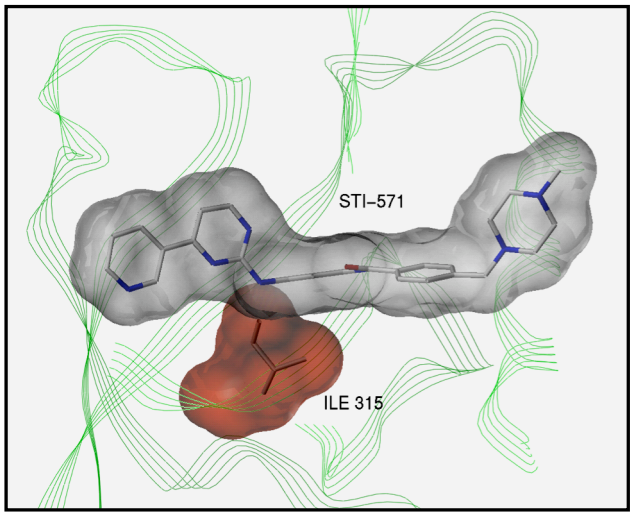
Normal - drug fits well in pocket



Development of

drug resistance

Resistant mutant - pocket no longer accomodates drug



The Awesome Potential of Stem Cells

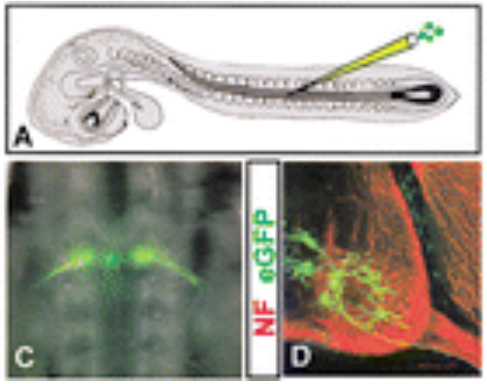
- Stem cells are self-renewing cells that can develop into mature cells of different types
- There are different types of stem cells
- Bone marrow stem cells can develop into blood cells
- Muscle stem cells can regenerate muscle
- Embryonic stem cells can generate all or most cell types
- Both adult (probably restricted potential) and embryonic (certainly multi-potential) stem cells offer enormous prospects for use in regenerative medicine!

A Few Examples of Future Uses of Stem Cells

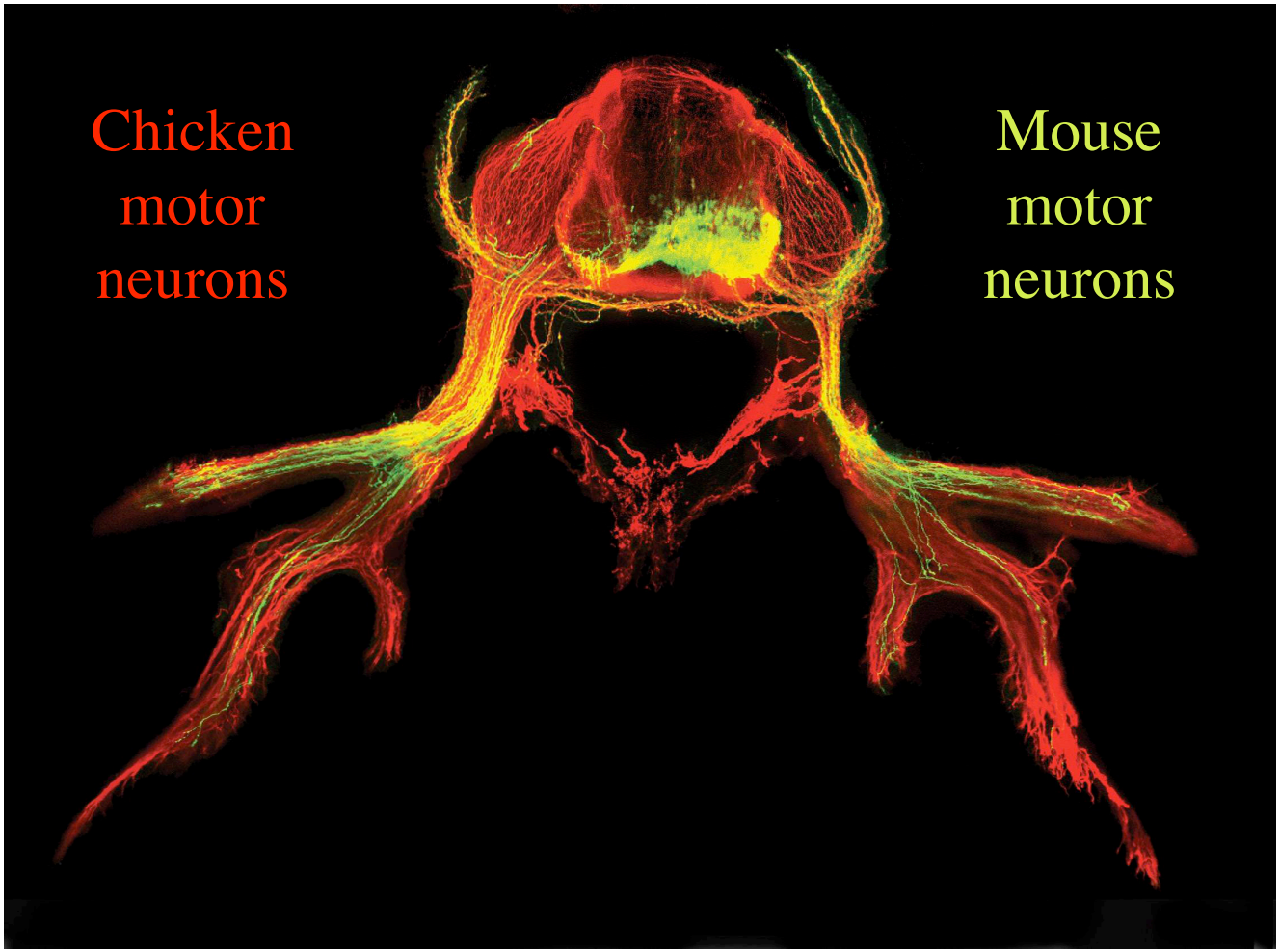
- Bone Marrow Transplants - already in use for restoring blood cell production - e.g. after cancer therapy
- Juvenile Diabetes - replacement of β cells of pancreas
- Muscular Dystrophy - replacement of degenerating muscle cells
- Parkinson's Disease - replacement of degenerating dopamine-producing neurons
- Lou Gehrig's Disease - replacement of motor neurons
- Spinal Cord Injuries - replacement of motor neurons

Generation of Motor Neurons from Embryonic Stem (ES) Cells

Motor neuron precursors derived from mouse ES cells injected into chicken embryo spinal cord develop into motor neurons.



Wichterle, Jessell et al
Cell 110:385-397 (2002)



What will it take to Exploit the Current Momentum in Biomedical Research?

- Continued Stable Support for Innovative Research
  - New People and Ideas
  - Interdisciplinary Training
- Development of new Infrastructures
  - Structural Biology, Proteomics, Imaging, etc
  - Libraries of genes, cDNAs and chemicals
  - Clinical Trials
  - Databases
- We have an unparalleled opportunity to develop radical new approaches to human health and safety
- It would be a tragic waste not to seize this opportunity
- Given Adequate Support (8-10% per year), we can Provide the Solutions

We need to accelerate discoveries in the life sciences before rising health threats become insurmountable.

This is a race we cannot afford to lose!

Elias Zerhouni - Director, NIH