IS BASIC SCIENCE ESSENTIAL FOR SIGNIFICANT AND FUNDAMENTAL DISCOVERIES?

Lindau NLM
27 June 2018

Michael Levitt

Robert W. & Vivian K. Cahill Professor in Cancer Research, Stanford School of Medicine

Structural Biology & Computer Science

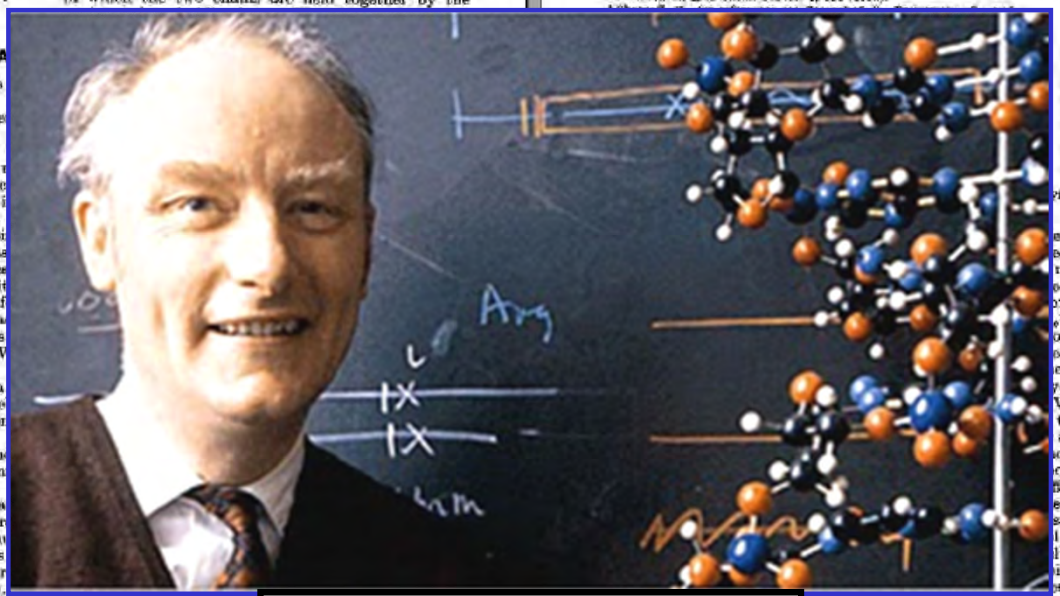
SUMMARY

1. A Biophysical Revolution in Biology.
2. Computational Structural Biology.
3. Applied Computational Structural Biology
4. Young Basic Scientists in the USA.
5. Is Basic Science Important?
6. How to Win Many Nobel Prizes?

1.
A REVOLUTION IN BIOLOGY

BETWEEN 1950 AND 1960 SCIENTISTS DEFINED MODERN BIOLOGY AS PHYSICS

1953: FRANCIS CRICK AND DNA



1916-2004

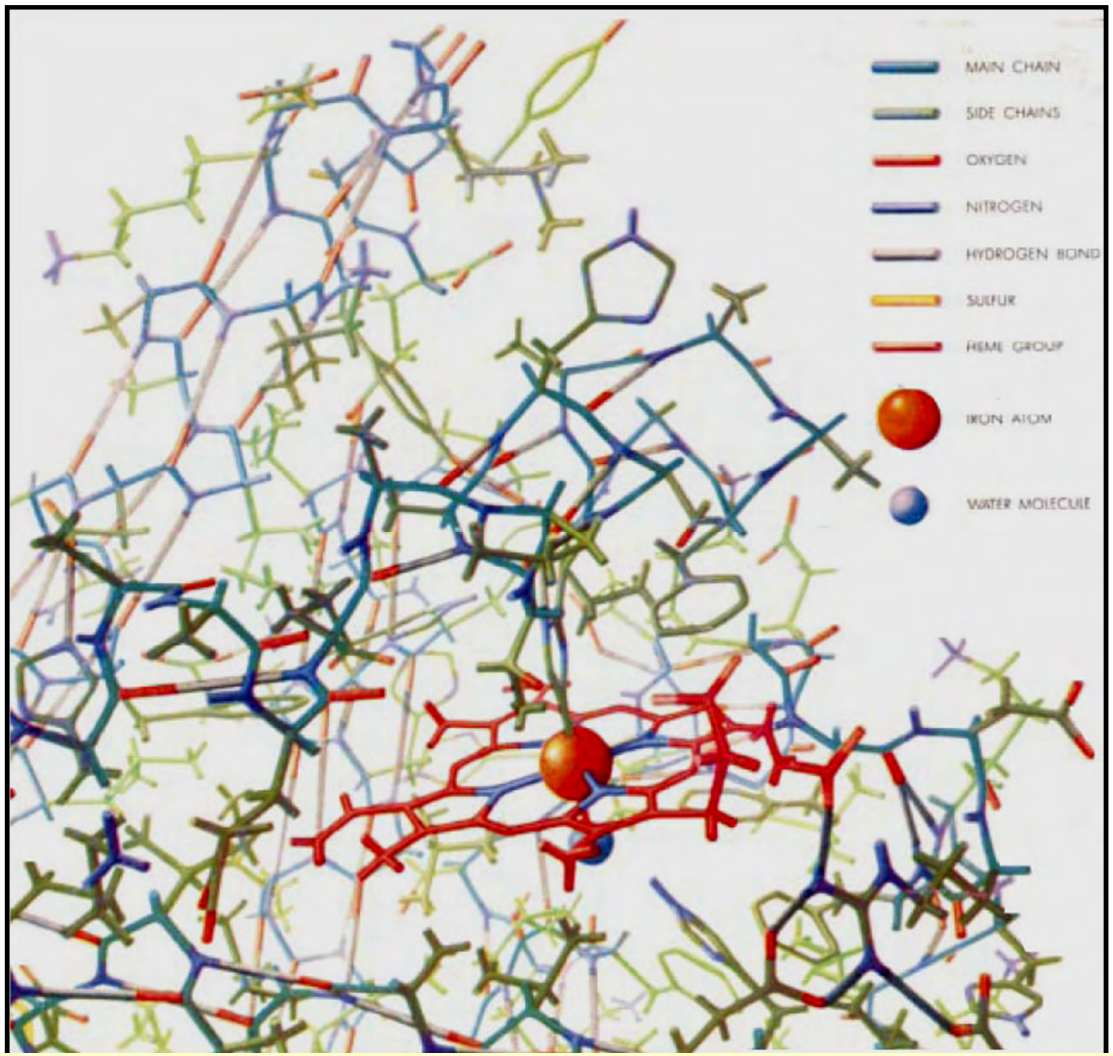
DNA Model and Experiment

1959: KENDREW AND MYOGLOBIN

1917-1997

First protein X-ray structure.

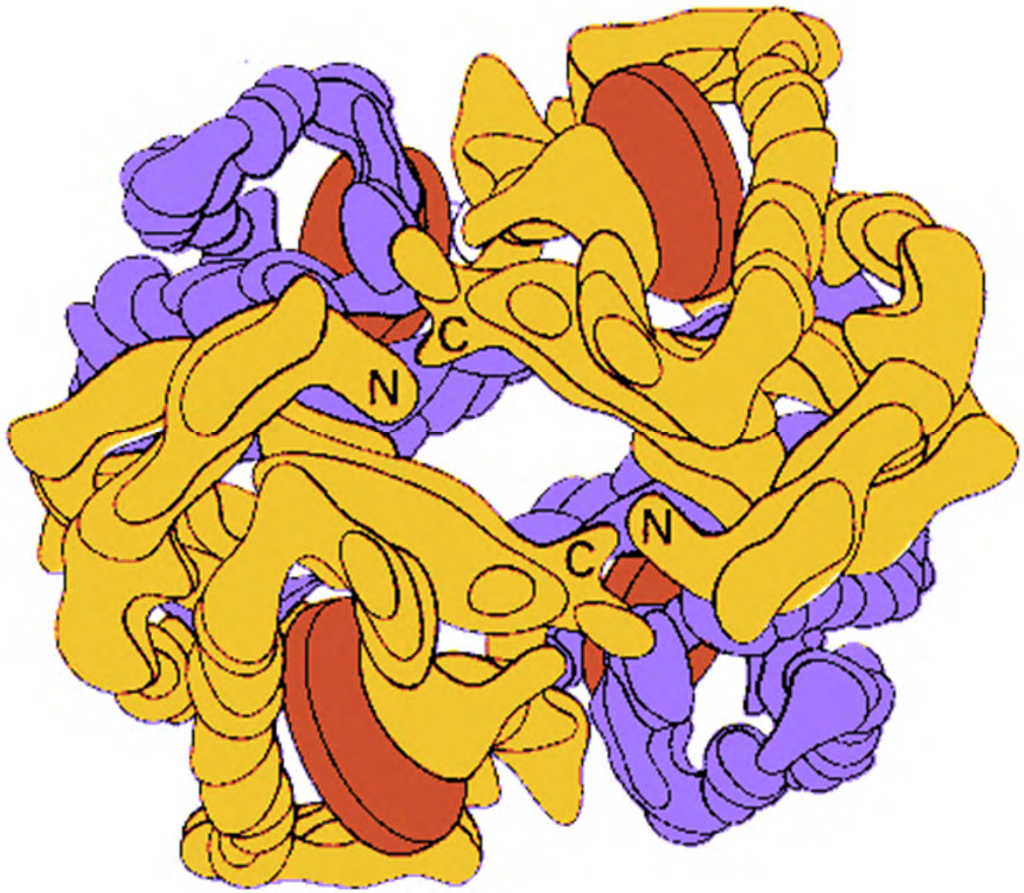
Scientific American 1961



Painted by artist Irving Geis

1962: PERUTZ AND HEMOGLOBIN

1914-2002



The REAL HERO of structural biology.

CRYSTALLOGRAPHY GIVES STRUCTURE

HOW DO WE GET FUNCTION?

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2.
COMPUTATIONAL STRUCTURAL BIOLOGY

KENDREW, ME & ISRAEL

amazon.com Prime | Michael's Amazon.com | Books | See all 41 Product Categories

The Thread of Life: an introduction to molecular biology. Based on the series of B.B.C. Television Lectures of the same title (Hardcover)

by John C. Kendrew (Author), b/w photos. Illustrated by Diagrams

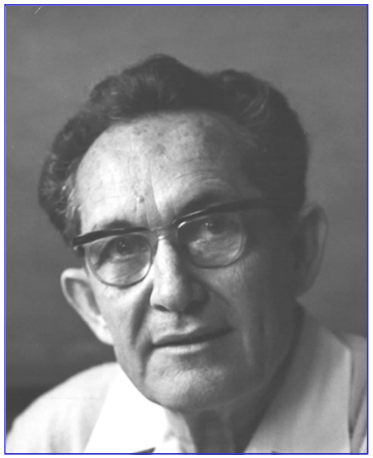
The Thread of Life: An INTRODUCTION TO MOLECULAR BIOLOGY

Episodes (BBC TV Winter 1964)

- **The REVOLUTION IN BIOLOGY (04/01/1964)**
- **INSIDE THE CELL (11/01/1964)**
- **PROTEINS IN ONE DIMENSION (18/01/1964)**
- **PROTEINS IN THREE DIMENSIONS (25/01/1964)**
- **REPRODUCTION AND GENETICS (01/02/1964)**
- **NUCLEIC ACID The INFORMATION CARRIER (08/02/1964)**
- **The MESSENGER OF THE GENES (15/02/1964)**
- **SOLVING THE CODE (22/02/1964)**
- **LIVING ARCHITECTURE The VIRUSES (29/02/1964)**
- **The WAY AHEAD (07/03/1964)**

Nobel Prize in 1962
Gave BBC Series in 1964
Sent me to Israel in 1967

CONSISTENT FORCE-FIELD 1968



Small molecules, Hydrocarbons, Saturated, -CH_2-

THE JOURNAL OF CHEMICAL PHYSICS VOLUME 49, NUMBER 11 1 DECEMBER 1968

Consistent Force Field for Calculations of Conformations, Vibrational Spectra, and Enthalpies of Cycloalkane and *n*-Alkane Molecules

S. LIFSON AND A. WARSHEL

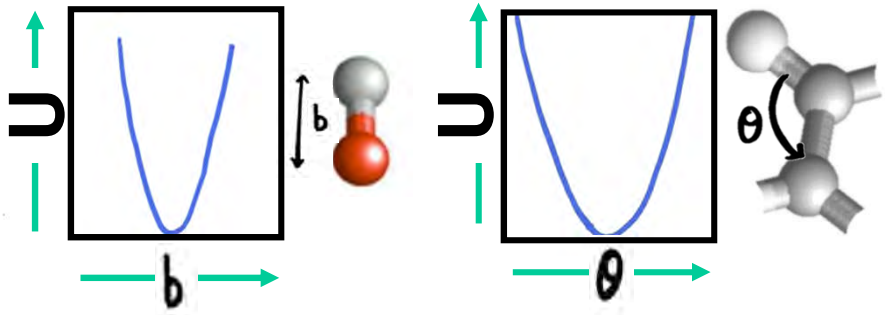
Department of Chemical Physics, Weizmann Institute of Science, Rehovot, Israel

(Received 13 May 1968)

MOLECULAR POTENTIAL ENERGY

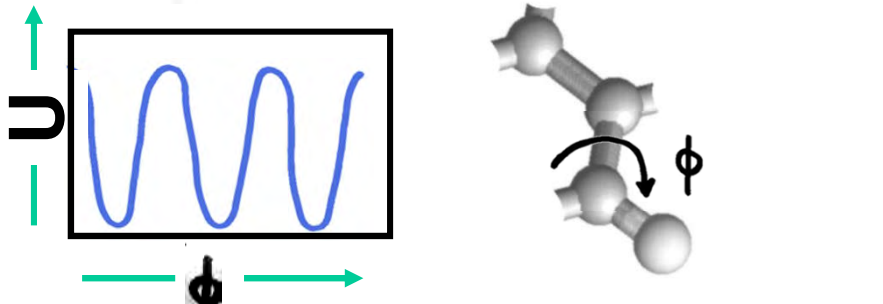
$$U = \sum \tfrac{1}{2} K_b (b - b_o)^2 - \sum \tfrac{1}{2} K_\theta (\theta - \theta_o)^2$$

All Bonds All Angles



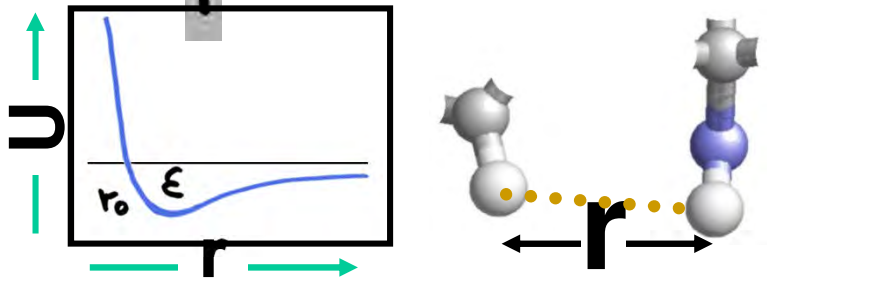
$$+ \sum K_\phi [1 - \cos(n\phi + \delta)]$$

All Torsion Angles



$$+ \sum \varepsilon \left[\left(r_o/r\right)^{12} - 2\left(r_o/r\right)^{6} \right]$$

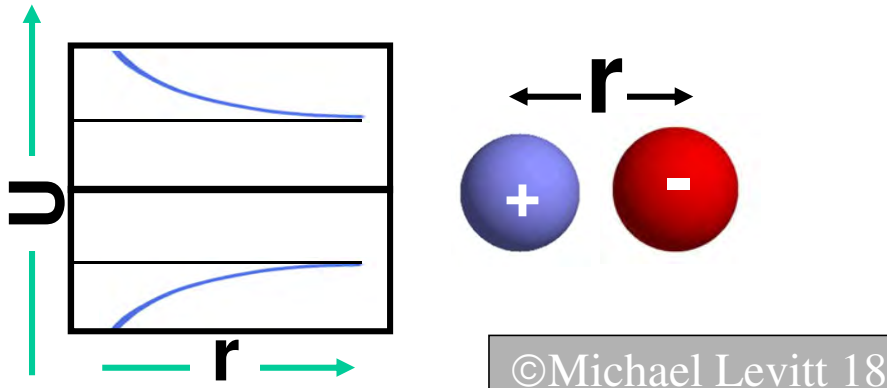
All nonbonded pairs



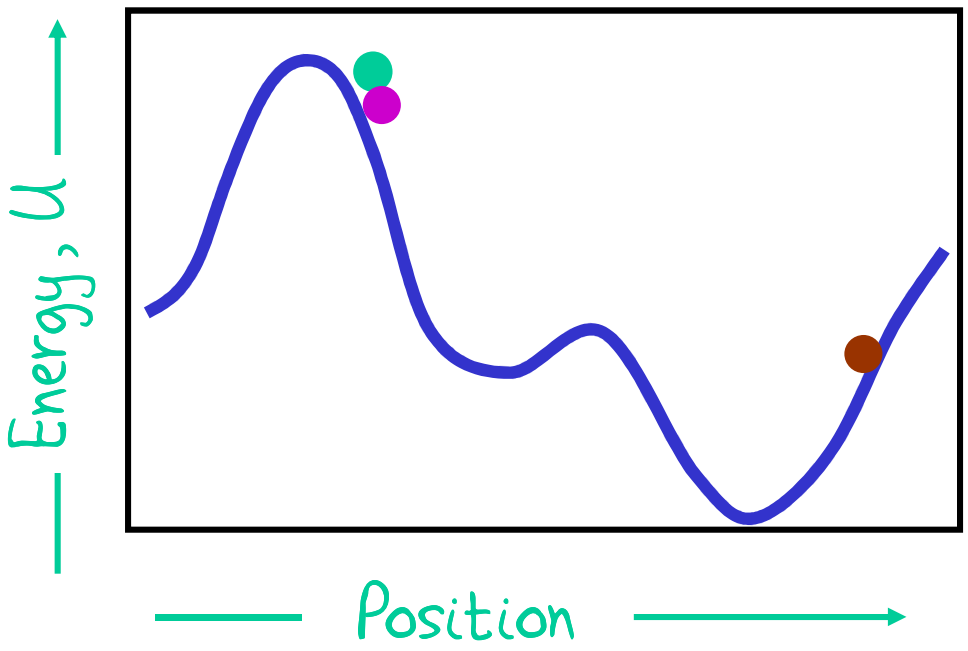
$$+ \sum 332 q_i q_j / r$$

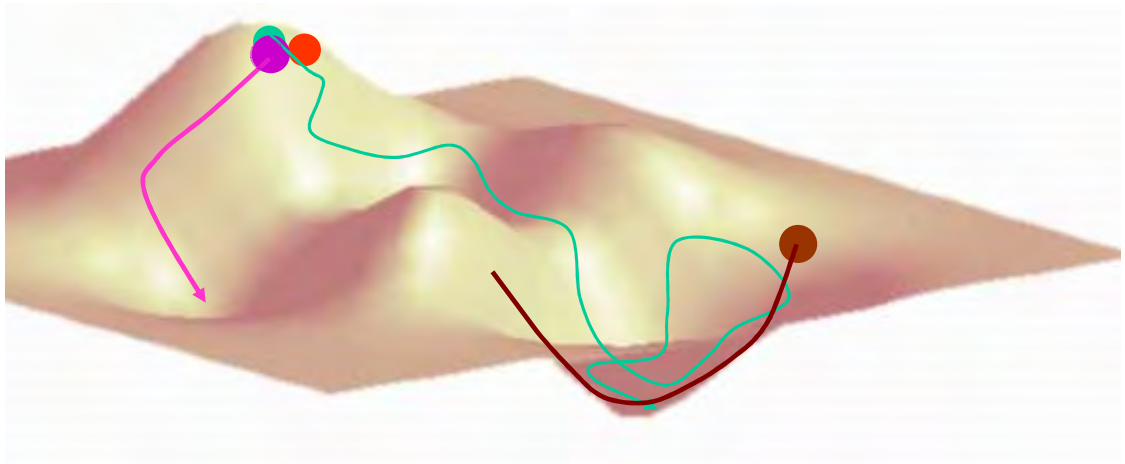
All partial charges

Simple sum over many terms



MOVING OVER ENERGY SURFACE





- EM: Energy Minimization drops into local minimum.
- NMD: Normal Mode Dynamics vibrates about minimum.
- MD: Molecular Dynamics uses thermal energy to move smoothly over surface.

MULTISCALE MODELING OF MACROMOLECULES

EINSTEIN* ON SIMPLIFICATION

"Everything Should Be Made As Simple
As It Can Be, But Not Simpler"

*Einstein may have crafted this aphorism, but there is no direct evidence in his writings. He did express a similar idea in a lecture but not concisely. Roger Sessions was a key figure in the propagation of the saying. In fact, he may have crafted it when he attempted to paraphrase an idea imparted by Einstein.
http://quoteinvestigator.com/2011/05/13/einstein-simple/

PROTEIN ENERGY MINIMIZATION 1969

MACROMOLECULAR ENERGY MINIMIZATION

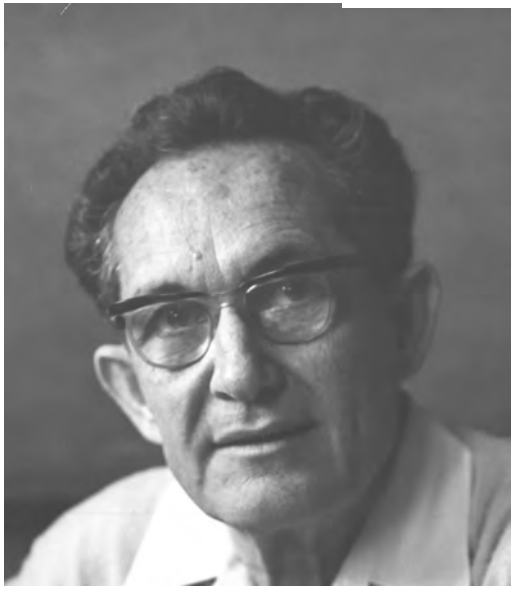
Refinement of Protein Conformations using a Macromolecular Energy Minimization Procedure

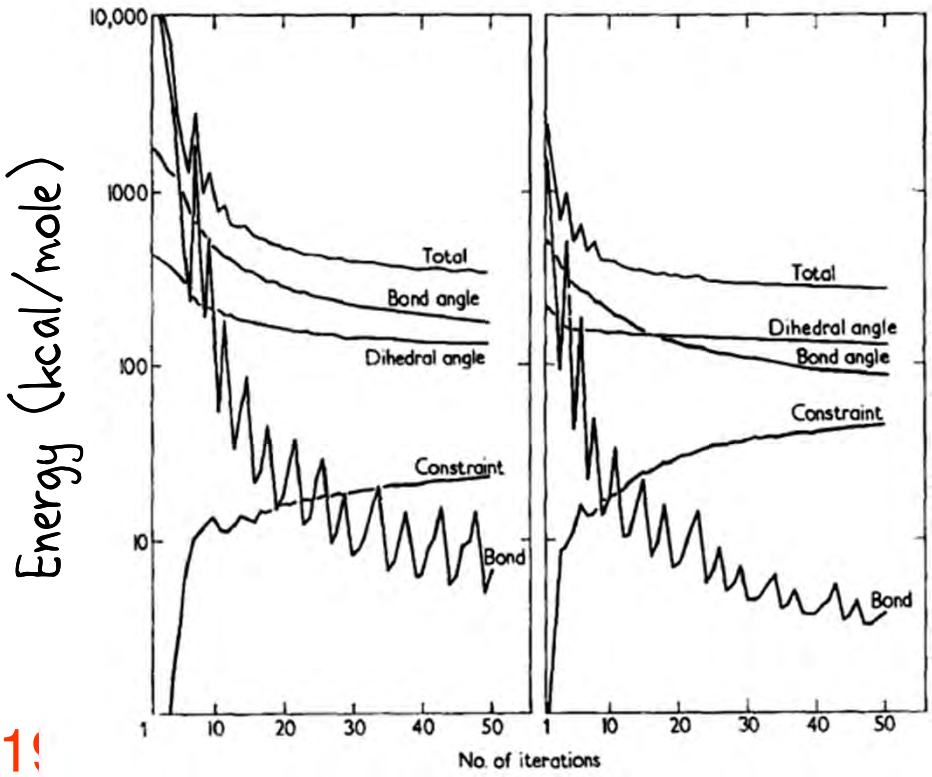
MICHAEL LEVITT† AND SHNEIOR LIFSON

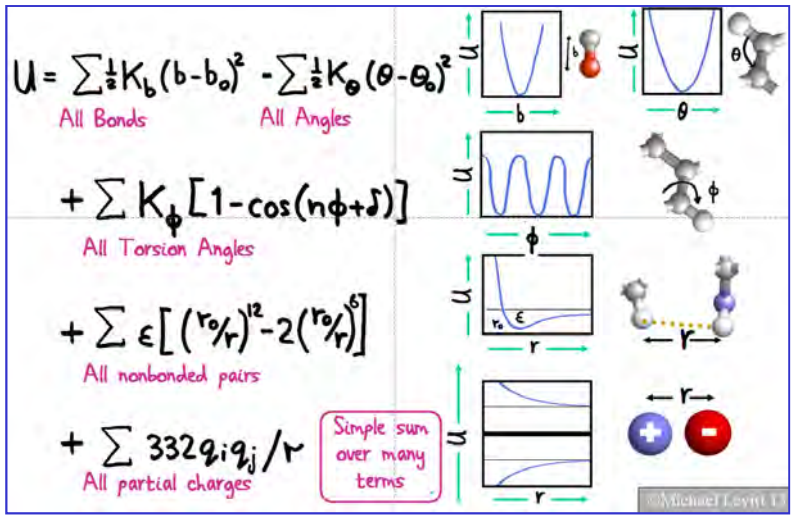
Weizmann Institute of Science

J. Mol. Biol. (1969) **46**, 269–279

$$E = \underset{\text{all bonds}}{\Sigma \tfrac{1}{2} K_b (b - b_0)^2} + \underset{\text{all bond angles}}{\Sigma \tfrac{1}{2} K_\tau (\tau - \tau_0)^2} + \underset{\text{all dihedral angles}}{\Sigma \tfrac{1}{2} K_\theta \{1 + \cos(n\theta - \delta)\}} + \underset{\text{all non-bonded pairs}}{\Sigma \epsilon_{ij} \{(r^0_{ij}/r_{ij})^{12} - 2(r^0_{ij}/r_{ij})^6\}} + \underset{\text{all atomic co-ordinates}}{\Sigma \tfrac{1}{2} w (x_i - x^0_i)^2}$$







Big molecules,
General,
H, C, N, O, S

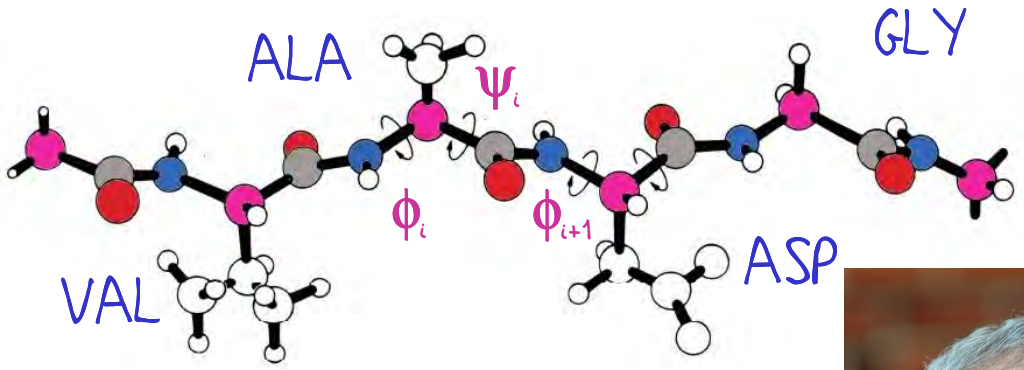
COARSE-GRAINED MODELS 1975

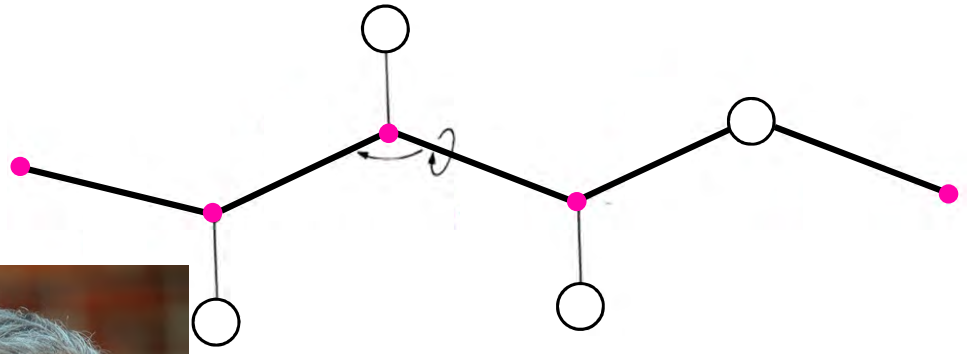
COMPUTER SIMULATION OF PROTEIN FOLDING

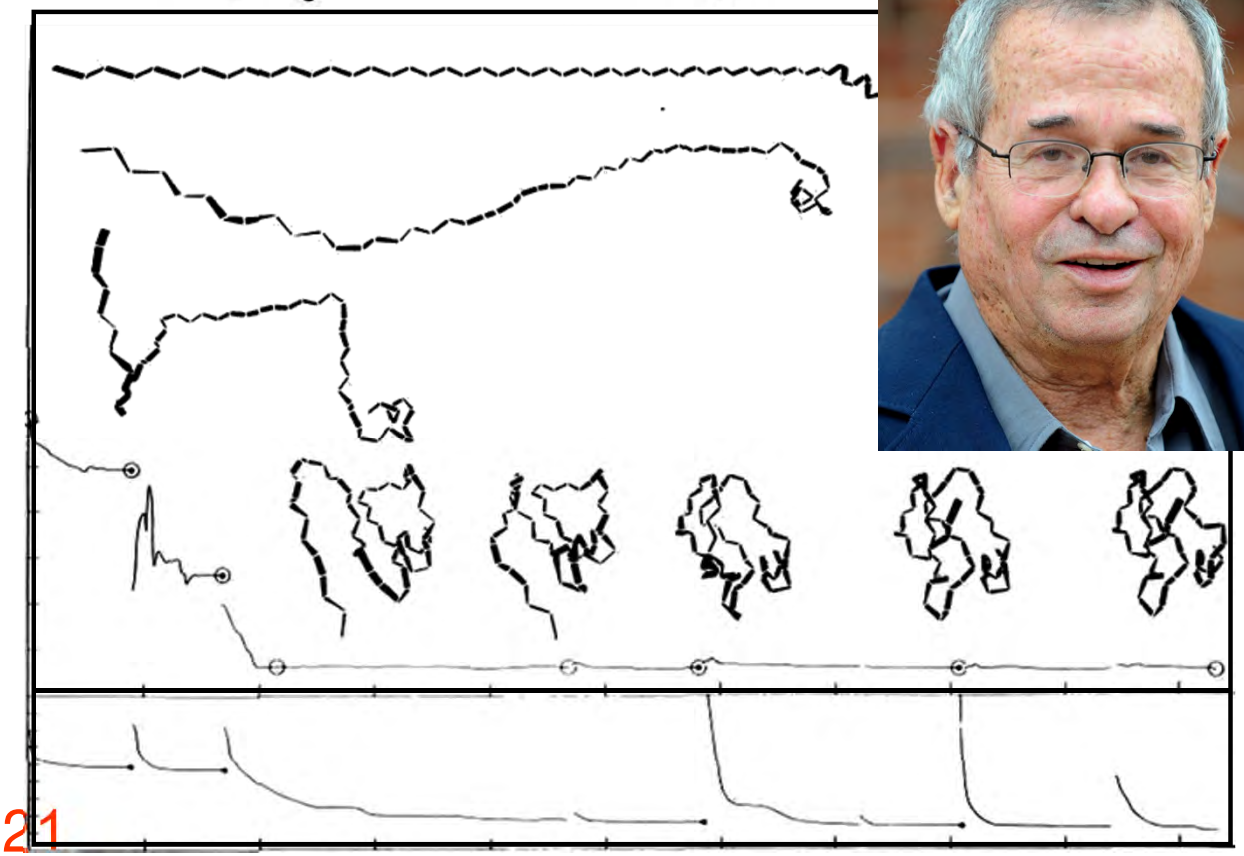
Michael Levitt* & Arieh Warshel*

Department of Chemical Physics, Weizmann Institute of Science, Rehovoth, Israel

Nature Vol. 253 February 27 1975







Reduced models

Fold protein with 1000 steps of minimization.

Escape from local minima with normal modes jumps.

QM/MM MODELS FOR CATALYSIS 1976

THEORETICAL STUDIES OF ENZYMIC REACTIONS

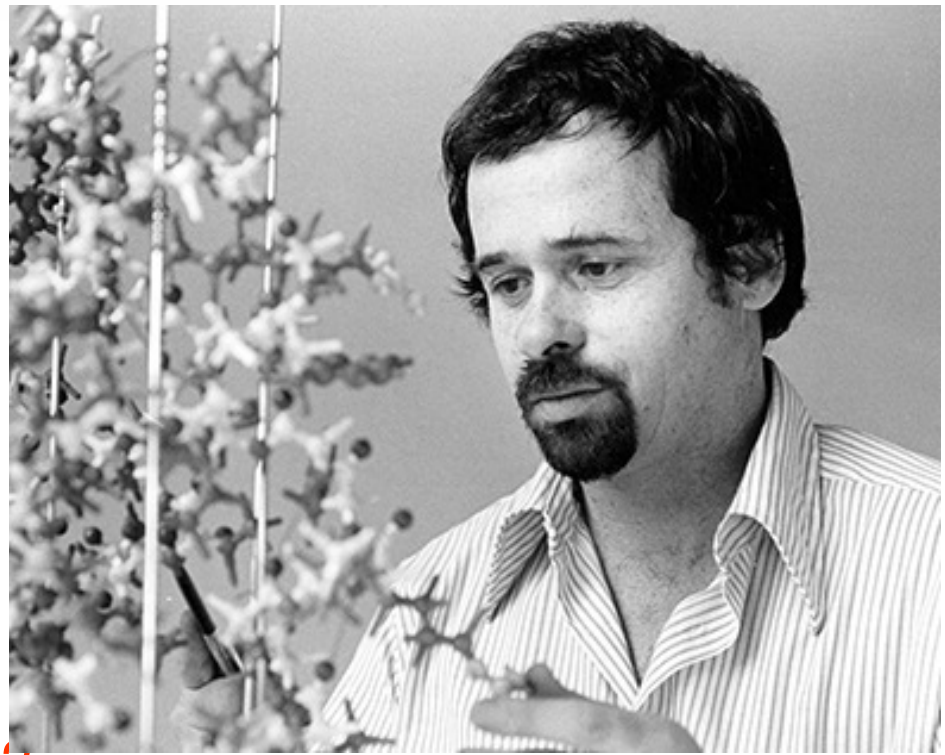
J. Mol. Biol. (1976) **103**, 227–249

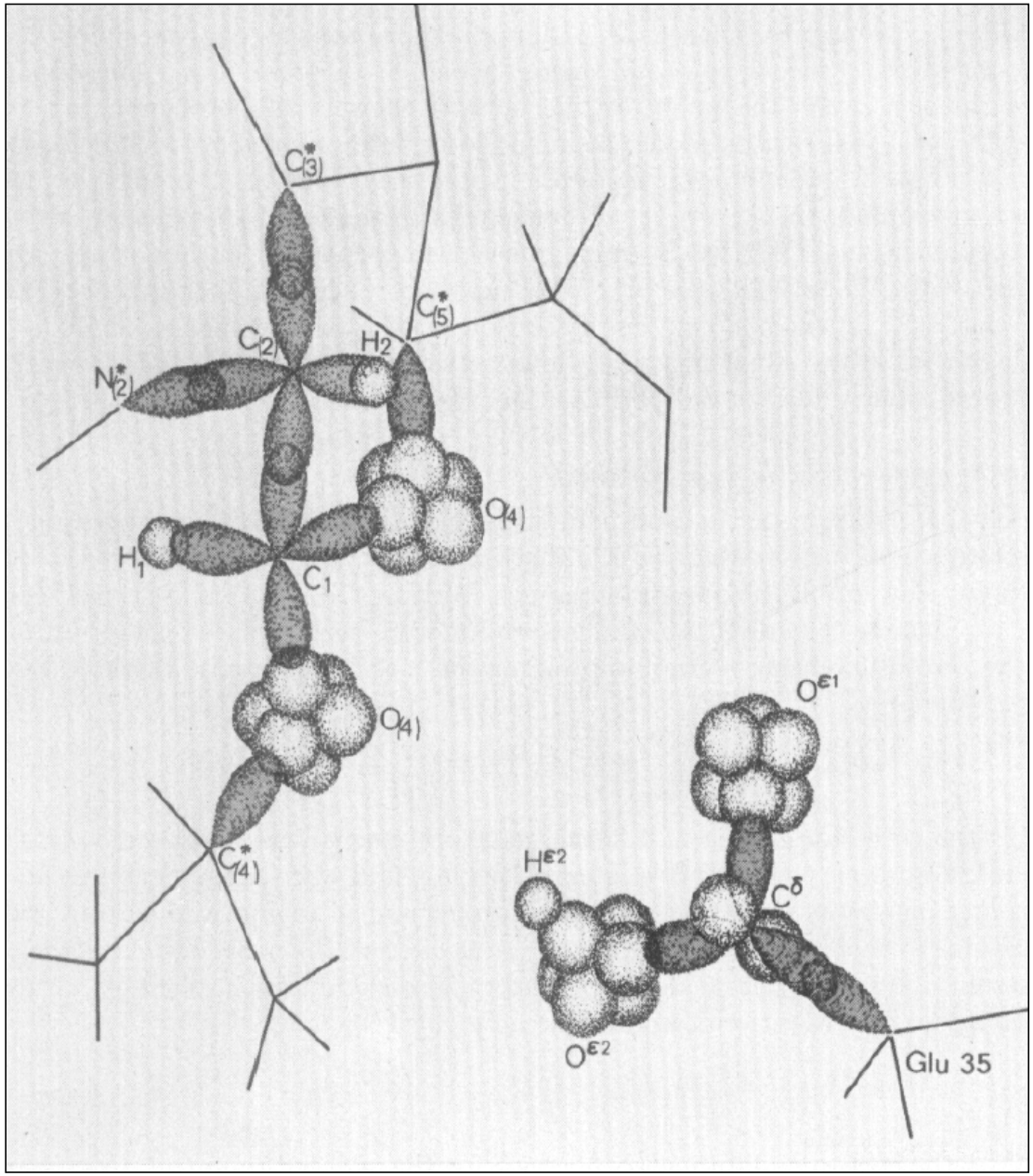
A. WARSHEL AND M. LEVITT

Medical Research Council Laboratory of Molecular Biology
Hills Road, Cambridge CB2 2QH, England

and

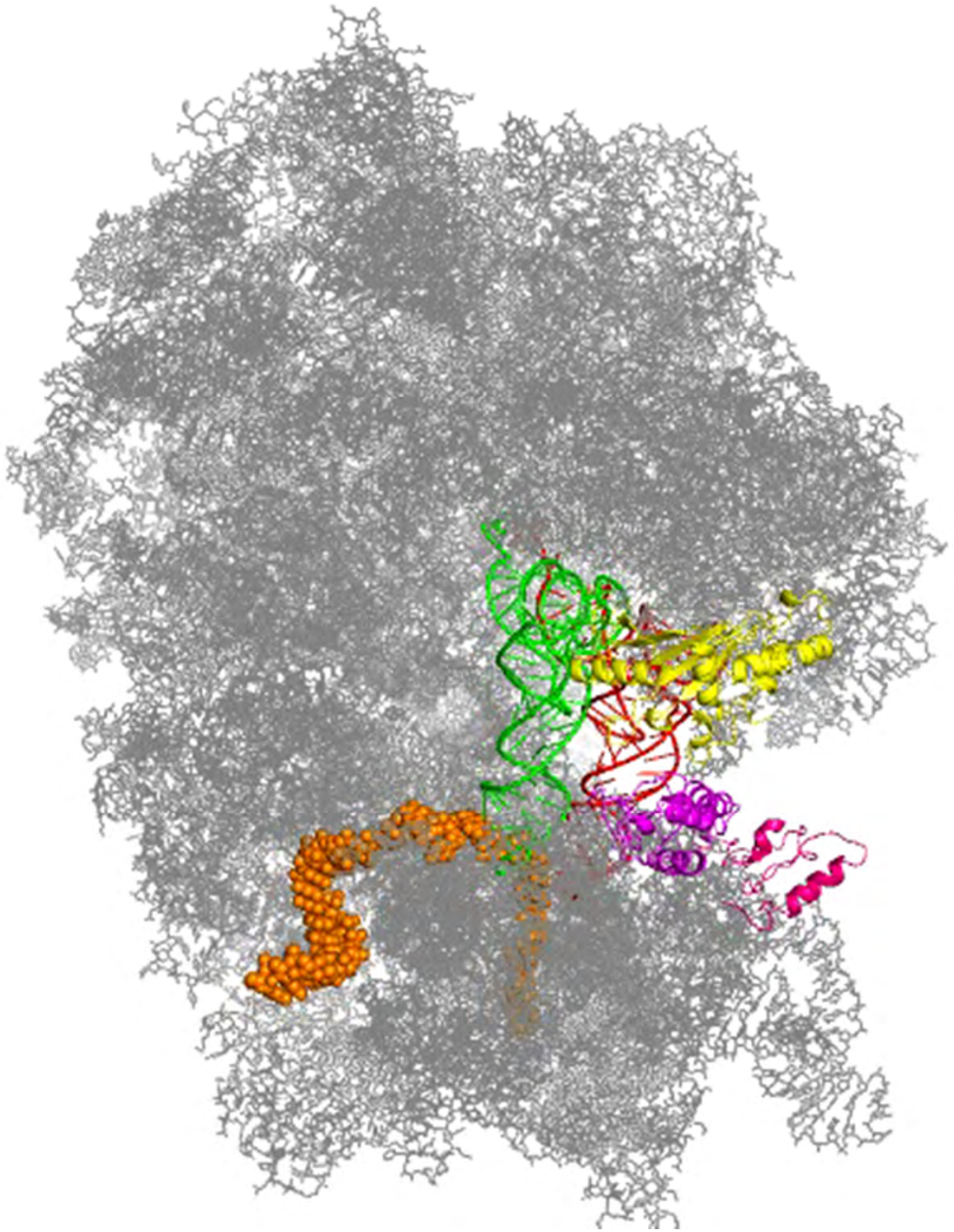
Department of Chemical Physics
The Weizmann Institute of Science
Rehovot, Israel



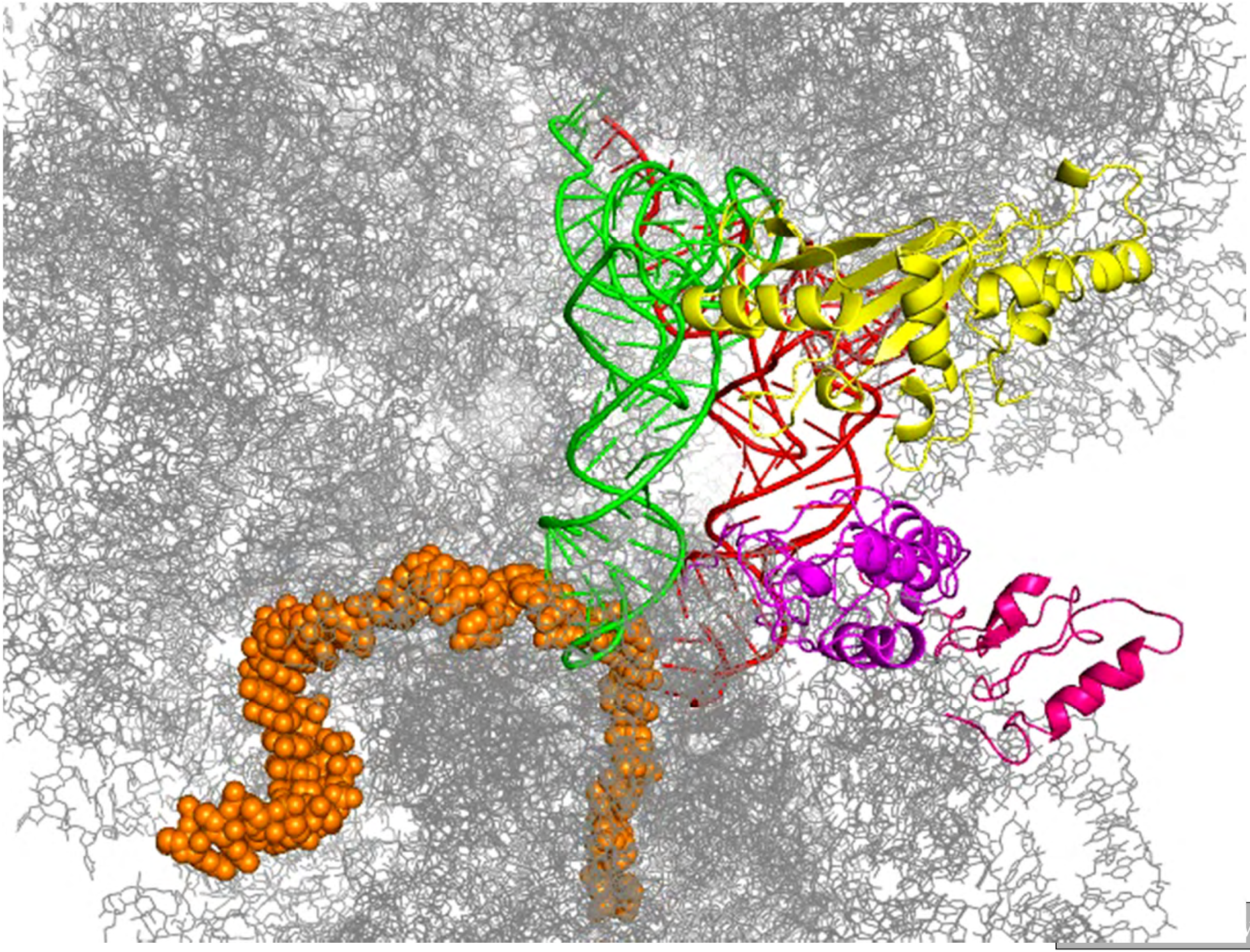


SIMULATING FUNCTIONAL MOTION

RIBOSOME TRANSLOCATION



RIGID BODY MORPHING



MY WORK IS ALL BASIC SCIENCE

BUT IS IT OF ANY USE OR VALUE?

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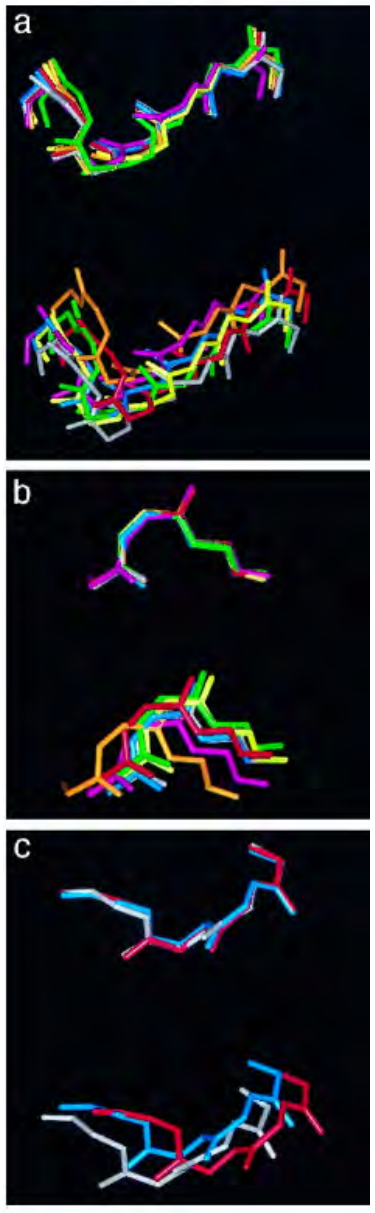
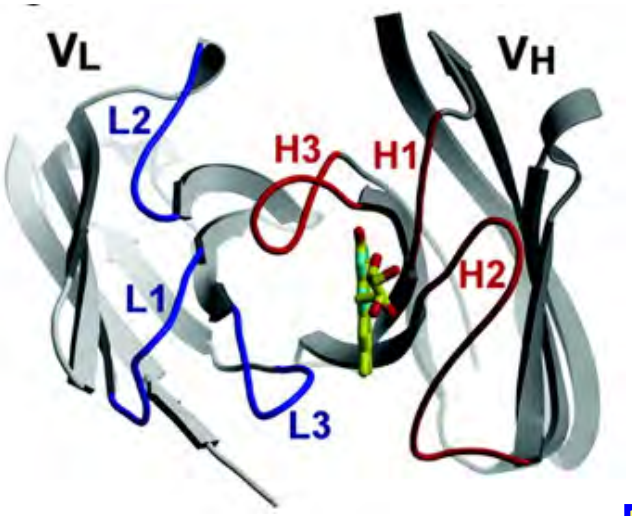
CANONICAL HYPER-VARIABLE REGIONS

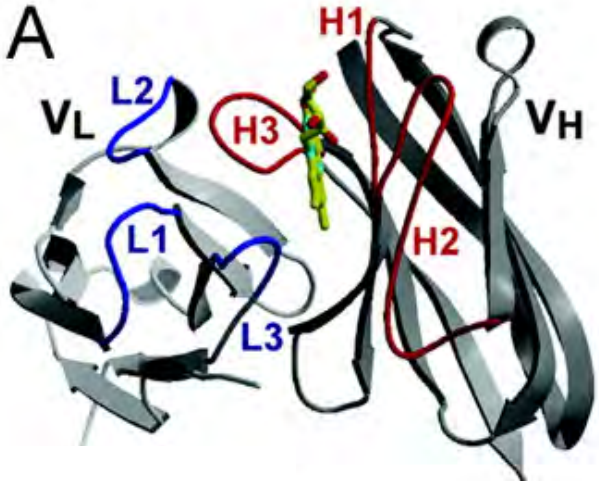


H1

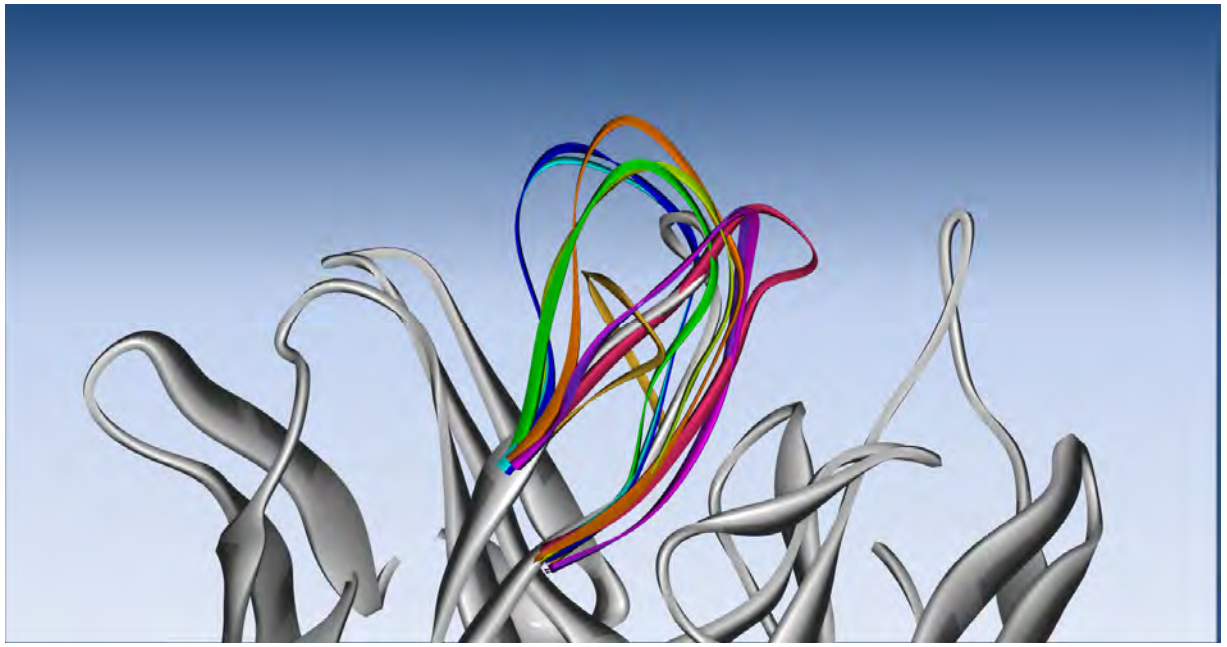
L2

H2





Lesk & Chothia, 1987



QUEEN ET AL 1989

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10029–10033, December 1989
Immunology

A humanized antibody that binds to the interleukin 2 receptor

(chimeric antibody/antibody affinity/autoimmune disease)

CARY QUEEN*, WILLIAM P. SCHNEIDER*, HAROLD E. SELICK*†, PHILIP W. PAYNE*, NICHOLAS F. LANDOLFI*, JAMES F. DUNCAN*‡, NEVENKA M. AVDALOVIC*, MICHAEL LEVITT§, RICHARD P. JUNGHANS¶, AND THOMAS A. WALDMANN¶

*Protein Design Labs, 3181 Porter Drive, Palo Alto, CA 94304; §Department of Cell Biology, Stanford University, Stanford, CA 94305; and ¶Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

Contributed by Thomas A. Waldmann, August 30, 1989

ABSTRACT **The anti-Tac monoclonal antibody is known to bind to the p55 chain of the human interleukin 2 receptor and to inhibit proliferation of T cells by blocking interleukin 2 binding. However, use of anti-Tac as an immunosuppressant drug would be impaired by the human immune response against this murine antibody. We have therefore constructed a "humanized" antibody by combining the complementarity-determining regions (CDRs) of the anti-Tac antibody with human framework and constant regions. The human framework regions were chosen to maximize homology with the anti-Tac antibody sequence. In addition, a computer model of murine anti-Tac was used to identify several amino acids which, while outside the CDRs, are likely to interact with the CDRs or antigen. These mouse amino acids were also retained in the humanized antibody. The humanized anti-Tac antibody has an affinity for p55 of $3 \times 10^9\ M^{-1}$, about 1/3 that of murine anti-Tac.**

partial or complete remission in three of nine patients with Tac-expressing adult T-cell leukemia (14). However, as a murine monoclonal antibody, anti-Tac elicits a strong human antibody response against itself, as does OKT3 (15). This response would prevent its long-term use in treating autoimmune conditions or suppressing organ transplant rejection.

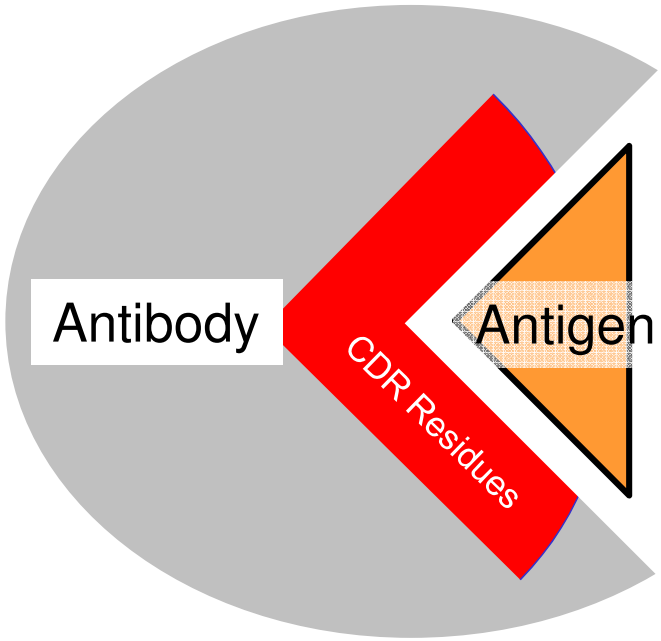
The immune response against a murine monoclonal antibody may potentially be reduced by transforming it into a chimeric antibody. Such antibodies, produced by methods of genetic engineering, combine the variable (V) region binding domain of a mouse (or rat) antibody with human antibody

KEY PAPER

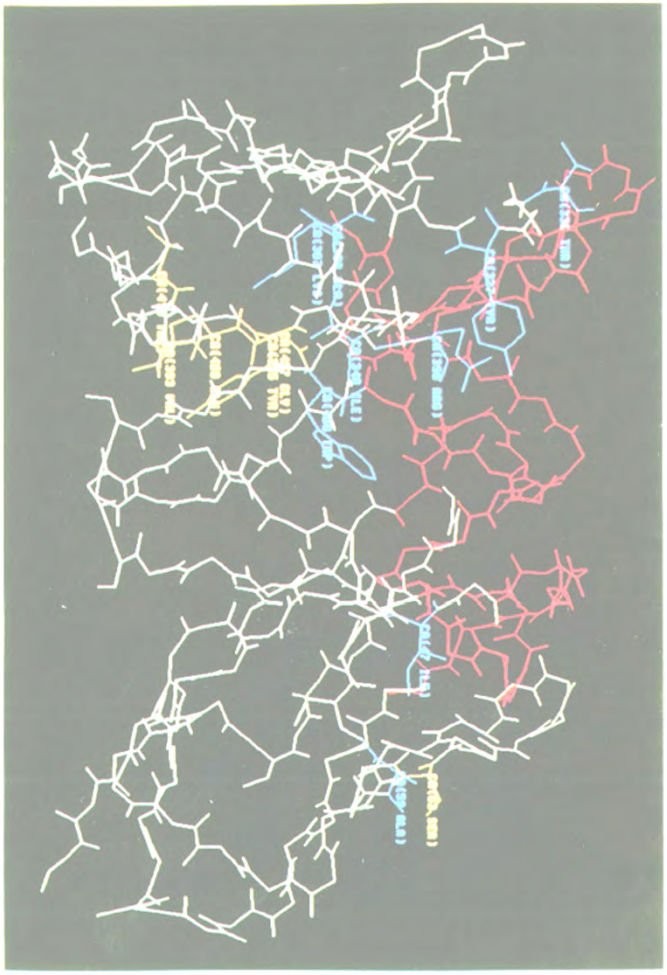
BETTER SCIENCE LED TO BETTER PATENTS

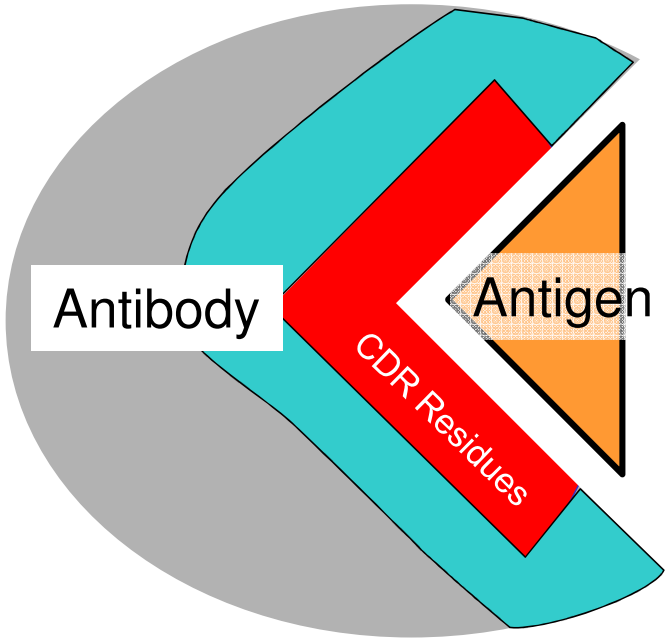
KEY IDEA

Think in three-dimensions



WINTER
LMB

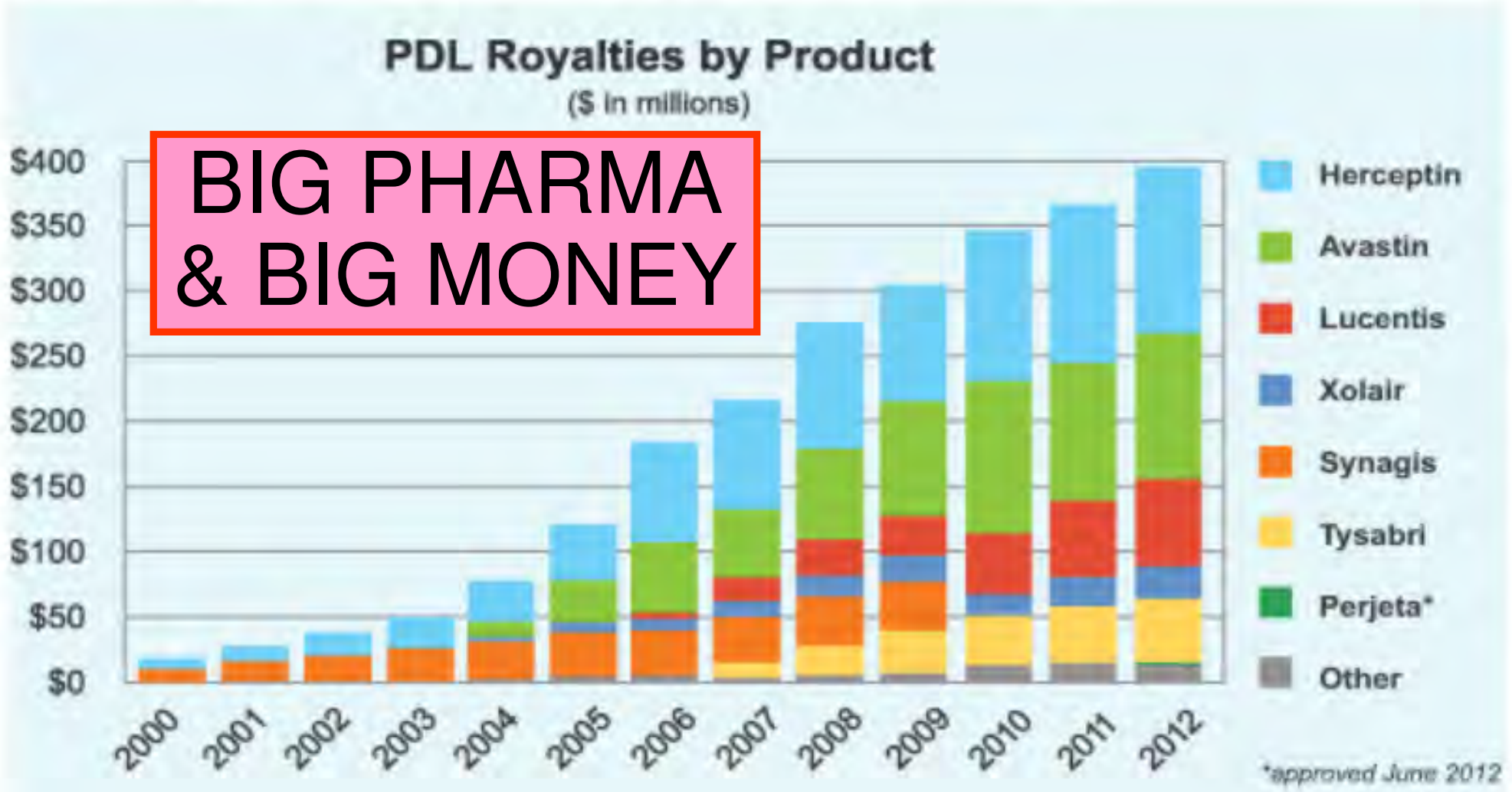




QUEEN
PDL

BETTER PATENTS LED TO BETTER DRUGS

Our royalty revenues have grown significantly over the last several years and we expect continued growth before the expiration of our Queen et al patents in December 2014.



I ENJOYED A WONDERFUL LIFE IN BASIC SCIENCE

WHAT ABOUT TODAY'S YOUNG SCIENTIST?

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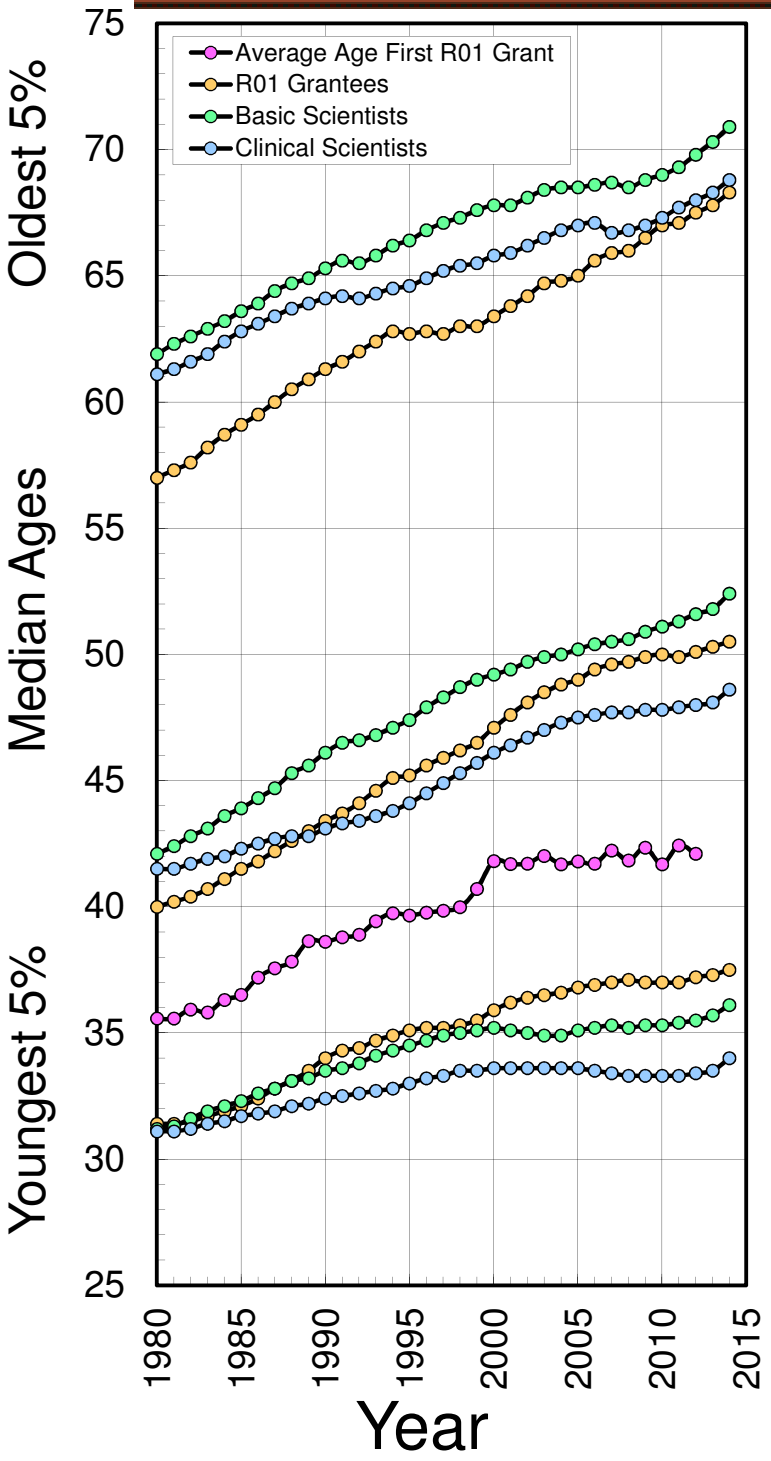
4. YOUNG BASIC SCIENTISTS IN THE USA

Levitt, M. and J.M. Levitt. Future of fundamental discovery in US biomedical research. *Proceedings of the National Academy of Sciences*, **114** (25) 6498-6503 (2017).

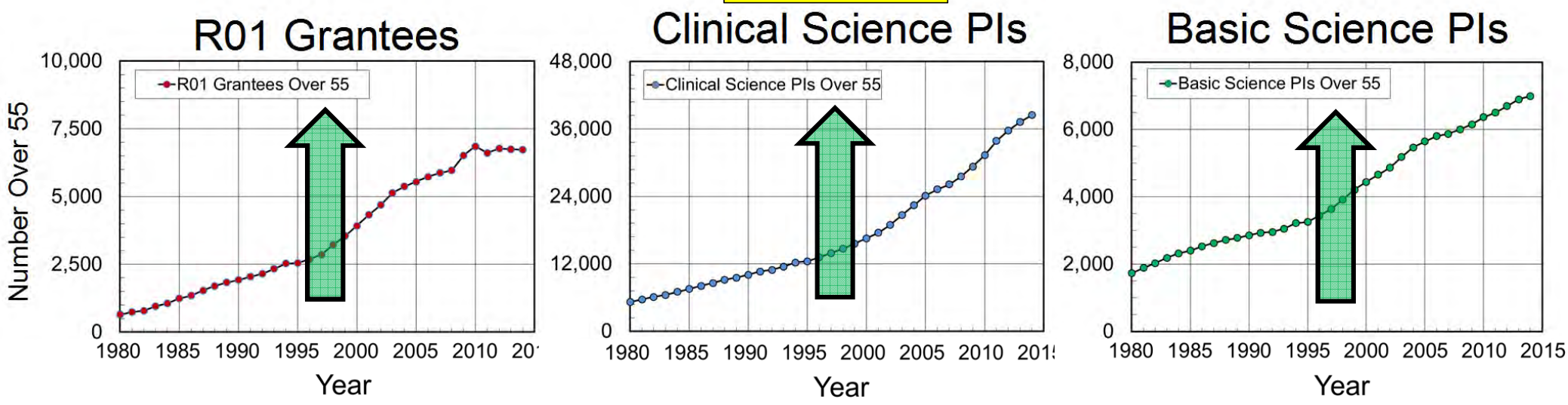
AGING OF R01 GRANTEES & PIs



- The First-Time PIs are not young; 5 years older than youngest 5%.
- All R01 Grantees are aging.
- Young Clinical Science PIs age least.
- Young Basic Science PIs age most.
- Clinical Science PIs aging less than Basic PIs for Median and Oldest 5%.

CHANGING NUMBERS IN AGE RANGES

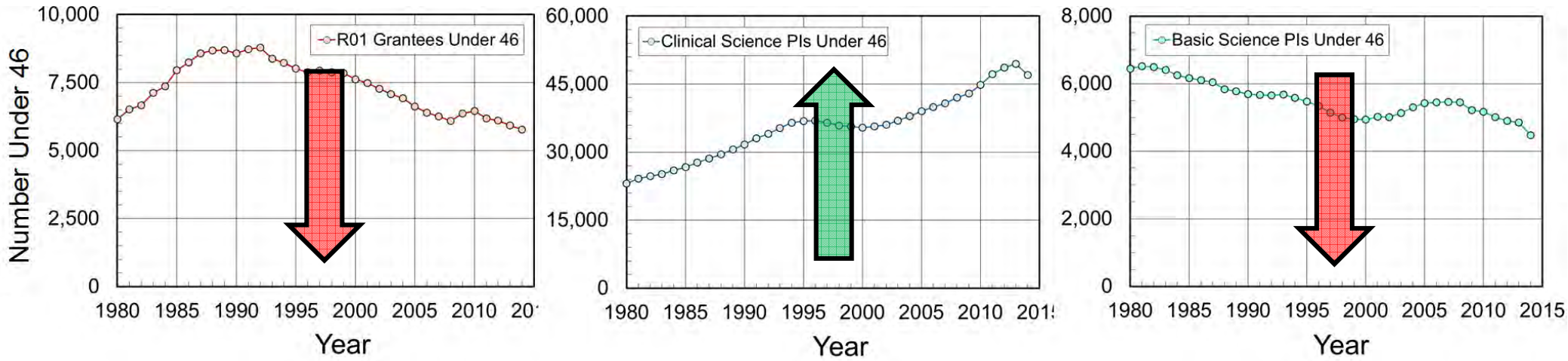
Over 55



Older Increase
Younger Decrease

Older Increase
Younger Increase

Older Increase
Younger Decrease

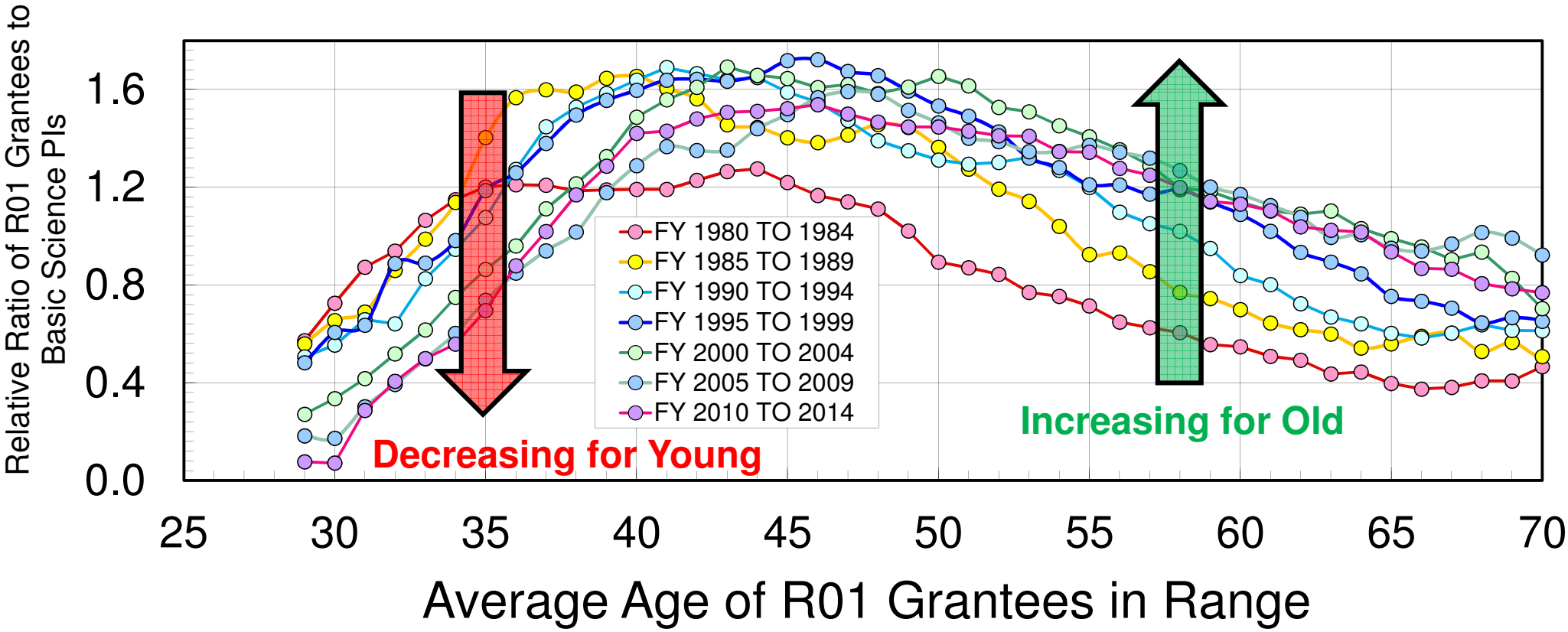


Under 46

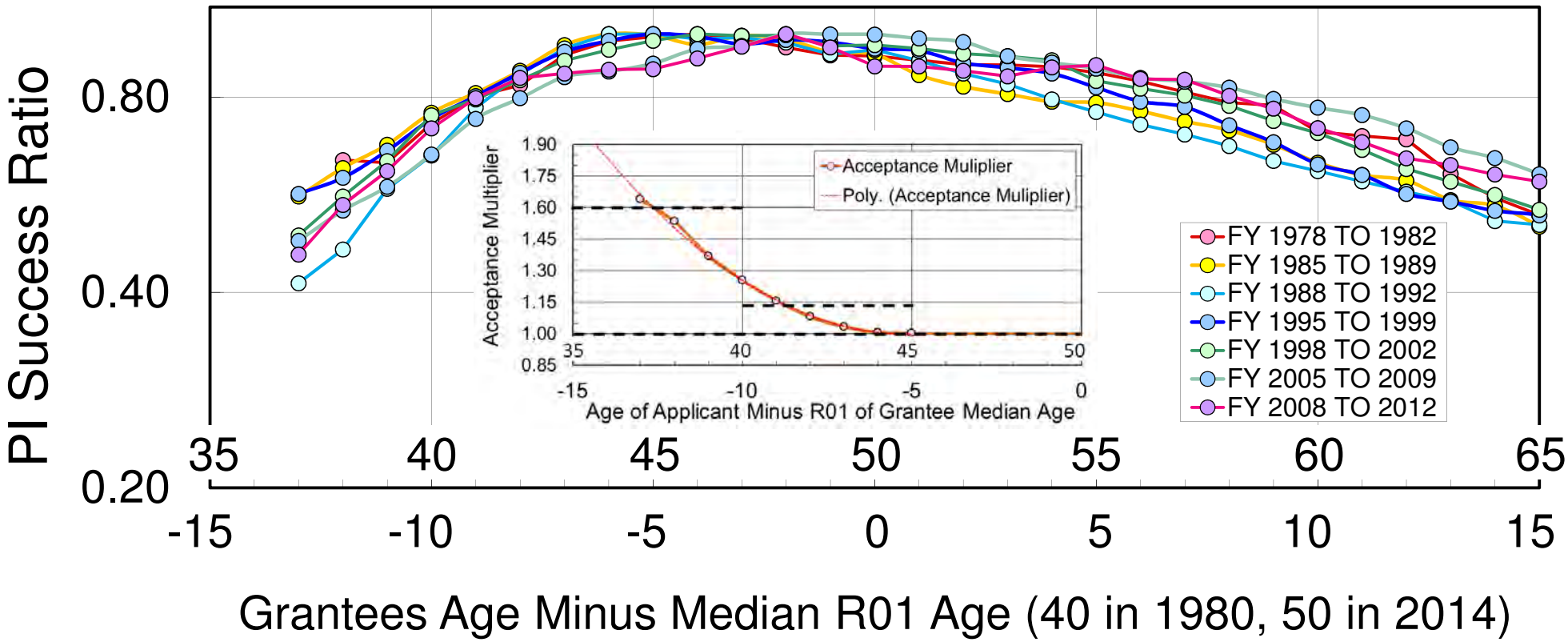
HOW RELATIVE PI SUCCESS RATIO HAS CHANGED

$$\text{PI Success Ratio} = \frac{\text{Number of R01 Grantees of Age in Year}}{\text{Number of Basic Science PIs of Same Age in Same Year}}$$

Grantees/Basic Science PIs



PI SUCCESS RATIO DRIVES NUMBER OF PIs



Grantees Age Minus Median R01 Age (40 in 1980, 50 in 2014)

- When a smaller and smaller fraction of PIs under 40 are getting grants, department will hire fewer young PIs.
- When more and more PIs between 50 and 70 are getting grants, departments will keep them on.

THE US BIOMEDICAL ENTERPRISE IS ELIMINATING YOUNG BASIC SCIENTISTS

DOES THIS REALLY MATTER?

WE CAN APPLY THE IDEAS WE HAVE!

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(5) IS BASIC SCIENCE IMPORTANT NATIONALLY?

SERENDIPITY OF BASIC SCIENCE

- Story: "The Three Princes of Serendip"
  Michele Tramezzino Venice 1557
  They were lucky and smart.

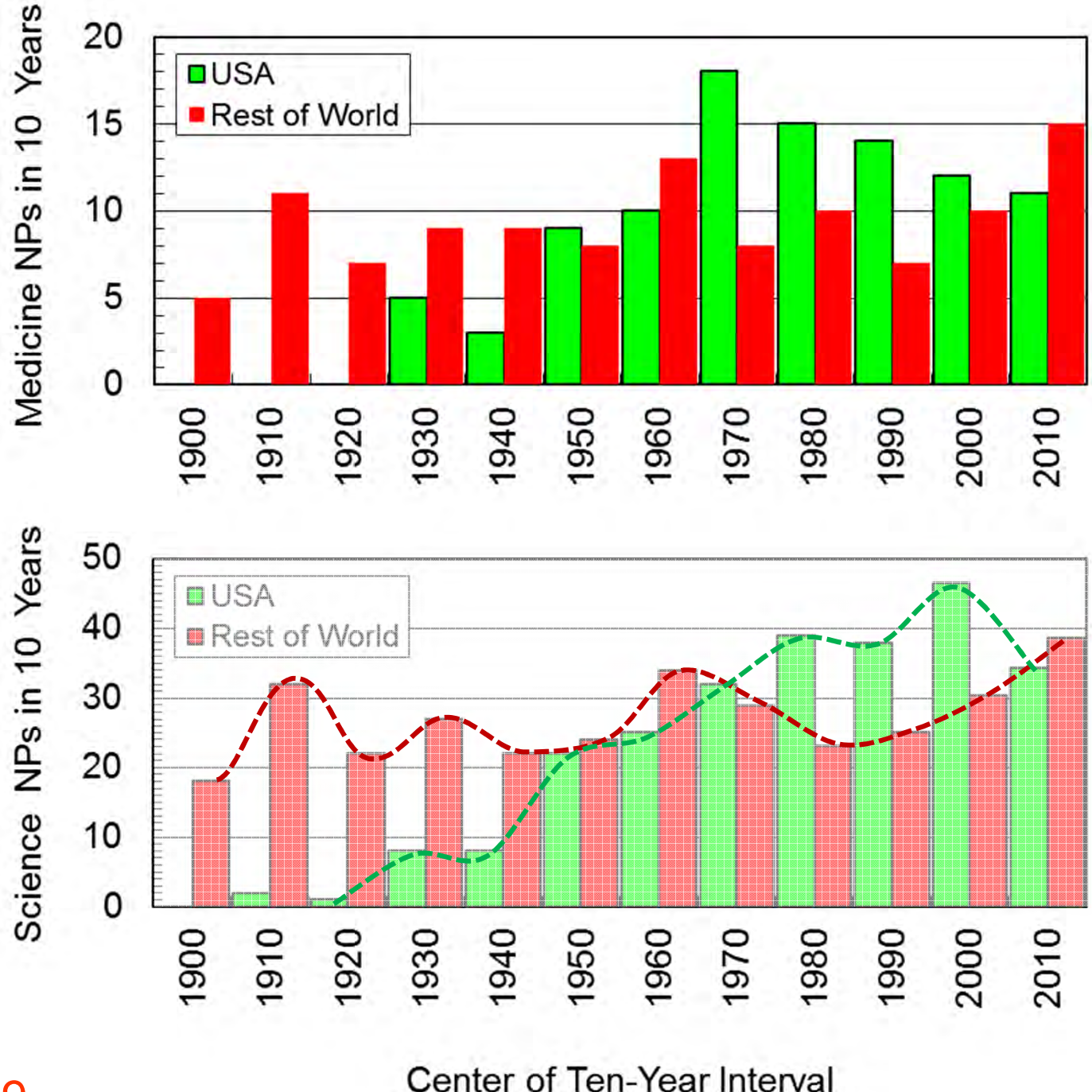
- Geography: Where is Serendip?

- A scientific discovery is like winning a lottery.
  Cannot really be planned or predicted.
  You have to have a ticket.
  Having more ticket than one ticket helps.

IS BASIC SCIENCE IMPORTANT?

- Very hard to tell who did what in science? Priority is a subject of intense argument and needs to be disentangled with great care. Ambitious scientists often bury the work of others.
- Not easy to estimate the value of Basic Science without intimate knowledge of the scientific field.
- Take the easy way out and rely on the Nobel Committee.
- They take more care than all other prize committees taken together and have done so for 121 years.

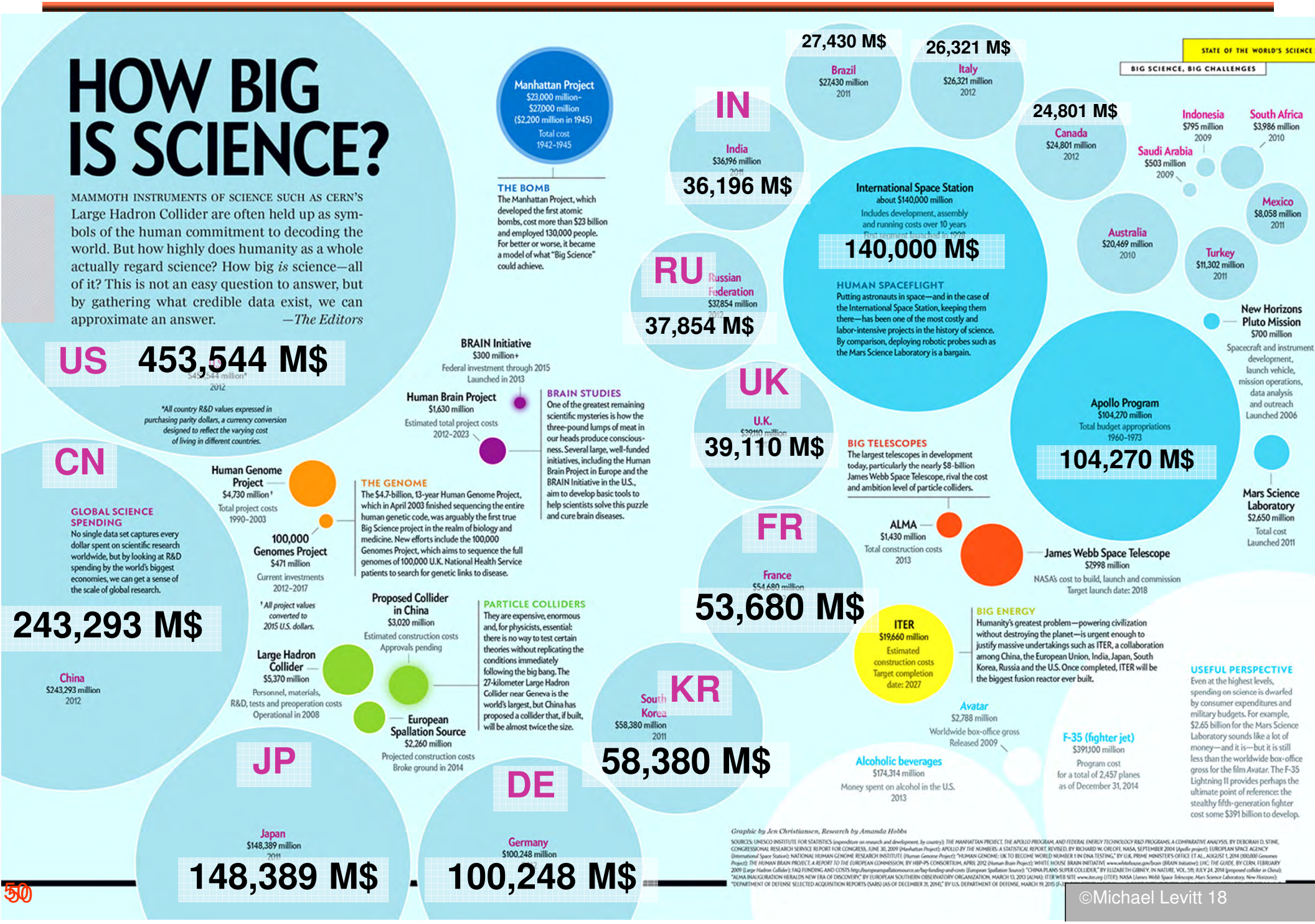
THE USA VS. THE REST OF THE WORLD?



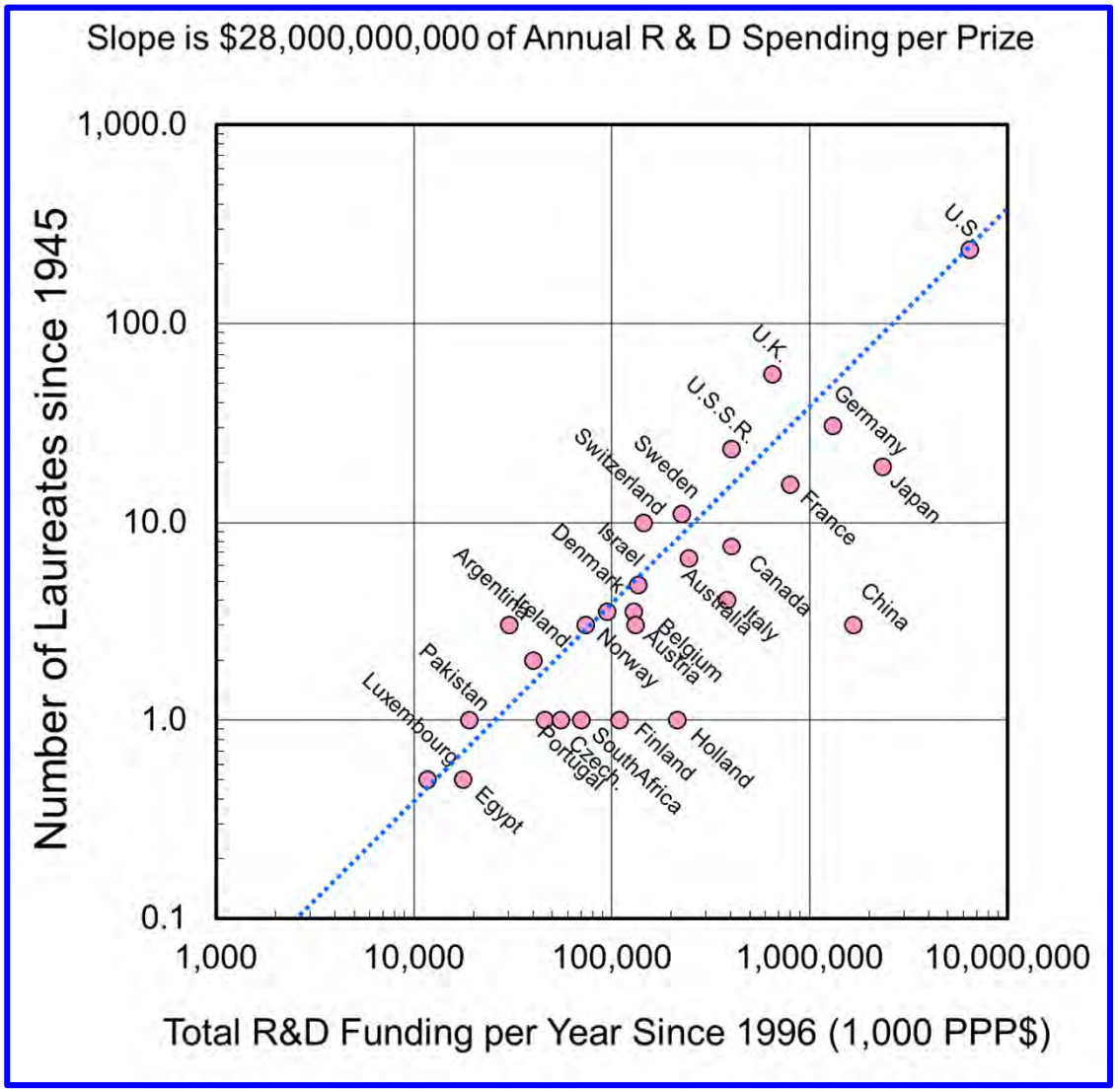
In four of the past five decades, the USA has won more Nobel Prizes than the rest of the world.

In the USA loosing is advantage?

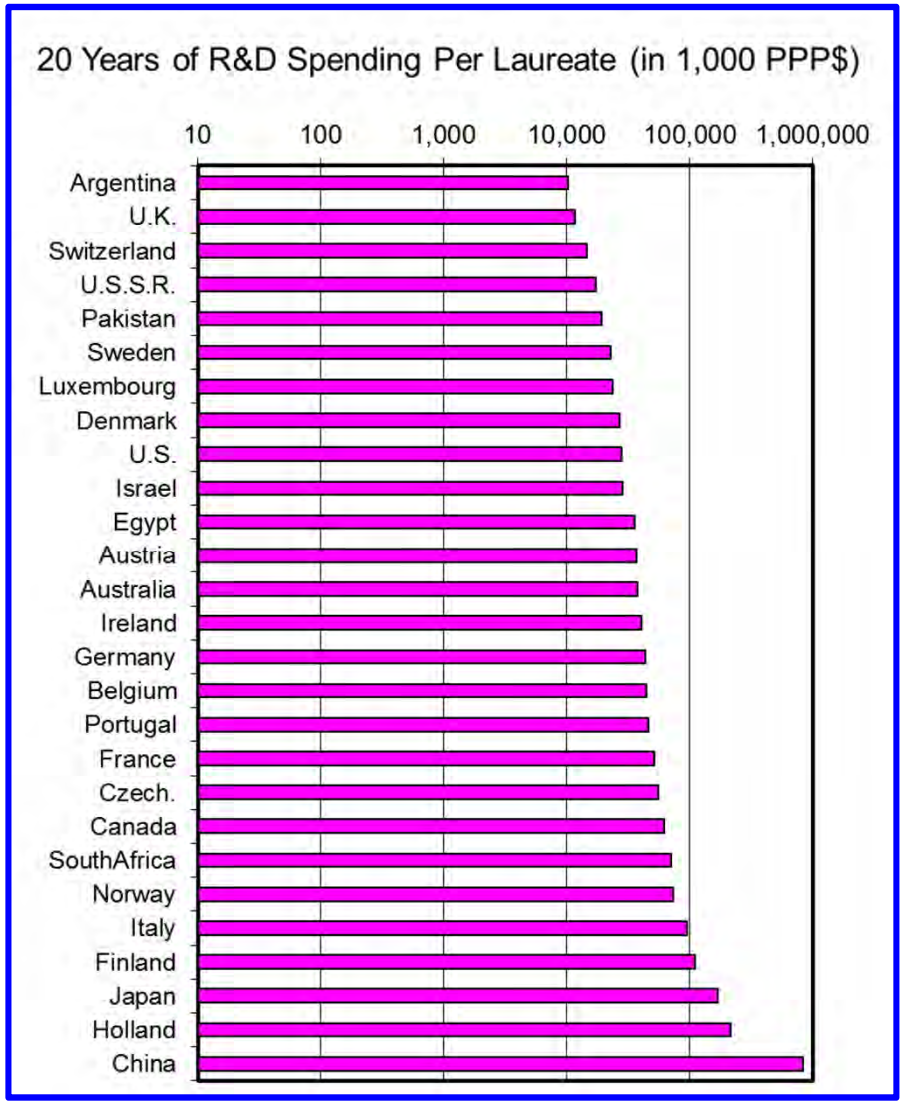
SCIENTIFIC AMERICAN SEPTEMBER 2015



MORE R&D SPENDING GIVES MORE NOBEL PRIZES



Linear dependence on R&D spending over range of 10,000x



Cost per laureate in PPP$ Billions:

US:	28 B$	UK:	13 B$
Germany:	66 B$	Holland:	214 B$
Japan:	168 B$	China:	840 B$

SUMMARY

✓1. A Biophysical Revolution in Biology.

✓2. Computational Structural Biology.

✓3. Applied Computational Structural Biology

✓4. Young Basic Scientists in the USA.

✓5. Is Basic Science Important?

6. How to Win Many Nobel Prizes?

QUALITY BASIC SCIENTIFIC RESEARCH NEEDS MONEY AND FULL-TIME RESEARCH COMMITMENT

BUT WHAT ELSE IS NEEDED?

(6) HOW TO WIN MANY NOBEL PRIZES

MEDICAL RESEARCH COUNCIL LABORATORY OF MOLECULAR BIOLOGY (LMB) IN CAMBRIDGE

27 LMB NOBEL PRIZES

1958	**Fred Sanger**	Chemistry	Determination of the Structure of the Insulin Molecule
1962	**Francis Crick**	Medicine	Discoveries Concerning the Molecular Structure of DNA
1962	**Jim Watson**	Medicine	Discoveries Concerning the Molecular Structure of DNA
1962	**John Kendrew**	Chemistry	Determination of the Structure of Hemoproteins
1962	**Max Perutz**	Chemistry	Determination of the Structure of Hemoproteins
1980	**Fred Sanger**	Chemistry	Development of Chemical and Biological Analyses of DNA Structure
1982	**Aaron Klug**	Chemistry	Determination of the Structure of Biological Substances
1984	**César Milstein**	Medicine	Theory and Development of a Technique for Producing Monoclonal Antibodies
1984	**Georges Köhler**	Medicine	Theory and Development of a Technique for Producing Monoclonal Antibodies
1989	**Sidney Altman**	Chemistry	Discovery of Certain Basic Properties of RNA
1993	**Michael Smith**	Chemistry	Invention of Techniques for Gene Study and Manipulation
1993	**Richard Roberts**	Medicine	Discovery of Split, or Interrupted, Genetic Structure
1997	**John Walker**	Chemistry	Explanation of the Enzymatic Conversion of Adenosine Triphosphate
2002	**Bob Horvitz**	Medicine	Discoveries Concerning Genetic Regulation of Organ Development and Programmed Cell Death
2002	**John Sulston**	Medicine	Discoveries Concerning Genetic Regulation of Organ Development and Programmed Cell Death
2002	**Sydney Brenner**	Medicine	Discoveries Concerning Genetic Regulation of Organ Development and Programmed Cell Death
2006	**Andrew Fire**	Medicine	Discovery of RNA Interference—Gene Silencing by Double-Stranded RNA
2006	**Roger Kornberg**	Chemistry	Work Concerning the Molecular Basis of Eukaryotic Transcription
2008	**Martin Chalfie**	Chemistry	Discovery and Development of the Green Fluorescent Protein, GFP
2009	**Elizabeth Blackburn**	Medicine	Discovery of How Chromosomes Are Protected by Telomeres and the Enzyme Telomerase
2009	**Tom Steitz**	Chemistry	Studies of the Structure and Function of the Ribosome
2009	**Venki Ramakrishnan**	Chemistry	Studies of the Structure and Function of the Ribosome
2012	**John Gurdon**	Medicine	Discovery that Mature Cells Can be Reprogrammed to Become Pluripotent
2013	**Arieh Warshel**	Chemistry	Development of Multiscale Models for Complex Chemical Systems
2013	**Martin Karplus**	Chemistry	Development of Multiscale Models for Complex Chemical Systems
2013	**Michael Levitt**	Chemistry	Development of Multiscale Models for Complex Chemical Systems
2017	**Richard Henderson**	Chemistry	Developing cryo-electron microscopy for the high-resolution structure determination of biomolecules

(1) Green from Southern Hemisphere

Light Yellow from USA

A RECIPE FOR NOBEL PRIZES

(1) Ample research support.

(2) No visible bureaucracy (hidden from us by leader):

Free supplies, advanced equipment, computing.

(3) Small groups (average three, often one).

(4) Collaborate with peers

(5) Intense peer pressure:

You are only as good as your next paper.

(6) No hierarchy: Students are as good as Nobel Laureates.

QUESTIONS

1. Does my life path generalize?

2. What does it take to be a scientist? **PPOK**
   Passion Persistence Originality Kindness

3. How are young scientists best encouraged?
   Independence or Collaboration? Teams or Stars?

4. Is universal fundamental research needed?

5. Should scientists be entrepreneurs?

6. Are Nobel Prizes important?

THE END