

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

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.K.S. *Discovery II* for their part in making the observations.

- ¹ Young, F. B., Gerard, H., and Jerome, W., *Phil. Mag.*, **46**, 149 (1928).
- ² Langsdorf-Higgins, M. S., *Mon. Not. Roy. Astr. Soc., Geophys. Supp.*, **3**, 285 (1949).
- ³ Van Arx, W. S., *Woods Hole Papers in Phys. Oceanogr. Meteor.*, **11** (3) (1956).
- ⁴ Elman, V. W., *Astrik. Mat. Astron. Fizik. (Stockholm)*, **2** (11) (1965).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the molecule of deoxyribose nucleic acid (D.N.A.), which has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the axis, and the bases on the outside. In our opinion this structure is unsatisfactory for two reasons: (1) We believe that the material which gives rise to X-ray diagrams is the salt, not the free acid. With the acidic hydrogen atoms it is not clear what would hold the structure together, especially as negatively charged phosphates near the axis repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram).

It has made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β -D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the atoms in the two chains near it is close to Furberg's 'standard configuration', sugar being roughly perpendicular to the attached base.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material. Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

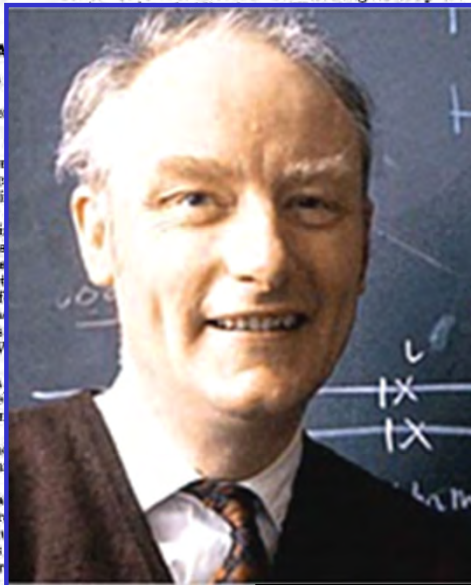
We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a letter from Dr. Pauling.

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

is a residue on each chain every 3.4 Å, in the z -direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphorus atom from the fibre axis is 10 Å. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the



King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge, April 2.

- ¹ Pauling, L., and Corey, R. B., *Nature*, **121**, 348 (1958); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
- ² Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).

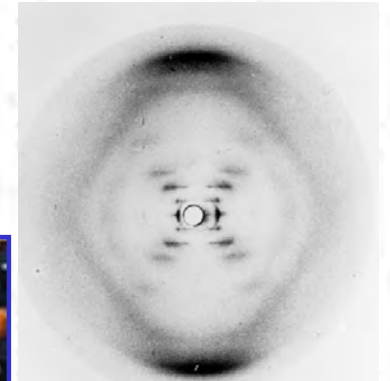


Fig. 1. Fibre diagram of deoxyribose nucleic acid from E. coli. Fibre axis vertical.

An innermost maxima of each Bessel function and a origin. The angle this line makes with the equator roughly equal to the angle between an element of a helix and the helix axis. If a unit repeats a times round the helix there will be a meridional reflection on the n th layer line. The helical configuration induces side bands on this fundamental frequency, the effect being to reproduce the intensity distribution about the origin around the n th origin, on the n th layer line, corresponding to C in Fig. 2.

We will now briefly analyse in physical terms some of the effects of the shape and size of the repeat unit nucleotide on the diffraction pattern. First, if the nucleotide consists of a unit having circular symmetry about an axis parallel to the helix axis, the whole fraction pattern is modified by the form factor of a nucleotide. Second, if the nucleotide consists of a series of points on a radius at right-angles to the helix axis, the phases of radiation scattered by the discs of different diameter passing through each unit are the same. Summation of the corresponding Bessel functions gives reinforcement for the inner-

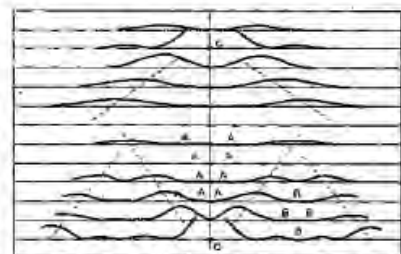


Fig. 2. Diffraction patterns of systems of helices corresponding to structure of deoxyribose nucleic acid. The squares of Bessel functions are plotted about U on the equator and on the first, second, third and fifth layer lines for half of the nucleotide mean at 20 Å diameter and remainder distributed along a radius, the axis at a given radius being proportional to the radius. About C on the fourth layer line angular functions are plotted for an outer diameter of 12 Å.

stitial water. The absence of reflections on or near the meridian immediately suggests a helical structure with axis parallel to fibre length.

Diffraction by Helices

It may be shown² (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is given by the squares of Bessel functions. A uniform continuous helix gives a series of layer lines of spacing corresponding to the helix pitch, the intensity distribution along the n th layer line being proportional

1916-2004

DNA Model and Experiment

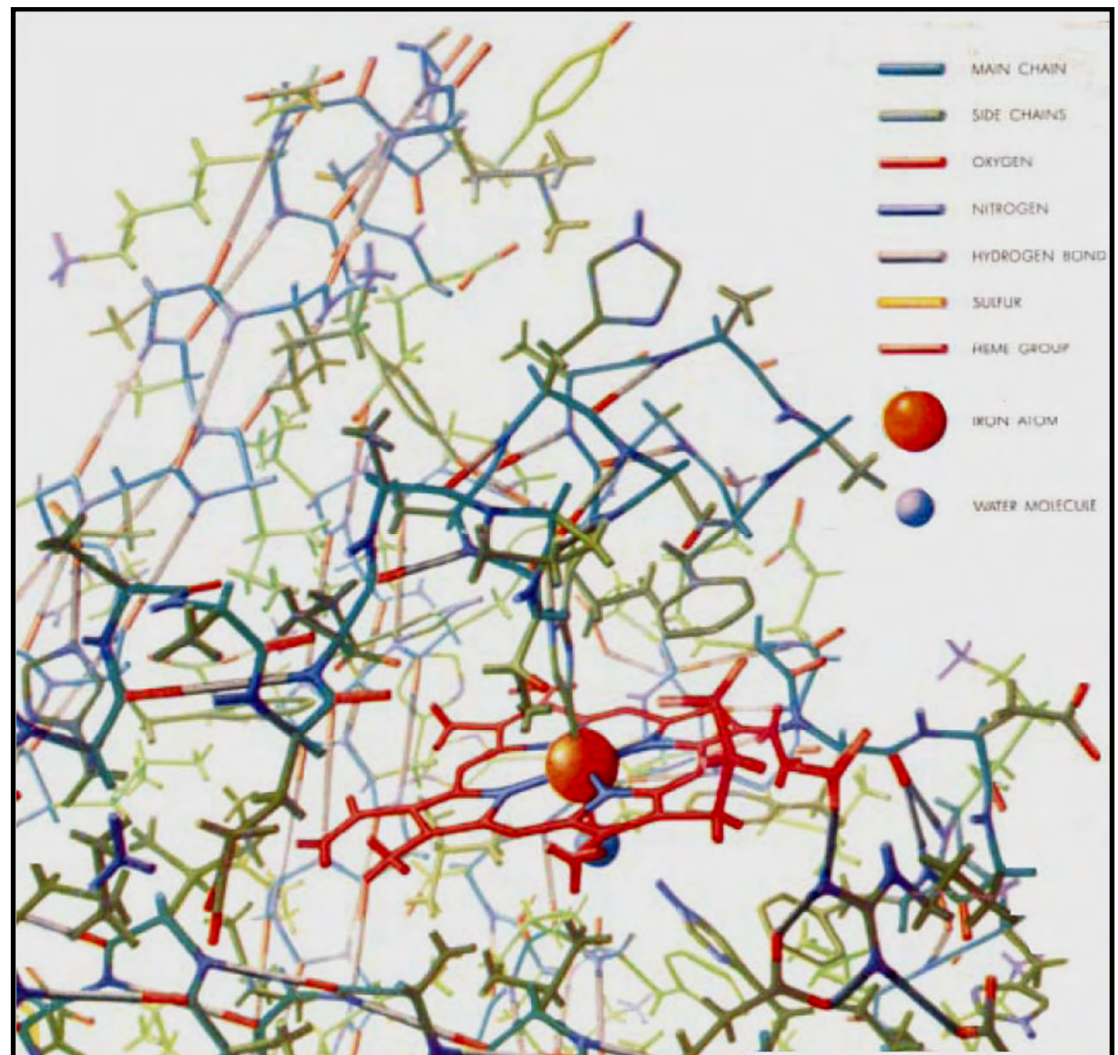
1959: KENDREW AND MYOGLOBIN

Scientific American 1961



1917-1997

First protein X-ray structure.



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?

SUMMARY

- ✓ 1. A Biophysical Revolution in Biology.
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6. How to Win Many Nobel Prizes?

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](#)

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

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)

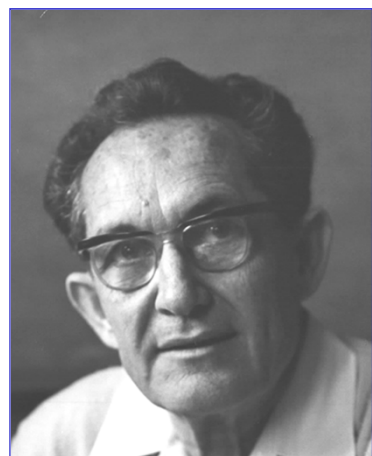
The WAY AHEAD (07/03/1964)



CONSISTENT FORCE-FIELD



1968



**Small molecules,
Hydrocarbons,
Saturated, -CH₂-**



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)

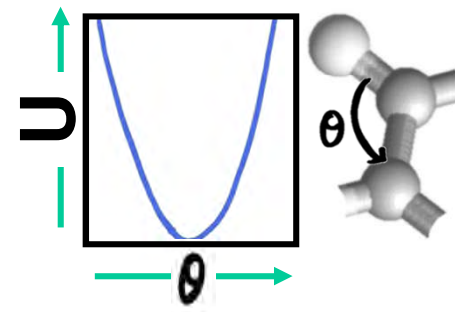
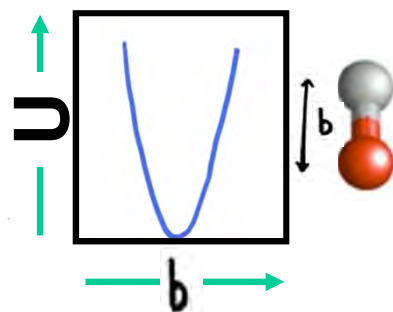
©Michael Levitt 18

MOLECULAR POTENTIAL ENERGY

$$U = \sum \frac{1}{2} K_b (b - b_0)^2 - \sum \frac{1}{2} K_\theta (\theta - \theta_0)^2$$

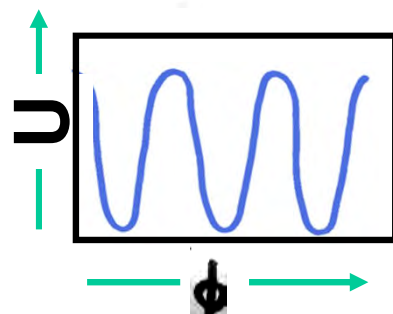
All Bonds

All Angles



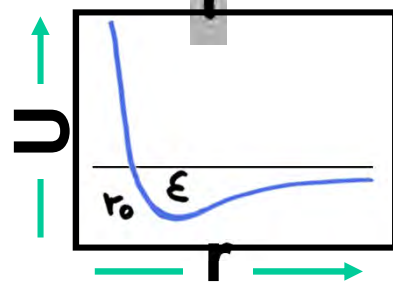
$$+ \sum K_\phi [1 - \cos(n\phi + \delta)]$$

All Torsion Angles



$$+ \sum \epsilon \left[\left(\frac{r_0}{r} \right)^{12} - 2 \left(\frac{r_0}{r} \right)^6 \right]$$

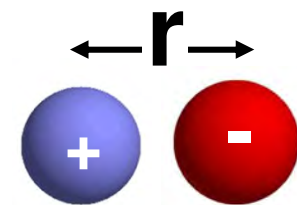
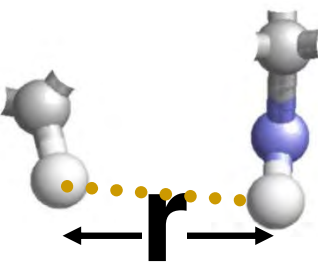
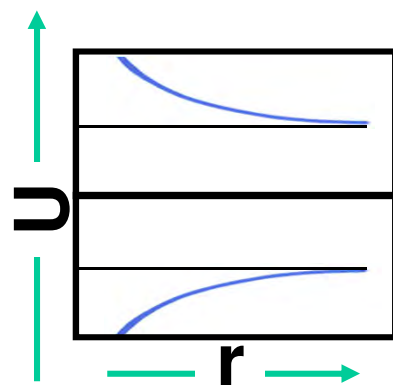
All nonbonded pairs



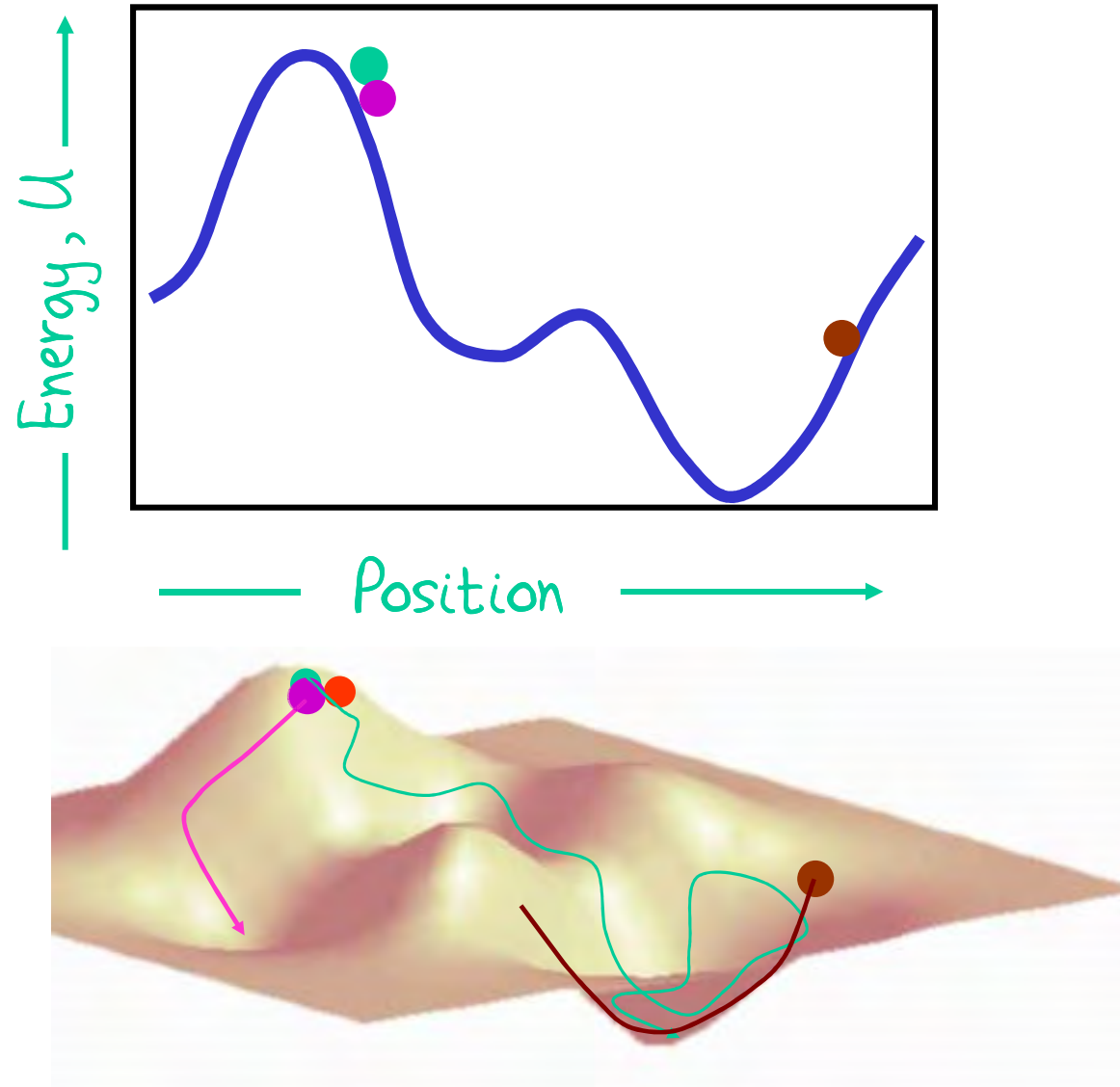
$$+ \sum \frac{332 q_i q_j}{r}$$

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

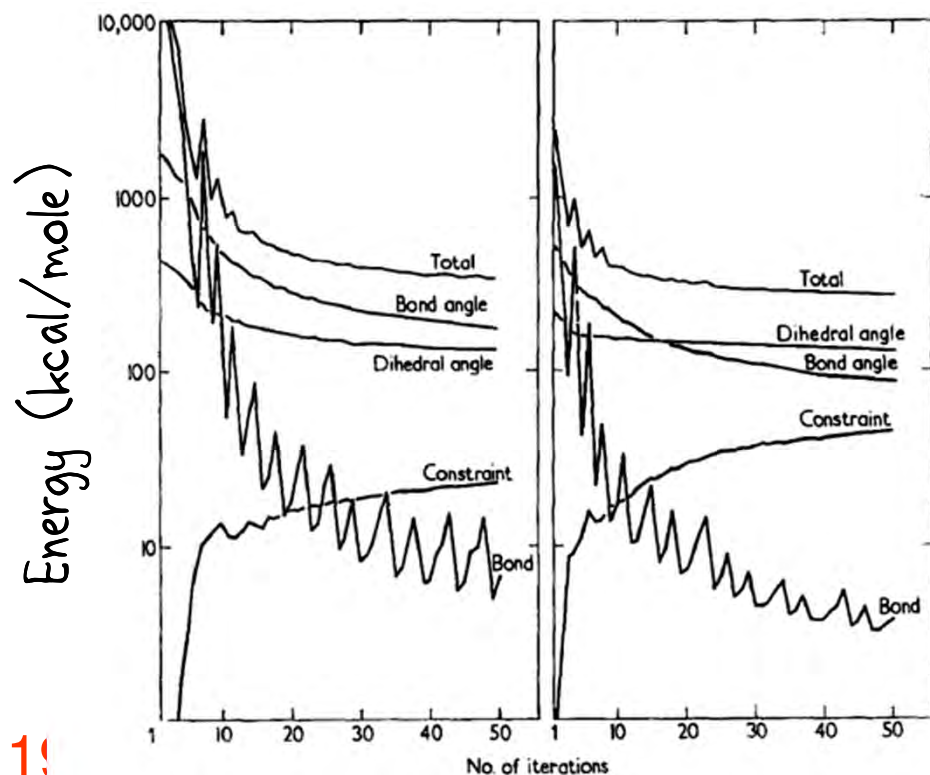
MICHAEL LEVITT† AND SHNEIOR LIFSON

Weizmann Institute of Science

J. Mol. Biol. (1969) **46**, 269-279



$$\begin{aligned}
 E = & \sum_{\text{all bonds}} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\text{all bond angles}} \frac{1}{2} K_\tau (\tau - \tau_0)^2 + \sum_{\text{all dihedral angles}} \frac{1}{2} K_\theta \{1 + \cos(n\theta - \delta)\} \\
 & + \sum_{\text{all non-bonded pairs}} \epsilon_{ij} \left\{ \left(\frac{r_{ij}^0}{r_{ij}}\right)^{12} - 2 \left(\frac{r_{ij}^0}{r_{ij}}\right)^6 \right\} + \sum_{\text{all atomic co-ordinates}} \frac{1}{2} w (x_i - x_i^0)^2
 \end{aligned}$$



$$\begin{aligned}
 U = & \sum_{\text{All Bonds}} \frac{1}{2} K_b (b - b_0)^2 - \sum_{\text{All Angles}} \frac{1}{2} K_\theta (\theta - \theta_0)^2 \\
 & + \sum_{\text{All Torsion Angles}} K_\phi [1 - \cos(n\phi + \delta)] \\
 & + \sum_{\text{All nonbonded pairs}} \epsilon \left[\left(\frac{r_0}{r}\right)^{12} - 2 \left(\frac{r_0}{r}\right)^6 \right] \\
 & + \sum_{\text{All partial charges}} \frac{332 q_i q_j}{r}
 \end{aligned}$$

Simple sum over many terms

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

COARSE-GRAINED MODELS 1975

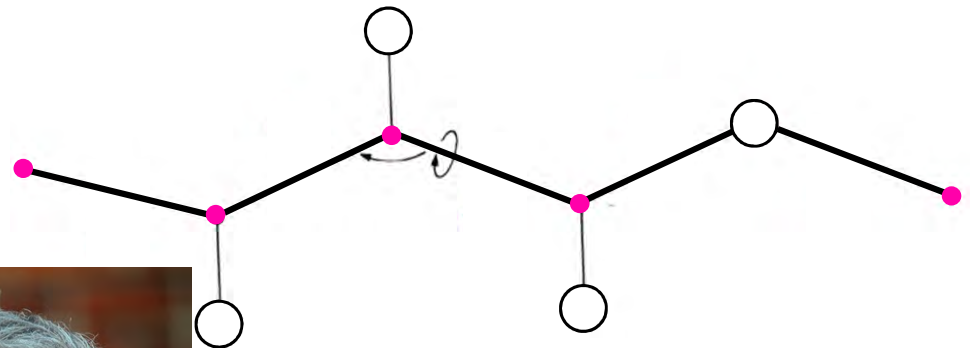
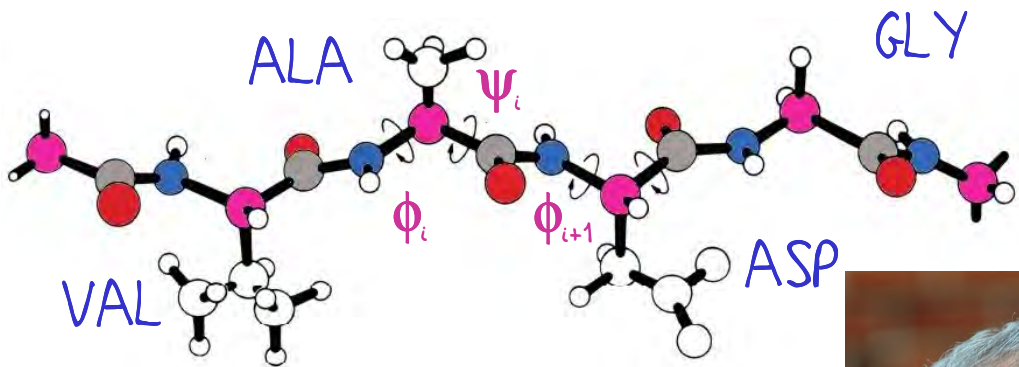


COMPUTER SIMULATION OF PROTEIN FOLDING

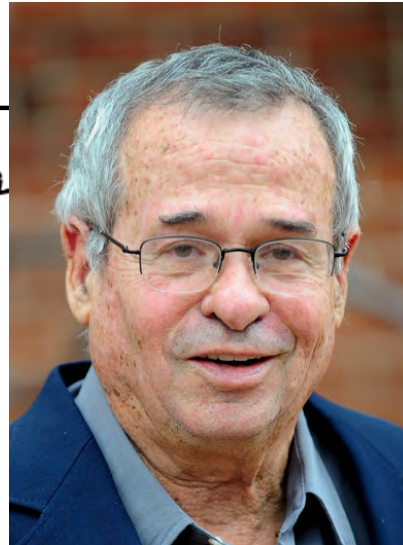
Michael Levitt* & Arieh Warshel*

Nature Vol. 253 February 27 1975

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

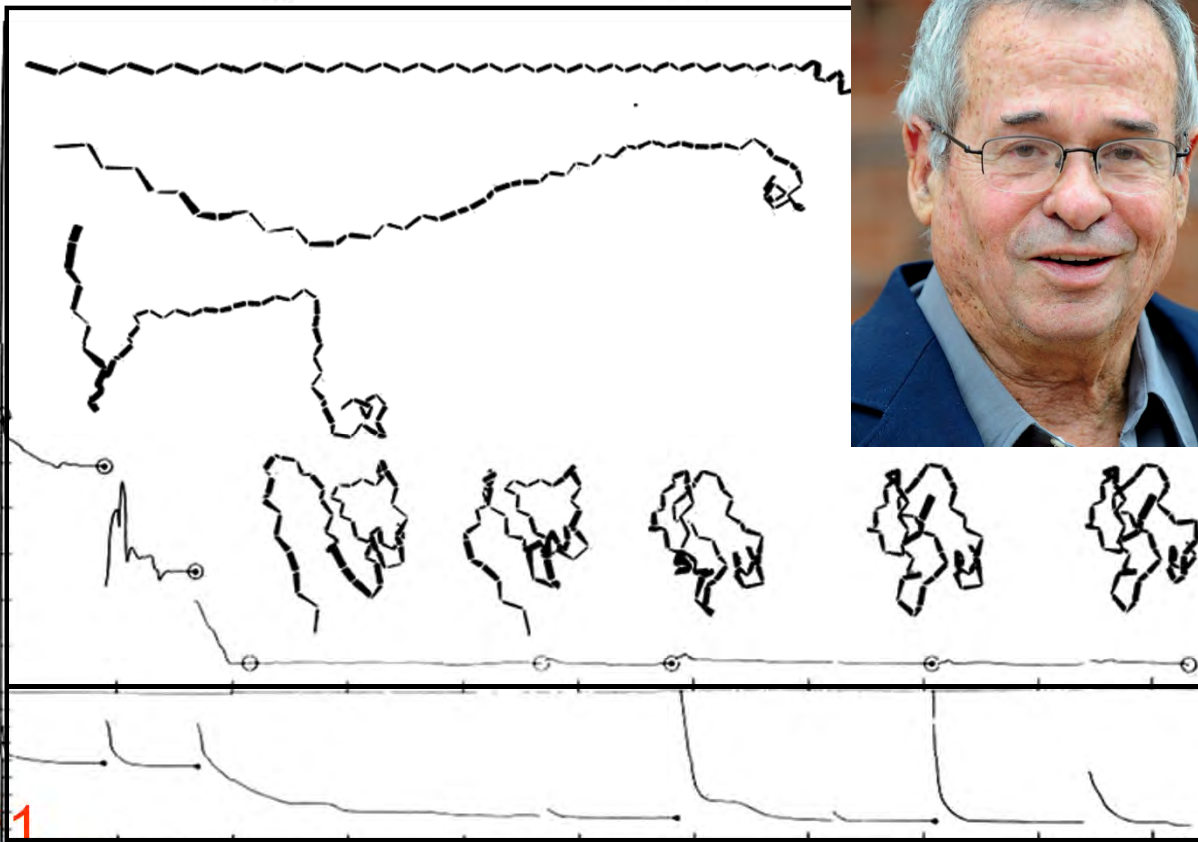


Reduced models



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

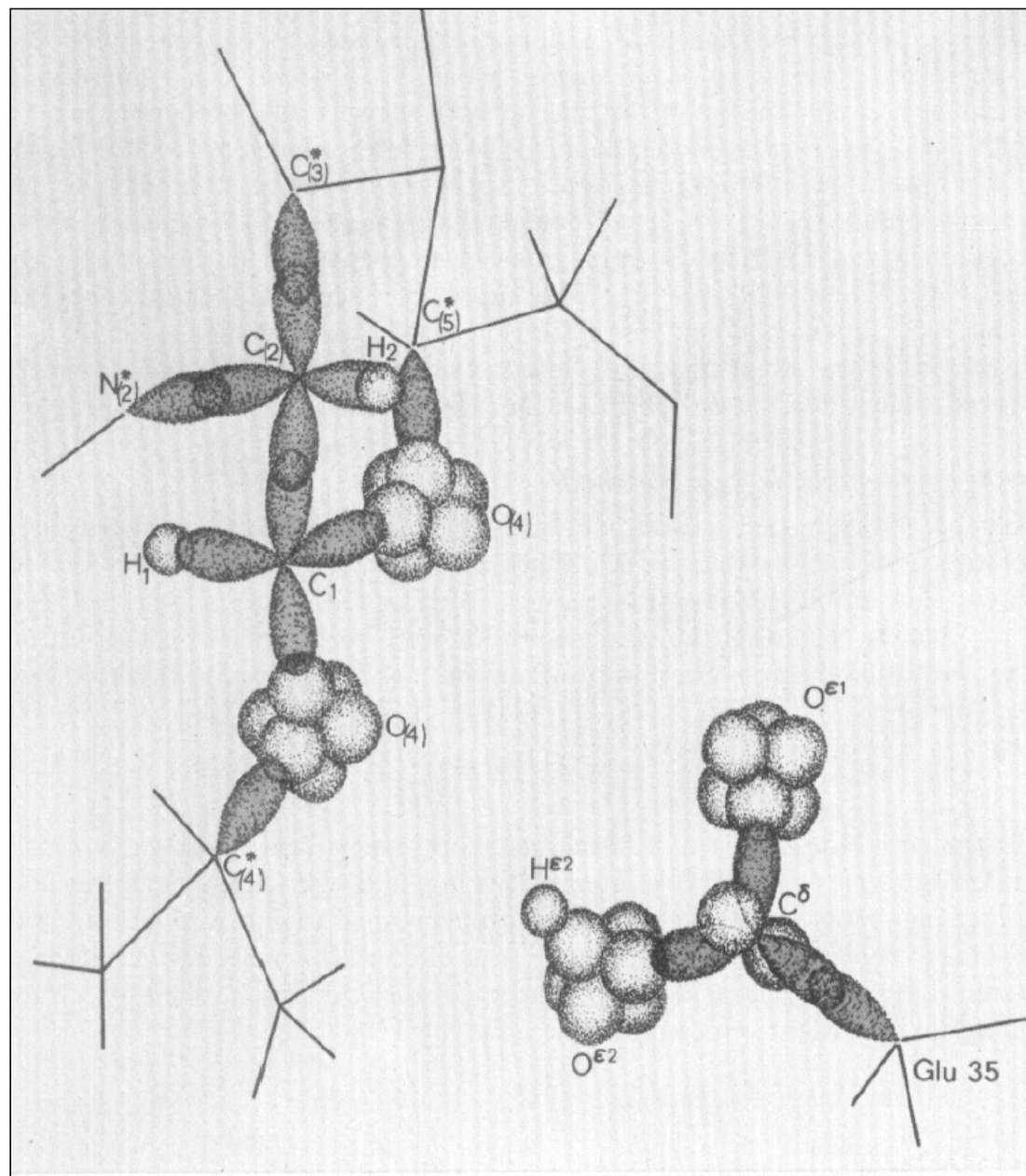
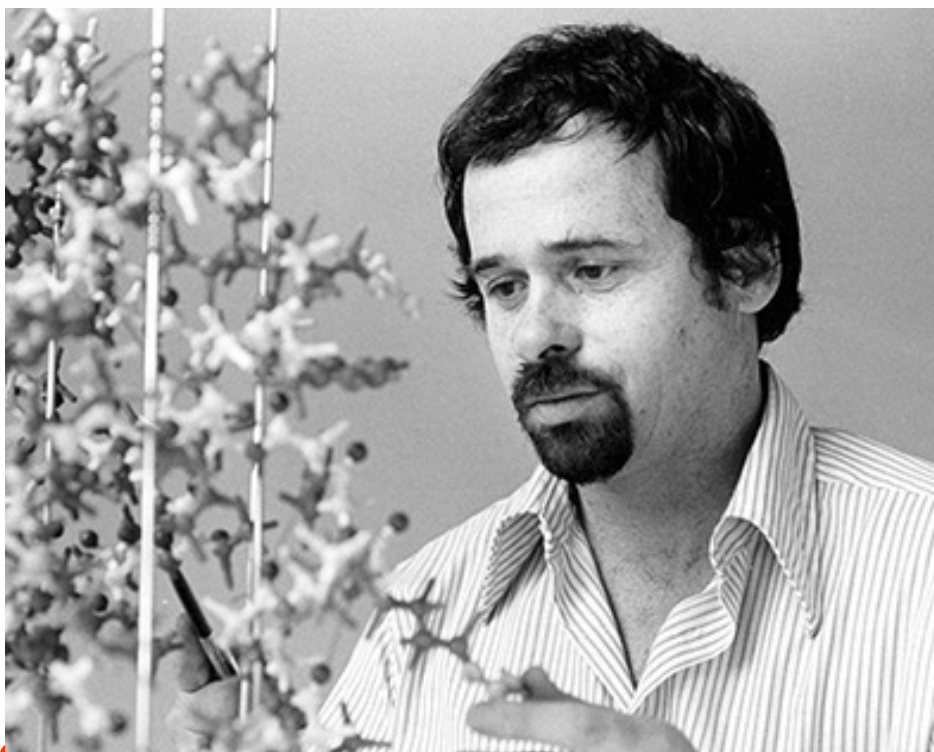
J. Mol. Biol. (1976) **103**, 227–249

A. WARSHEL AND M. LEVITT

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

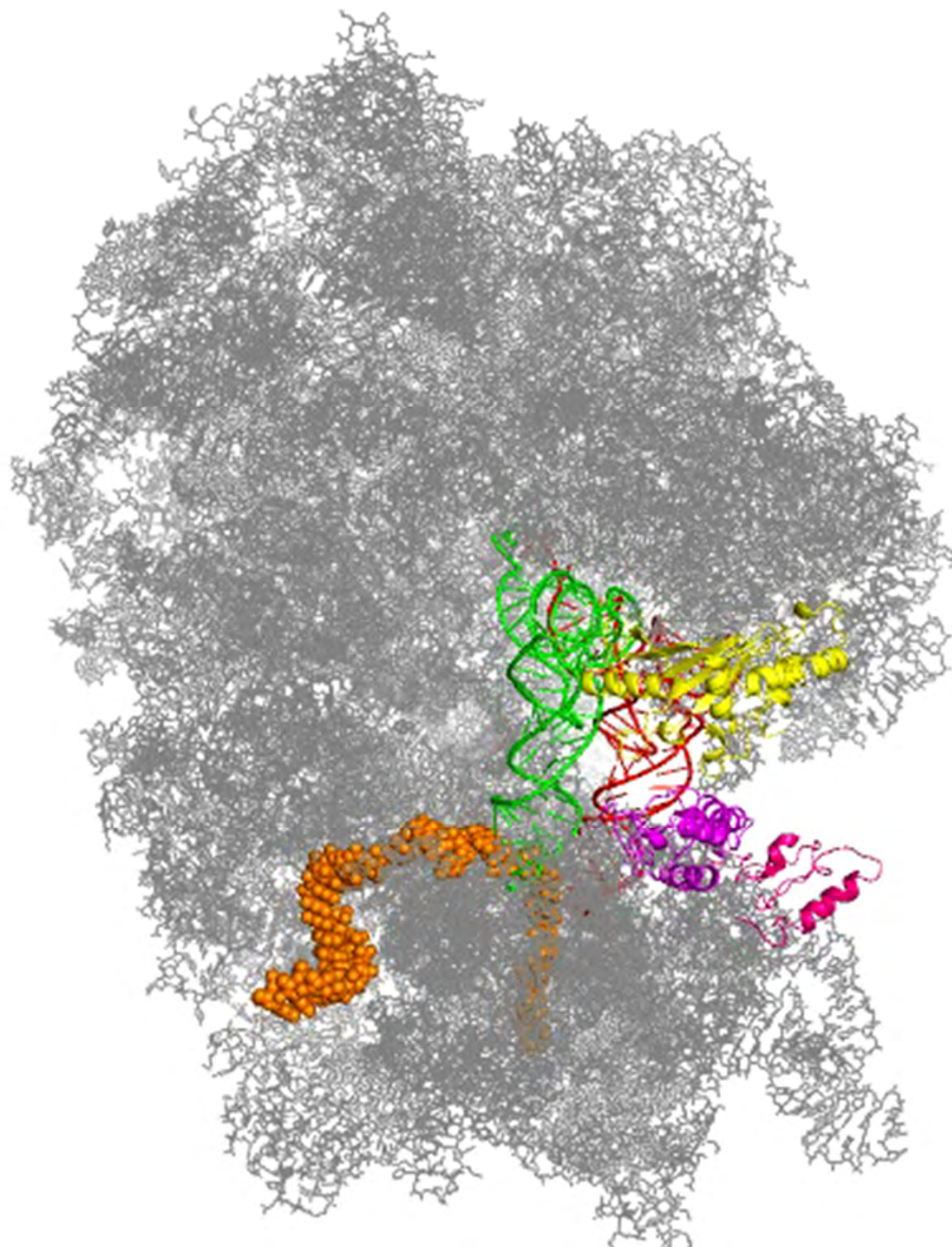
and

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

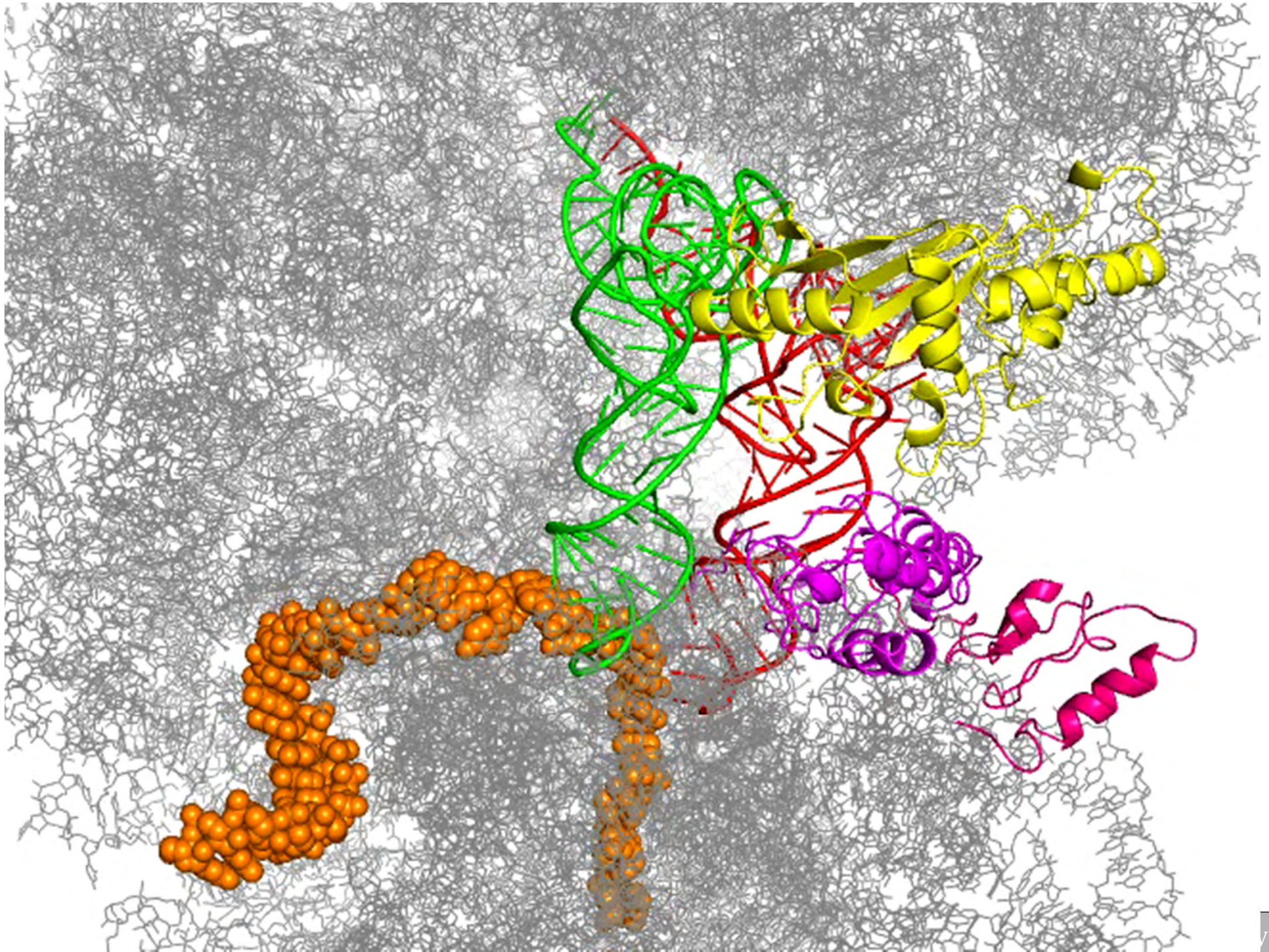


SIMULATING FUNCTIONAL MOTION

RIBOSOME TRANSLOCATION



RIGID BODY MORPHING



**MY WORK IS
ALL BASIC
SCIENCE**

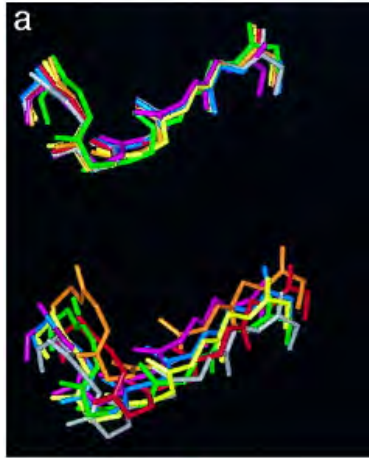
**BUT IS IT
OF ANY
USE OR
VALUE?**

SUMMARY

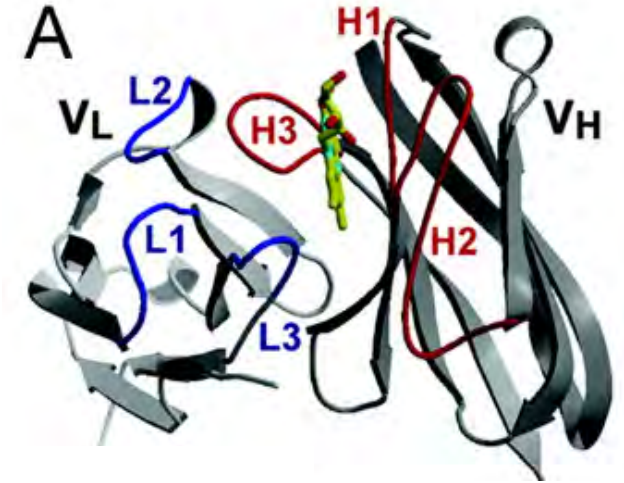
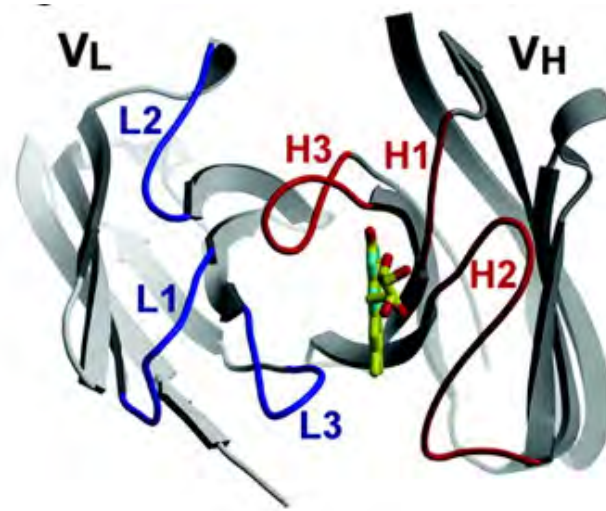
- ✓ 1. A Biophysical Revolution in Biology.
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**3. APPLIED
COMPUTATIONAL
STRUCTURAL
BIOLOGY**

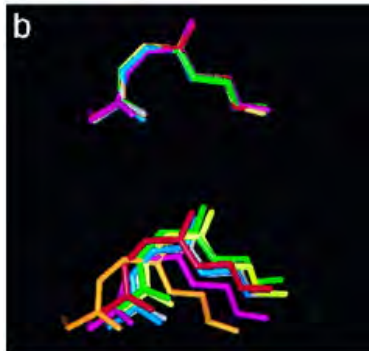
CANONICAL HYPER-VARIABLE REGIONS



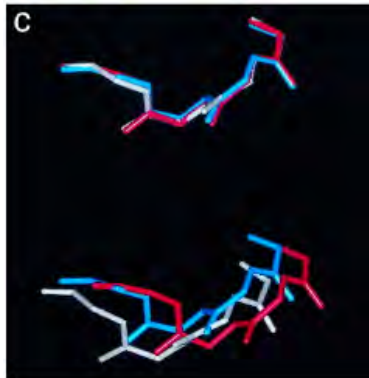
H1



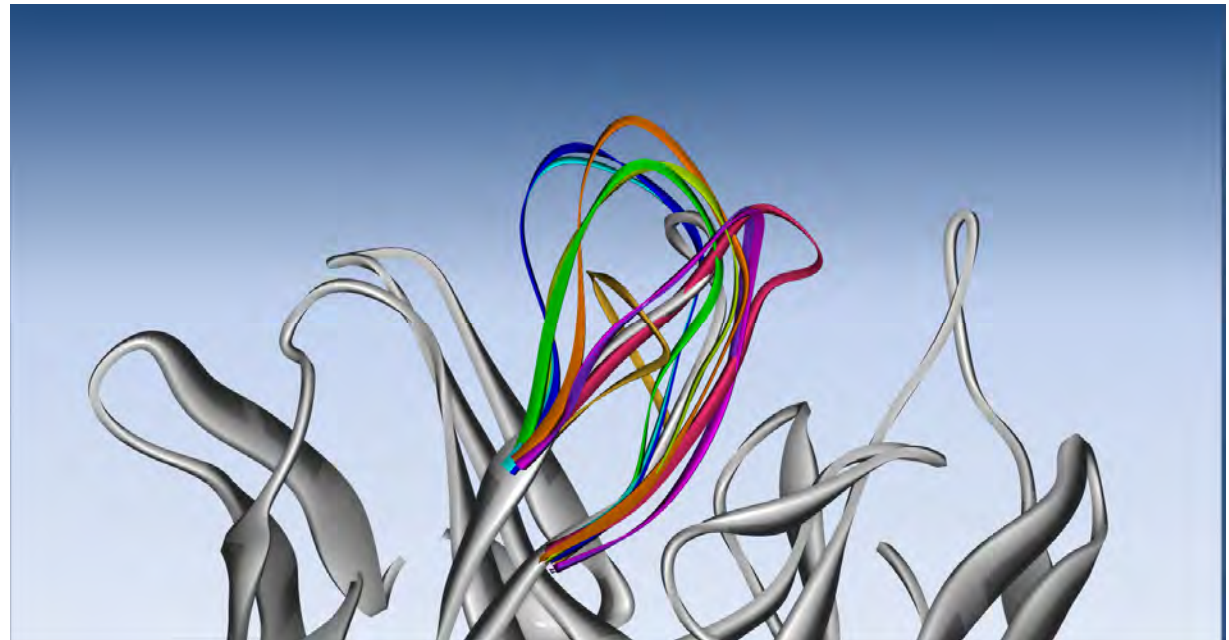
Lesk & Chothia, 1987



L2



H2



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 $3 \times 10^9 \text{ M}^{-1}$, 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.

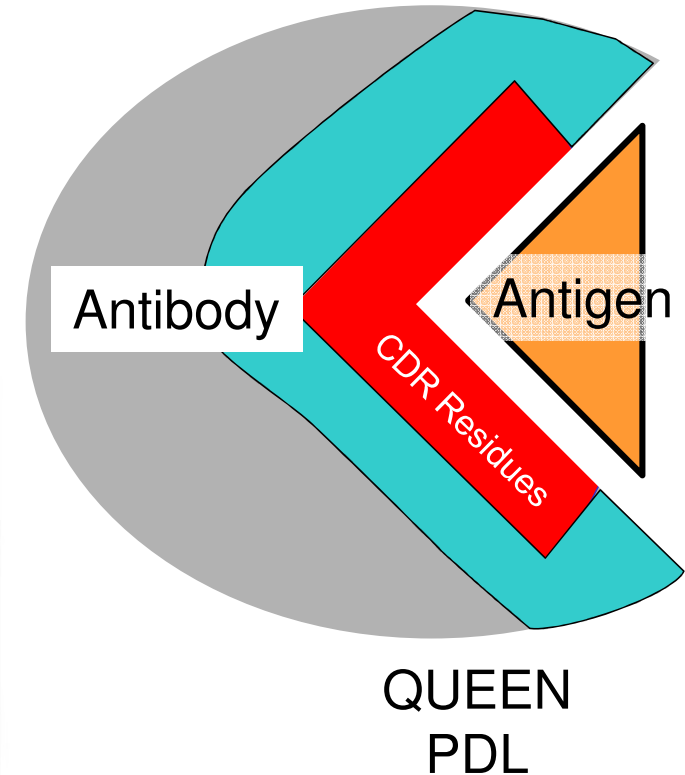
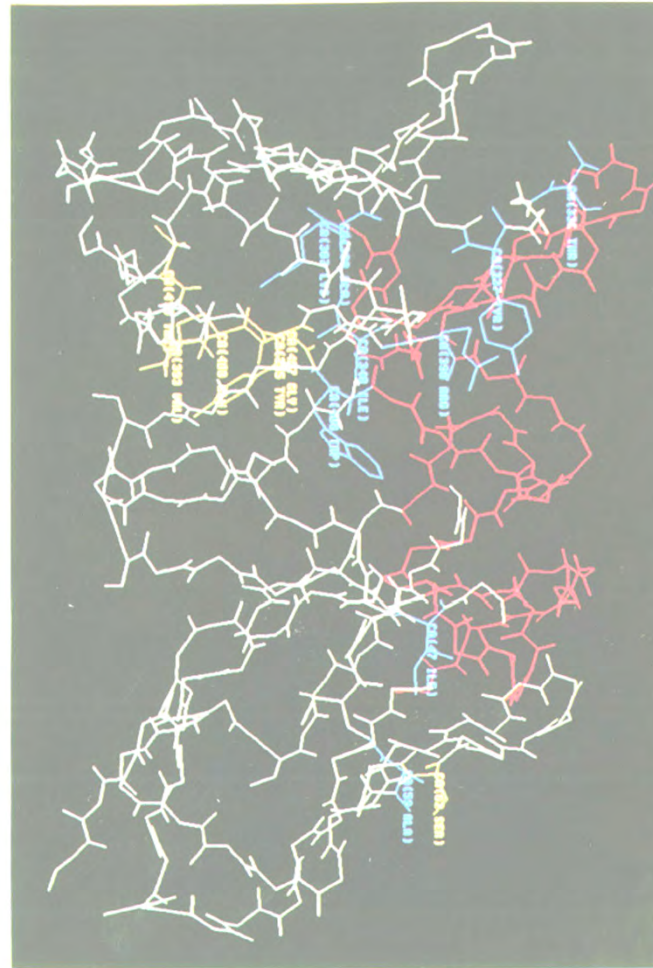
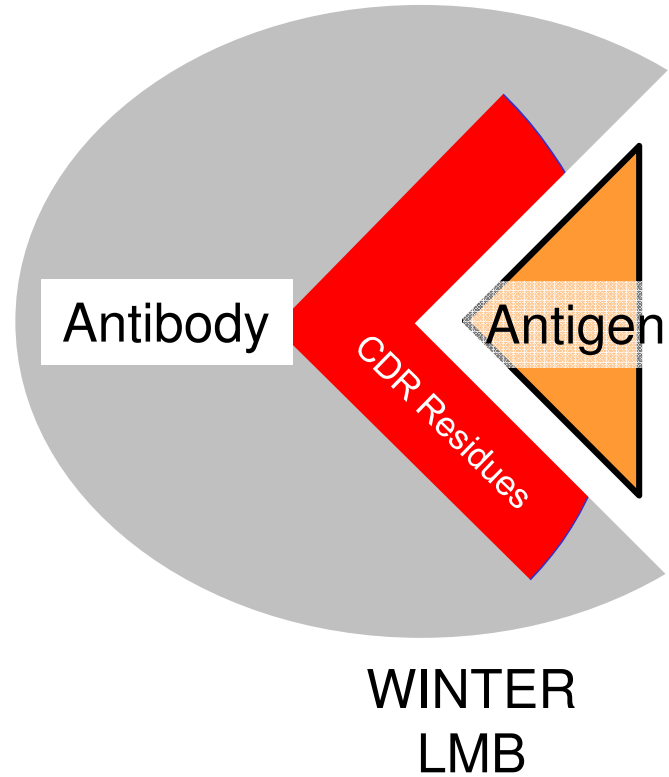
The immune response against a murine monoclonal antibody may potentially be reduced by transforming it into a chimeric antibody. Such antibodies, produced by methods of genetic engineering, combine the variable (V) region binding domain of a mouse (or rat) antibody with human antibody

KEY PAPER

BETTER SCIENCE LED TO BETTER PATENTS

KEY IDEA

Think in three-dimensions



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.

PDL Royalties by Product
(\$ in millions)



*approved June 2012

I ENJOYED A
WONDERFUL
LIFE IN BASIC
SCIENCE

**WHAT
ABOUT
TODAY'S
YOUNG
SCIENTIST?**

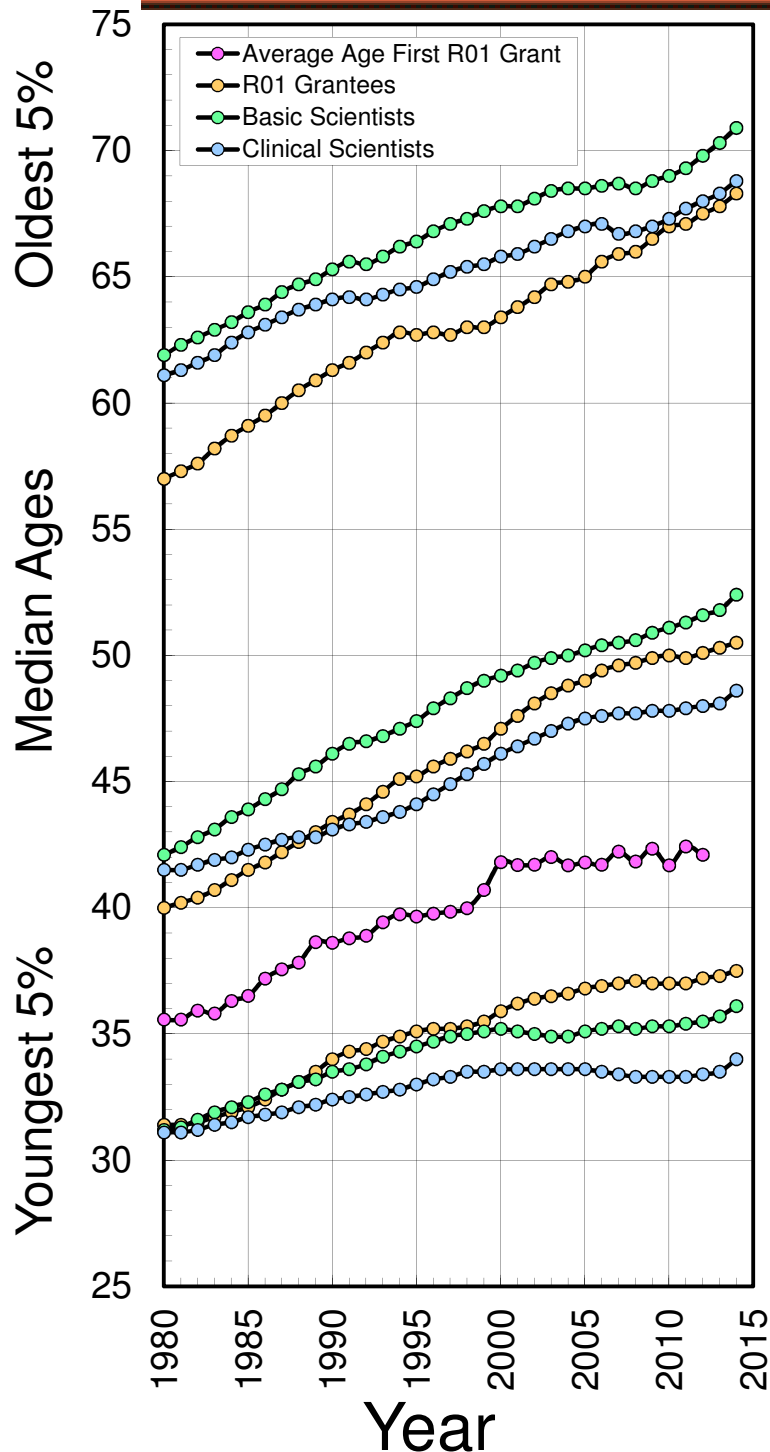
SUMMARY

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4. Young Basic Scientists in the USA.
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6. How to Win Many Nobel Prizes?

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

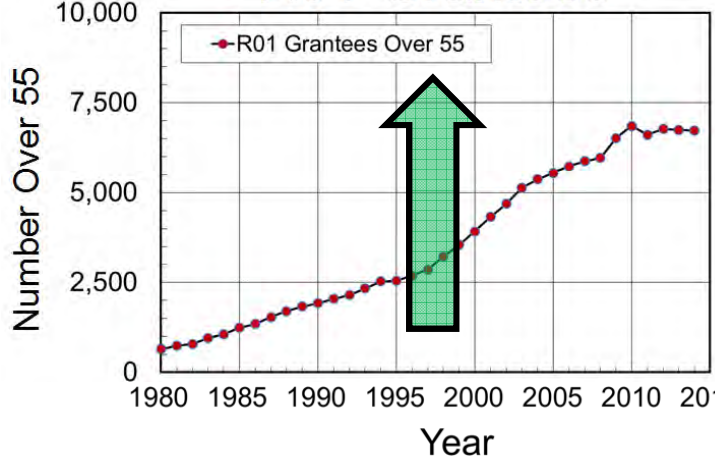


- The First-Time PIs are not young; 5 years older than youngest 5%.
- All R01 Grantees are aging.
- Young Clinical Science PIs age least.
- Young Basic Science PIs age most.
- Clinical Science PIs aging less than Basic PIs for Median and Oldest 5%.

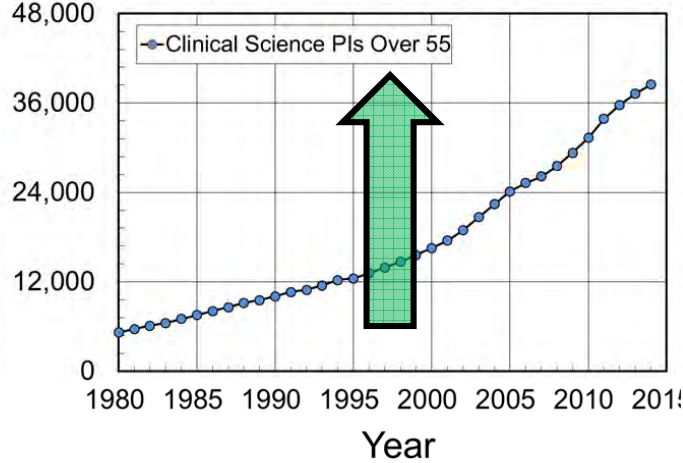
CHANGING NUMBERS IN AGE RANGES

Over 55

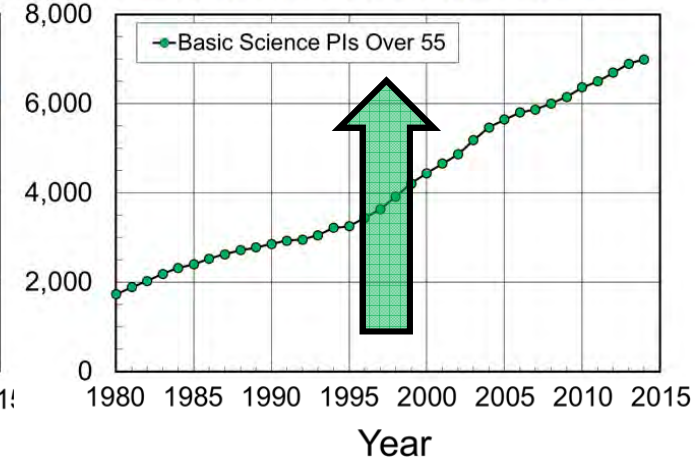
R01 Grantees



Clinical Science PIs



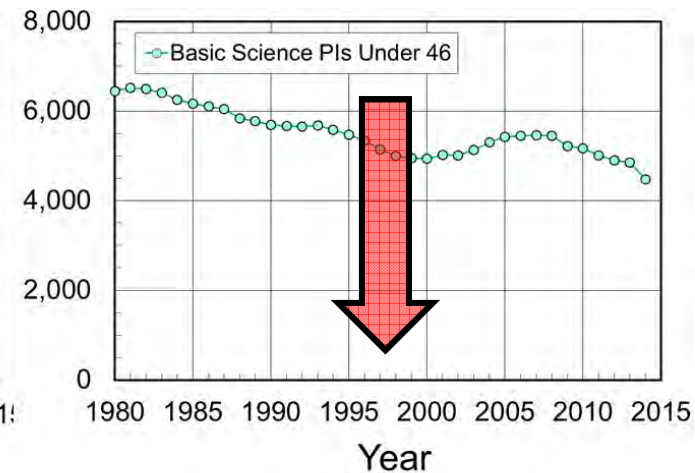
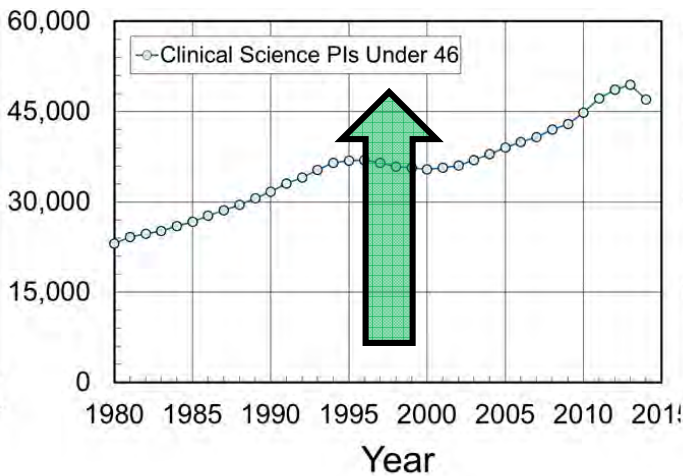
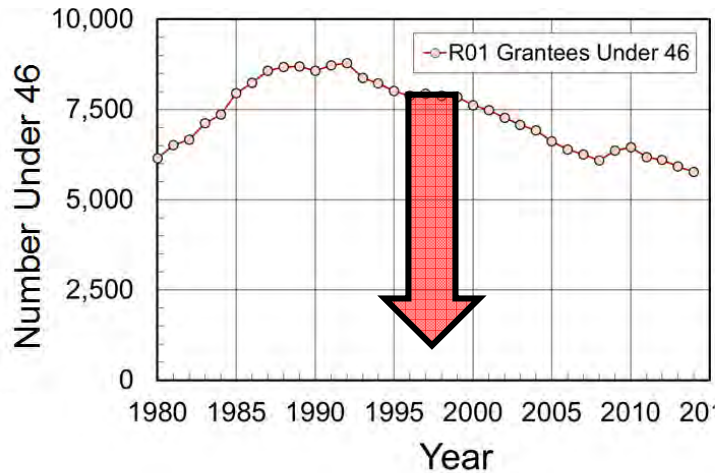
Basic Science PIs



Older Increase
Younger Decrease

Older Increase
Younger Increase

Older Increase
Younger Decrease

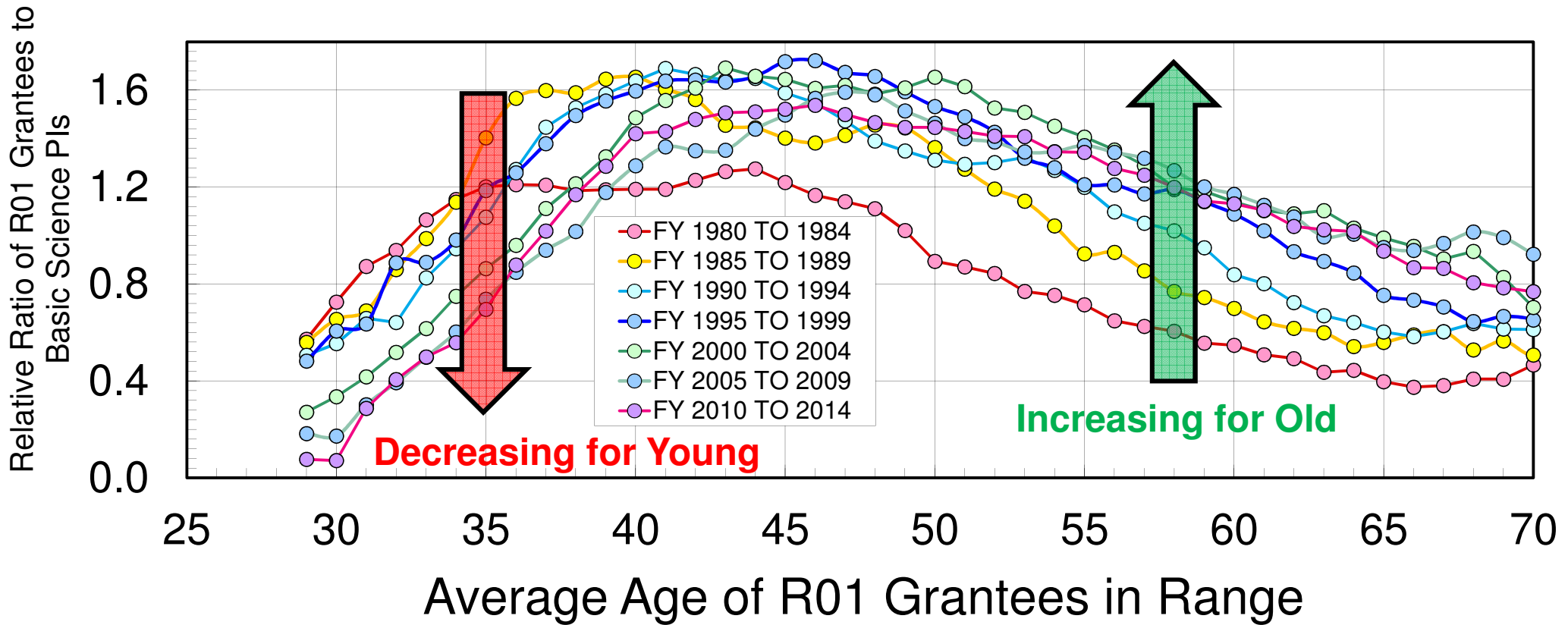


Under 46

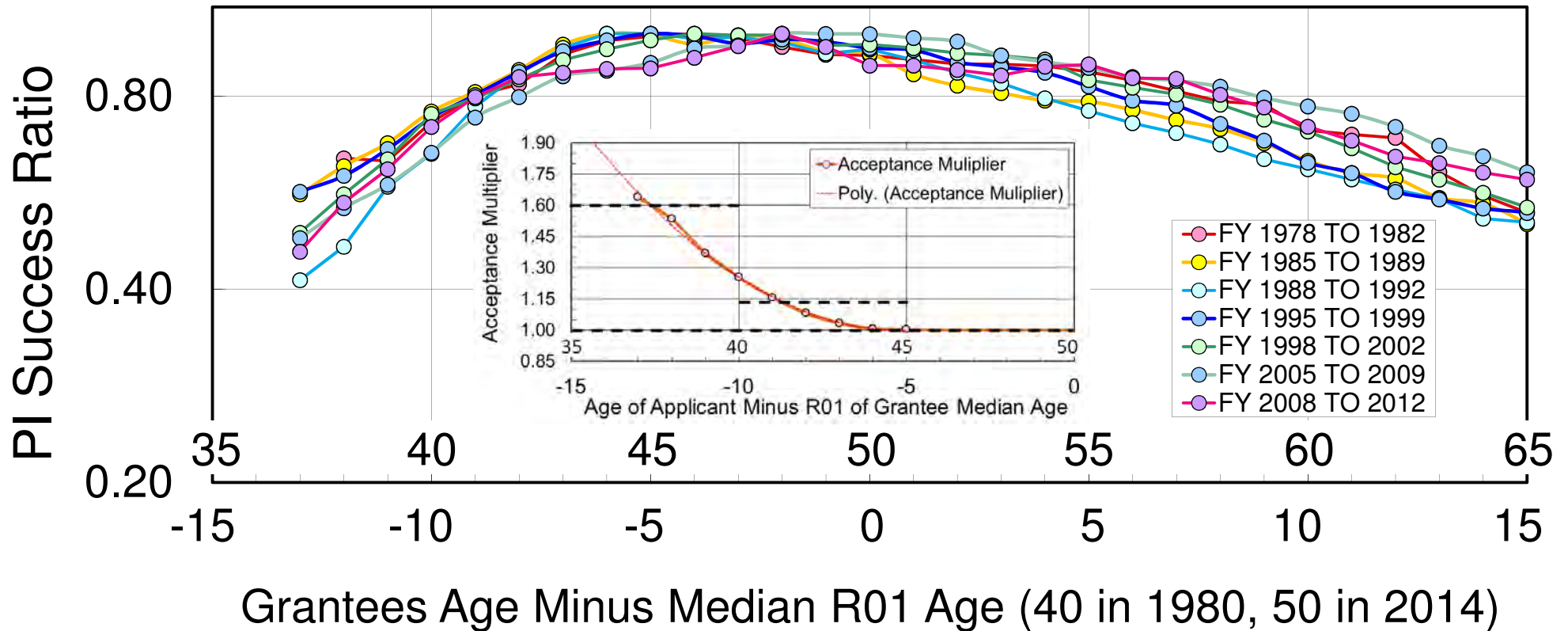
HOW RELATIVE PI SUCCESS RATIO HAS CHANGED

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

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!**

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?

**(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?

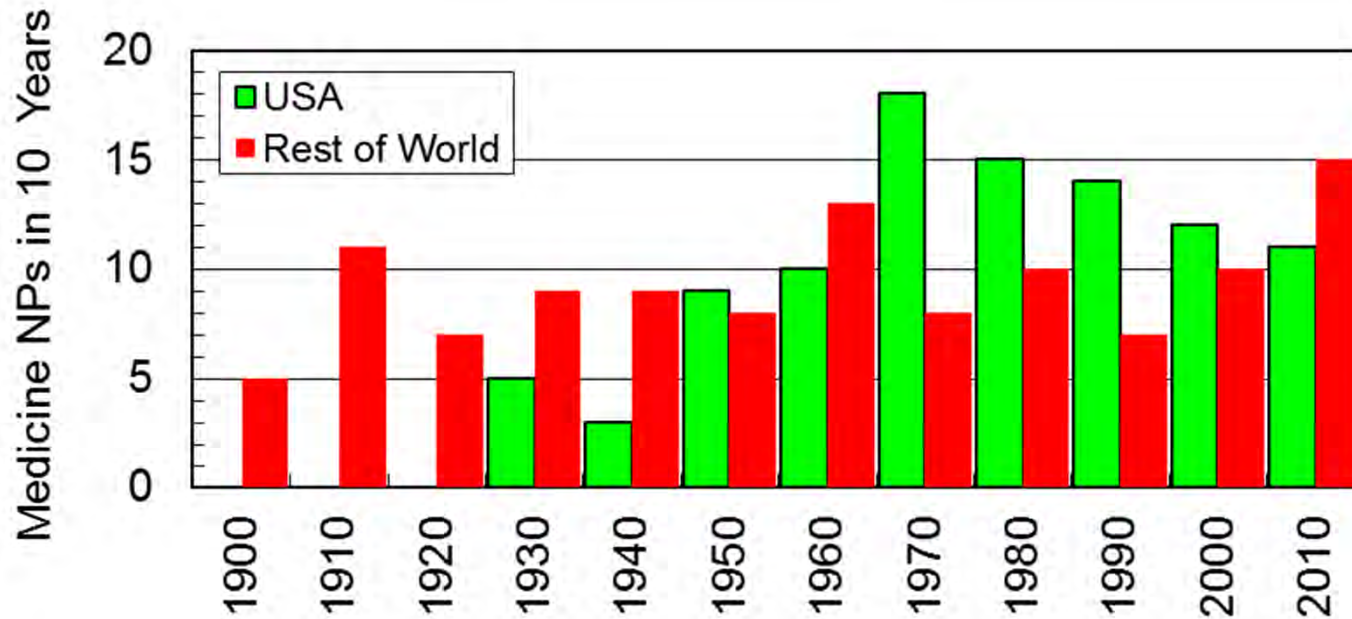


- A scientific discovery is like winning a lottery.
Cannot really be planned or predicted.
You have to have a ticket.
Having more ticket than one ticket helps.

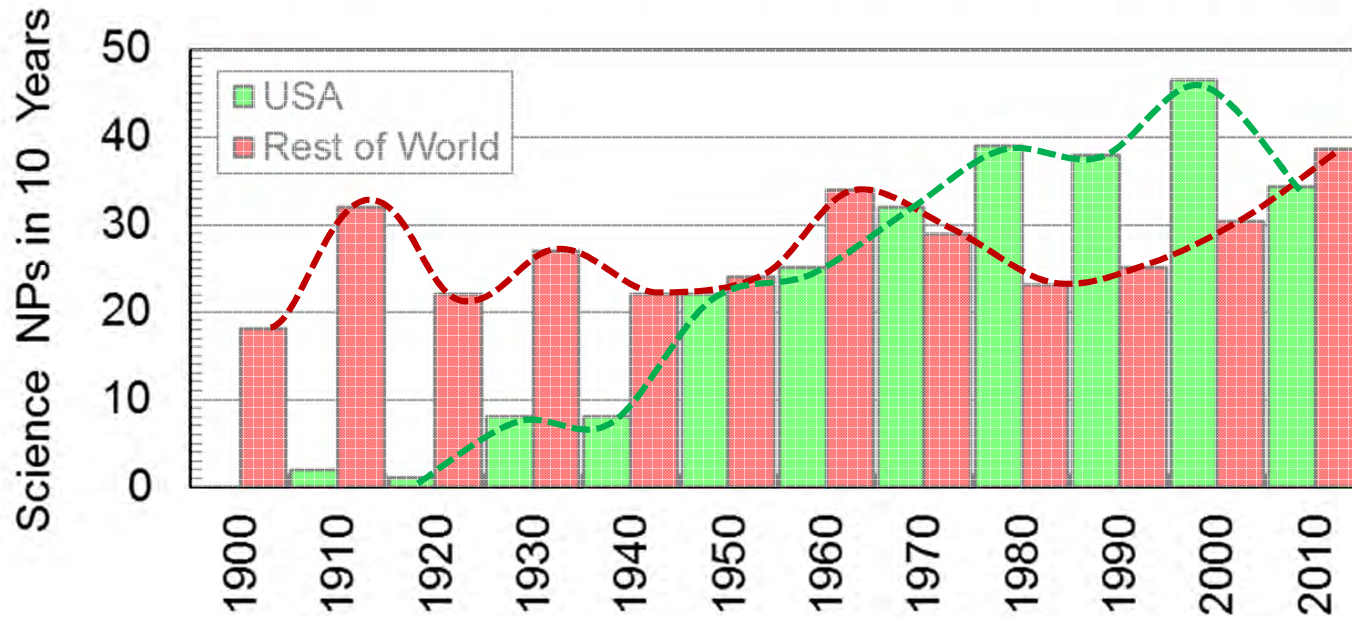
IS BASIC SCIENCE IMPORTANT?

- 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?

Center of Ten-Year Interval

SCIENTIFIC AMERICAN SEPTEMBER 2015

HOW BIG IS SCIENCE?

MAMMOTH INSTRUMENTS OF SCIENCE SUCH AS CERN'S Large Hadron Collider are often held up as symbols of the human commitment to decoding the world. But how highly does humanity as a whole actually regard science? How big *is* science—all of it? This is not an easy question to answer, but by gathering what credible data exist, we can approximate an answer. —The Editors

US 453,544 M\$
\$453,544 million*
 2012

*All country R&D values expressed in purchasing parity dollars, a currency conversion designed to reflect the varying cost of living in different countries.

CN

GLOBAL SCIENCE SPENDING

No single data set captures every dollar spent on scientific research worldwide, but by looking at R&D spending by the world's biggest economies, we can get a sense of the scale of global research.

243,293 M\$

China
 \$243,293 million
 2012

Human Genome Project
 \$4,730 million*
 Total project costs 1990–2003

100,000 Genomes Project
 \$471 million
 Current investments 2012–2017

*All project values converted to 2015 U.S. dollars.

Large Hadron Collider
 \$5,370 million
 Personnel, materials, R&D, tests and preparation costs
 Operational in 2008

JP

Japan
 \$148,389 million
 2011

148,389 M\$

THE GENOME

The \$4.7-billion, 13-year Human Genome Project, which in April 2003 finished sequencing the entire human genetic code, was arguably the first true Big Science project in the realm of biology and medicine. New efforts include the 100,000 Genomes Project, which aims to sequence the full genomes of 100,000 U.K. National Health Service patients to search for genetic links to disease.

Proposed Collider in China
 \$3,020 million
 Estimated construction costs
 Approvals pending

European Spallation Source
 \$2,260 million
 Projected construction costs
 Broke ground in 2014

PARTICLE COLLIDERS

They are expensive, enormous and, for physicists, essential: there is no way to test certain theories without replicating the conditions immediately following the big bang. The 27-kilometer Large Hadron Collider near Geneva is the world's largest, but China has proposed a collider that, if built, will be almost twice the size.

DE

Germany
 \$100,248 million
 2011

100,248 M\$

Manhattan Project
 \$23,000 million–\$27,000 million
 (\$2,200 million in 1945)
 Total cost 1942–1945

THE BOMB

The Manhattan Project, which developed the first atomic bombs, cost more than \$23 billion and employed 130,000 people. For better or worse, it became a model of what "Big Science" could achieve.

BRAIN Initiative

\$300 million+
 Federal investment through 2015
 Launched in 2013

Human Brain Project
 \$1,630 million
 Estimated total project costs 2012–2023

BRAIN STUDIES

One of the greatest remaining scientific mysteries is how the three-pound lumps of meat in our heads produce consciousness. Several large, well-funded initiatives, including the Human Brain Project in Europe and the BRAIN Initiative in the U.S., aim to develop basic tools to help scientists solve this puzzle and cure brain diseases.

IN

India
 \$36,196 million
 2011

36,196 M\$

RU

Russian Federation
 \$37,854 million
 2012

37,854 M\$

UK

U.K.
 \$39,110 million
 2012

39,110 M\$

FR

France
 \$54,680 million
 2012

53,680 M\$

KR

South Korea
 \$58,380 million
 2011

58,380 M\$

27,430 M\$

Brazil
 \$27,430 million
 2011

26,321 M\$

Italy
 \$26,321 million
 2012

24,801 M\$

Canada
 \$24,801 million
 2012

STATE OF THE WORLD'S SCIENCE
 BIG SCIENCE, BIG CHALLENGES

Indonesia
 \$795 million
 2009

South Africa
 \$3,986 million
 2010

Saudi Arabia
 \$503 million
 2009

Mexico
 \$8,058 million
 2011

Australia
 \$20,469 million
 2010

Turkey
 \$11,302 million
 2011

International Space Station
 about \$140,000 million
 Includes development, assembly and running costs over 10 years
 First shipment launched in 1998

140,000 M\$

HUMAN SPACEFLIGHT
 Putting astronauts in space—and in the case of the International Space Station, keeping them there—has been one of the most costly and labor-intensive projects in the history of science. By comparison, deploying robotic probes such as the Mars Science Laboratory is a bargain.

New Horizons Pluto Mission
 \$700 million

Spacecraft and instrument development, launch vehicle, mission operations, data analysis and outreach
 Launched 2006

Apollo Program
 \$104,270 million
 Total budget appropriations 1960–1973

104,270 M\$

Mars Science Laboratory
 \$2,650 million
 Total cost
 Launched 2011

BIG TELESCOPES

The largest telescopes in development today, particularly the nearly \$8-billion James Webb Space Telescope, rival the cost and ambition level of particle colliders.

ALMA
 \$1,430 million
 Total construction costs 2013

James Webb Space Telescope
 \$7,998 million
 NASA's cost to build, launch and commission
 Target launch date: 2018

ITER
 \$19,660 million
 Estimated construction costs
 Target completion date: 2027

BIG ENERGY

Humanity's greatest problem—powering civilization without destroying the planet—is urgent enough to justify massive undertakings such as ITER, a collaboration among China, the European Union, India, Japan, South Korea, Russia and the U.S. Once completed, ITER will be the biggest fusion reactor ever built.

Avatar
 \$2,788 million
 Worldwide box-office gross
 Released 2009

F-35 (fighter jet)
 \$391,100 million
 Program cost for a total of 2,457 planes as of December 31, 2014

Alcoholic beverages
 \$174,314 million
 Money spent on alcohol in the U.S.
 2013

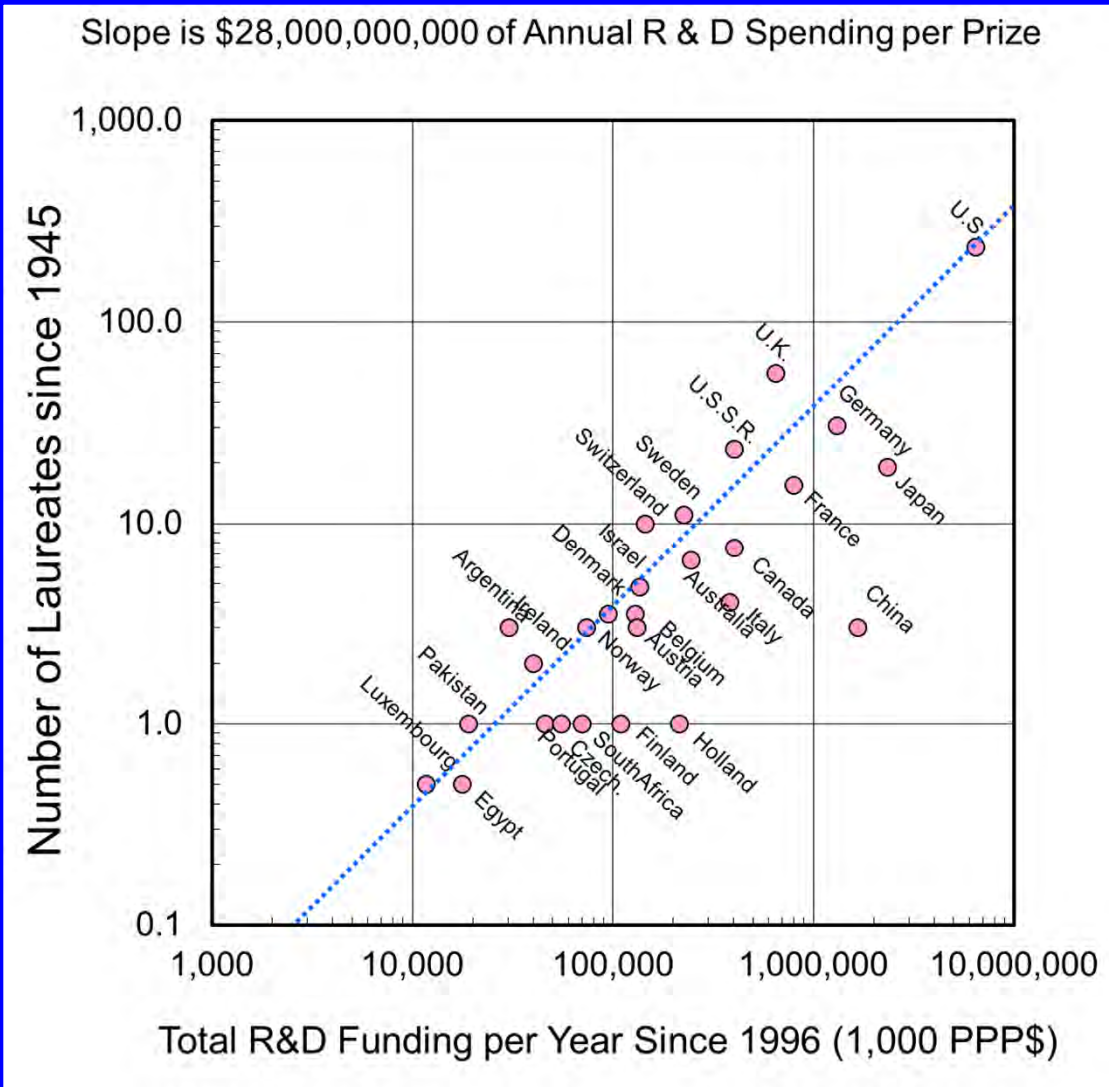
USEFUL PERSPECTIVE

Even at the highest levels, spending on science is dwarfed by consumer expenditures and military budgets. For example, \$2.65 billion for the Mars Science Laboratory sounds like a lot of money—and it is—but it is still less than the worldwide box-office gross for the film *Avatar*. The F-35 Lightning II provides perhaps the ultimate point of reference: the stealthy fifth-generation fighter cost some \$391 billion to develop.

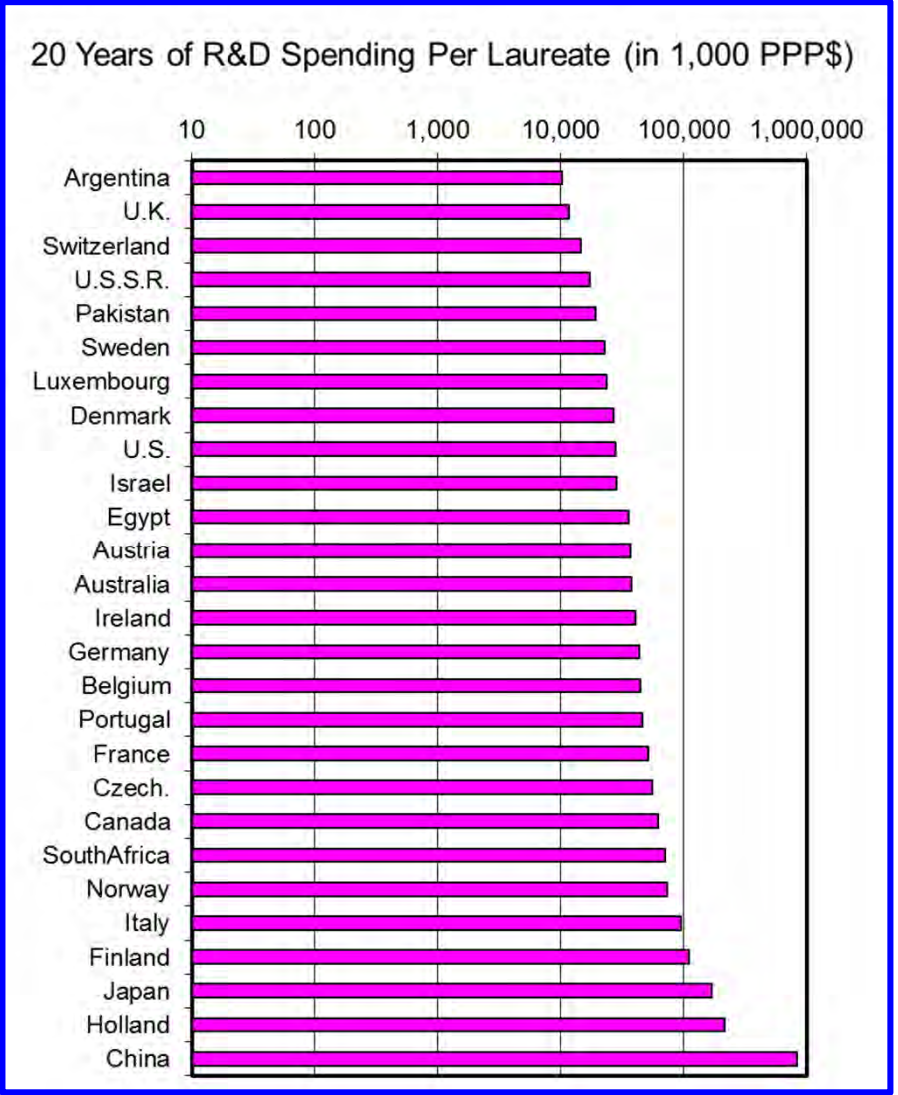
Graphic by Jen Christiansen, Research by Amanda Hobbs

SOURCES: UNESCO INSTITUTE FOR STATISTICS (expenditure on research and development, by country); THE MANHATTAN PROJECT, THE APOLLO PROGRAM, AND FEDERAL ENERGY TECHNOLOGY R&D PROGRAMS: A COMPARATIVE ANALYSIS, BY DEBORAH D. STINE, CONGRESSIONAL RESEARCH SERVICE REPORT FOR CONGRESS, JUNE 30, 2009 (Manhattan Project); APOLLO BY THE NUMBERS: A STATISTICAL REPORT REVISED BY RICHARD W. CRECH, NASA, SEPTEMBER 2004 (Apollo projects); EUROPEAN SPACE AGENCY (International Space Station); NATIONAL HUMAN GENOME RESEARCH INSTITUTE (Human Genome Project); "HUMAN GENOME: IN TO BECOME WORLD NUMBER IN DNA TESTING," BY U.S. PRIME MINISTER'S OFFICE (ET AL.), AUGUST 1, 2004 (100,000 Genomes Project); THE HUMAN BRAIN PROJECT: A REPORT TO THE EUROPEAN COMMISSION, BY HBP-PS CONSORTIUM, APRIL 2012 (Human Brain Project); WHITE HOUSE BRAIN INITIATIVE (BRAIN Initiative); LNC, THE GENOME, BY CERN, FEBRUARY 2009 (Large Hadron Collider); FAQ FUNDING AND COSTS (http://fundingandcosts.cern.org/funding-and-costs) (European Spallation Source); "CHINA PLANS SUPER COLLIDER," BY ELIZABETH GIBNEY, IN NATURE, VOL. 517, JULY 24, 2009 (proposed collider in China); "ALMA REACCELERATION HERADS NEW ERA OF DISCOVERY," BY EUROPEAN SOUTHERN OBSERVATORY ORGANIZATION, MARCH 13, 2013 (ALMA); ITER WEB SITE (www.iter.org) (ITER); NASA (James Webb Space Telescope, Mars Science Laboratory, New Horizons); "DEPARTMENT OF DEFENSE SELECTED ACQUISITION REPORTS (SARS) (AS OF DECEMBER 31, 2014)," BY U.S. DEPARTMENT OF DEFENSE, MARCH 19, 2015 (F-35).

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

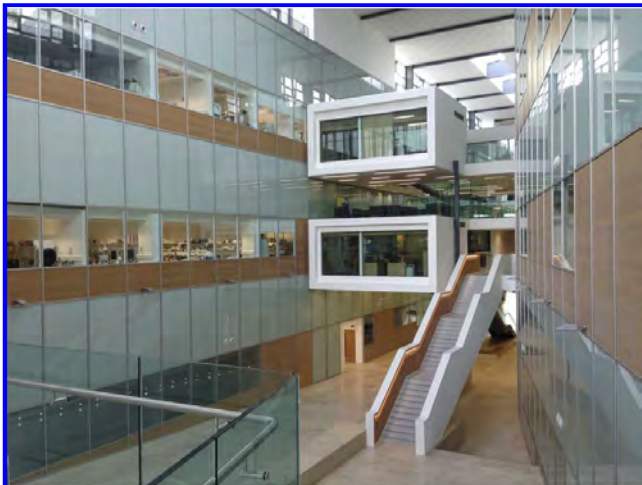
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QUALITY BASIC
SCIENTIFIC
RESEARCH NEEDS
MONEY AND FULL-
TIME RESEARCH
COMMITMENT

**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

57

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