The Problems and Challenges in Biomedical Sciences: Keeping Science Healthy

University of Illinois at Chicago
GEMS Symposium
September 16, 2016

Bruce Alberts,
Chancellor's Leadership Chair in Biochemistry and Biophysics
for Science and Education
University of California, San Francisco (UCSF)

I will start with a little personal history
(life as an education!)

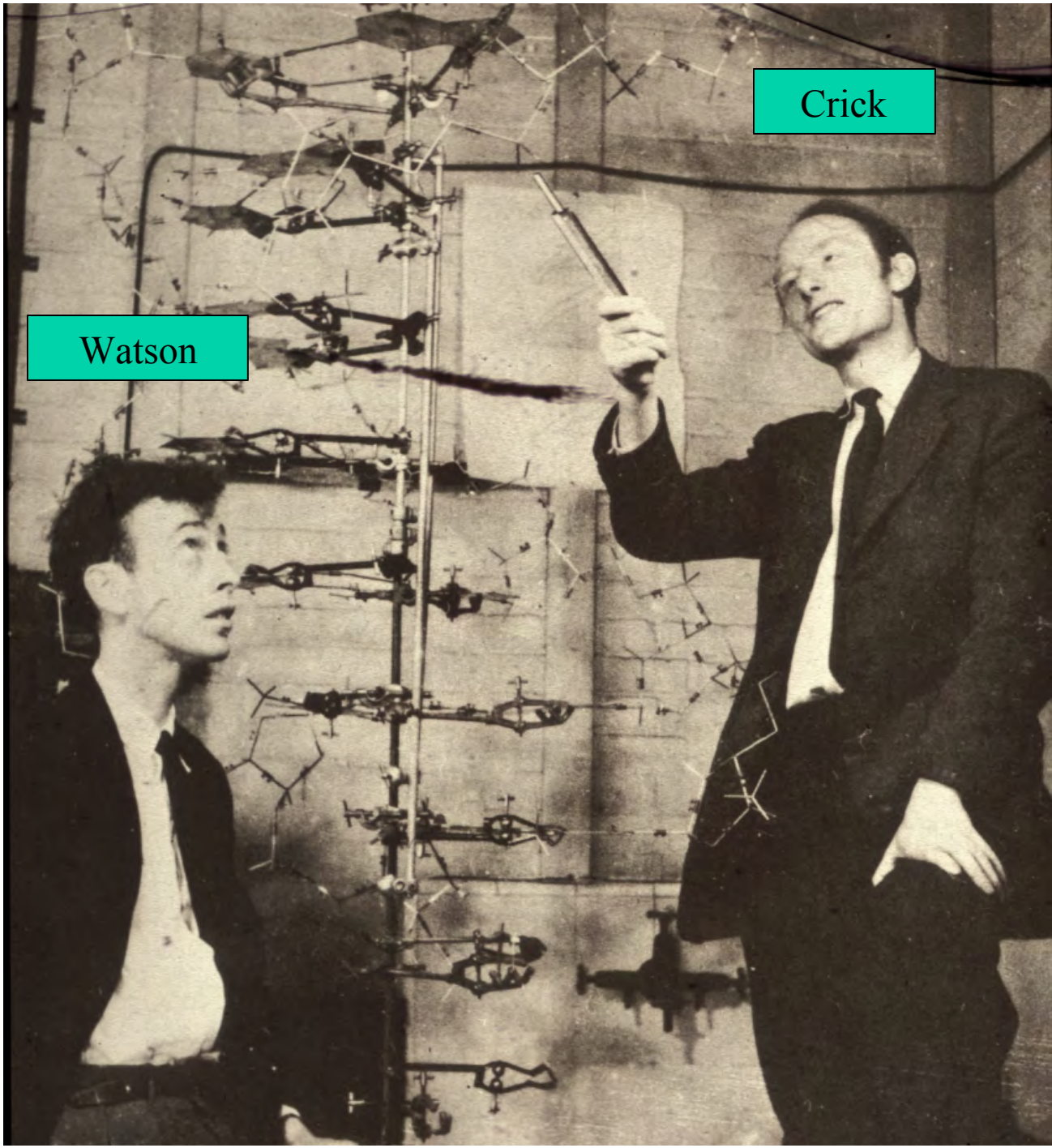
Learning from textbook writing:

The many unsolved problems in cell and molecular biology

How it all started

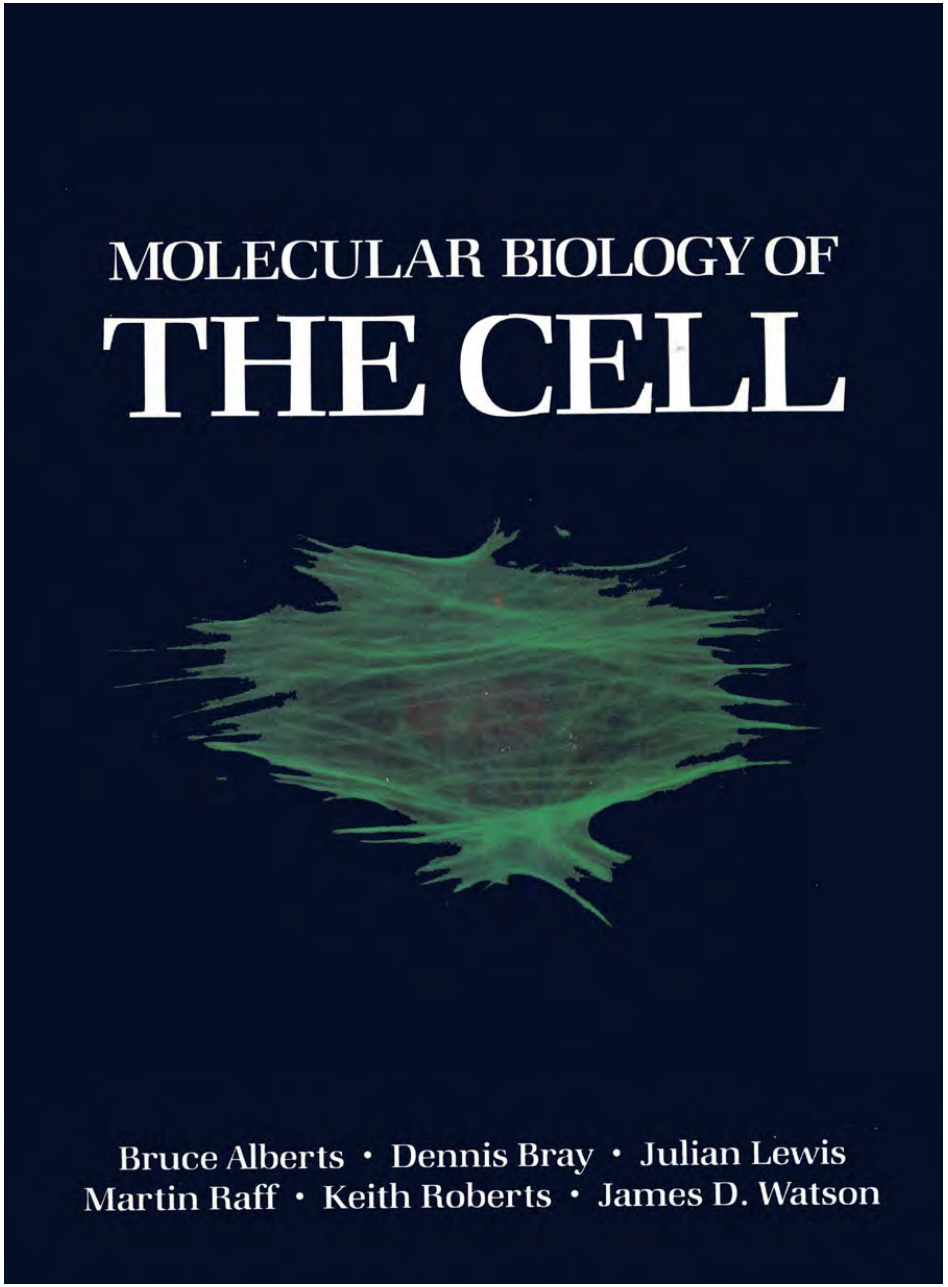
A phone call from **Jim Watson** in early 1978 — Watson was then 50 years old (he was only 25 in this famous photo).

He asked me to join him and 2 others as an author of a new textbook, to be called ***Molecular Biology of the Cell***.



Watson Roberts Raff Lewis Bray Alberts

The initial set of authors



Producing a book was very much harder than we had expected!

This first edition, finally published in 1983, required that all the authors live together at long "book meetings" for a total of over 365 12-hour days.

6th edition, December 2014

Each time we write a new edition, we are humbled by how much we still don't know

New Feature at End of Each Chapter
(more than 100 of these)

WHAT WE DON'T KNOW

- What new approaches might provide a clearer view of the anaerobic archaeon that is thought to have formed the nucleus of the first eukaryotic cell? How did its symbiosis with an aerobic bacterium lead to the mitochondrion? Somewhere on Earth, are there cells not yet identified that can fill in the details of how eukaryotic cells originated?

- DNA sequencing has revealed a rich and previously undiscovered world of microbial cells, the vast majority of which fail to grow in a laboratory. How might these cells be made more accessible for detailed study?

- What new model cells or organisms should be developed for scientists to study? Why might a concerted focus on these models speed progress toward understanding a critical aspect of cell function that is poorly understood?

WHAT WE DON'T KNOW

- What are the functions of the surprisingly large amount of unfolded polypeptide chain found in proteins?

- How many types of protein functions remain to be discovered? What are the most promising approaches for discovering them?

- When will scientists be able to take any amino acid sequence and accurately predict both that protein's three-dimensional conformations and its chemical properties? What breakthroughs will be needed to accomplish this important goal?

- Are there ways to reveal the detailed workings of a protein machine that do not require the purification of each of its component parts in large amounts, so that the machine's functions can be reconstituted and dissected using chemical techniques in a test tube?

How we viewed the cell when I started graduate school in 1961

As physical chemists, we were impressed by the enormous collision rate of molecules.

We therefore thought of the cell as a tiny test tube, composed of an enormously concentrated mixture of **disorganized individual macromolecules** that were freely diffusing and colliding randomly.

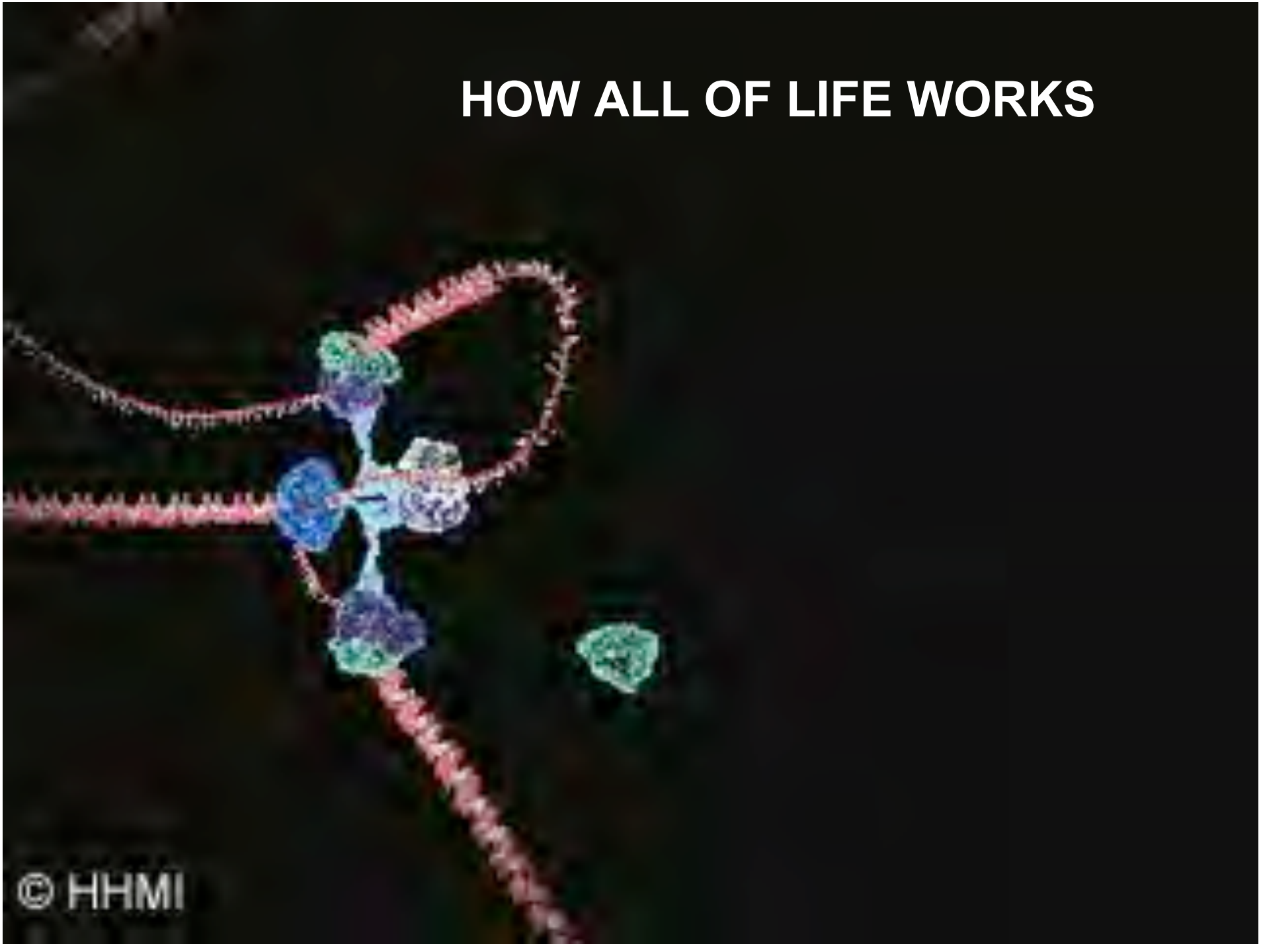
THIS IS ALL WRONG!

An early discovery was the importance of "Protein machines"

Almost every process in the cell is now recognized to be driven by a complex of 10 or more proteins

- These protein machines function very much like the machines in everyday life that are driven by electric energy.
- They undergo **ordered movements** that are driven by proteins in the set that harness the energy of ATP or GTP hydrolysis.

HOW ALL OF LIFE WORKS



A Recent Breakthrough

ARTICLE

doi:10.1038/nature14285

Regulated eukaryotic DNA replication origin firing with purified proteins

Joseph T. P. Yeeles[1], Tom D. Deegan[1], Agnieszka Janska[1], Anne Early[1] & John F. X. Diffley[1]

Eukaryotic cells initiate DNA replication from multiple origins, which must be tightly regulated to promote precise genome duplication in every cell cycle. To accomplish this, initiation is partitioned into two temporally discrete steps: a double hexameric minichromosome maintenance (MCM) complex is first loaded at replication origins during G1 phase, and then converted to the active CMG (Cdc45–MCM–GINS) helicase during S phase. Here we describe the reconstitution of budding yeast DNA replication initiation with 16 purified replication factors, made from 42 polypeptides. Origin-dependent initiation recapitulates regulation seen *in vivo*. Cyclin-dependent kinase (CDK) inhibits MCM loading by phosphorylating the origin recognition complex (ORC) and promotes CMG formation by phosphorylating Sld2 and Sld3. Dbf4-dependent kinase (DDK) promotes replication by phosphorylating MCM, and can act either before or after CDK. These experiments define the minimum complement of proteins, protein kinase substrates and co-factors required for regulated eukaryotic DNA replication.

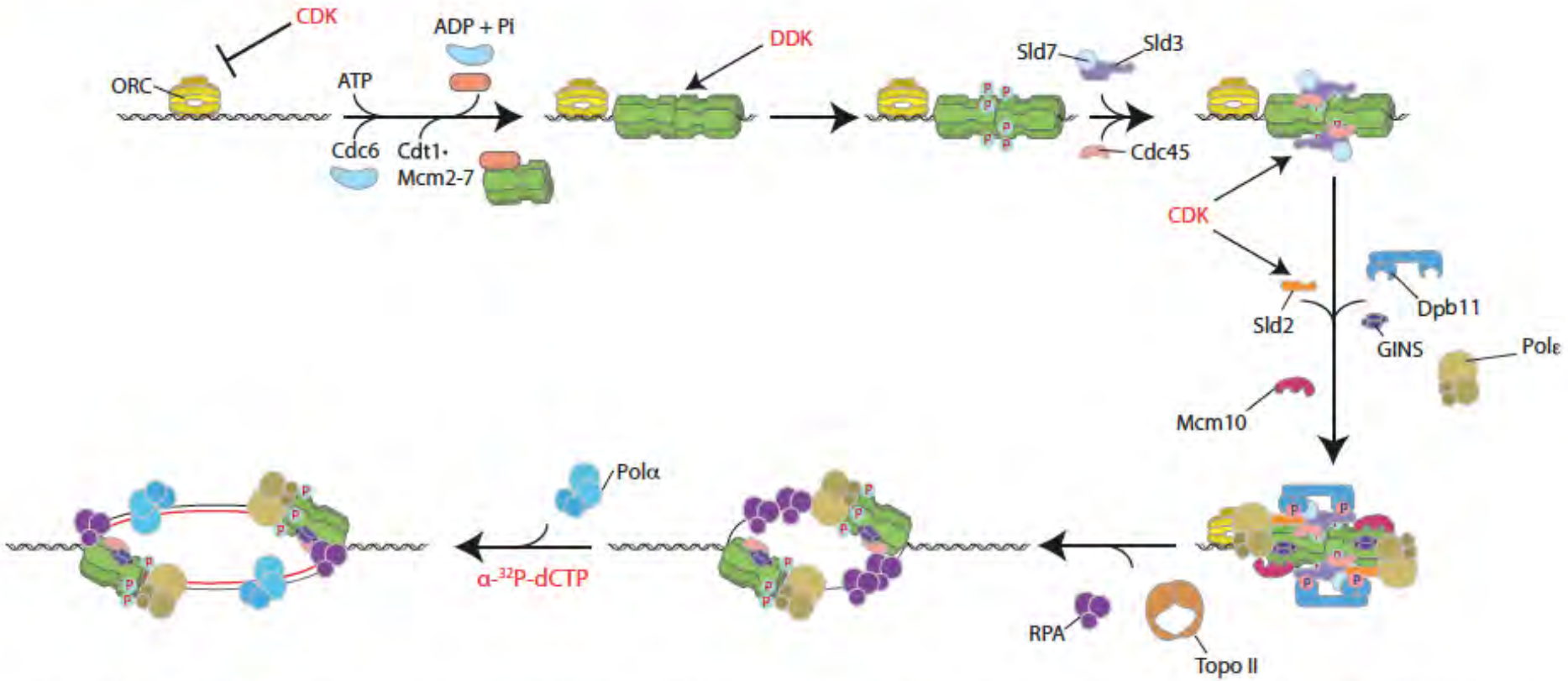
The initiation of eukaryotic DNA replication origin firing is understood in outline[1,2], but the process has not been reconstituted with purified proteins. MCM can be loaded onto DNA with purified ORC, Cdc6 and

was phosphorylated with DDK[6], beads were isolated and Sld3/7 and Cdc45 were added ('DDK step'). Beads were again isolated and the remaining firing factors were added with A-Cdk2 ('CDK step'). After washing the

This is only the tip of the iceberg!

(perhaps a tenth of the proteins critical to DNA replication and DNA repair)

RESEARCH ARTICLE



Extended Data Figure 6 | Cartoon illustrating protein kinase regulated eukaryotic DNA replication origin firing with purified proteins. Firing factors are recruited to loaded MCM in a DDK- and CDK-dependent manner. DNA synthesis is initiated once the DNA template has been unwound. CDK also functions to inhibit MCM loading by phosphorylating ORC.

Understanding the molecular details of these DNA replication and DNA repair pathways will be critical to improving human health

As one example, tumor progression selects for **hyper-mutability**, and different tumors will by chance acquire a very **different** defect in one of these pathways.

There is great potential in exploiting each particular defect to eradicate a cancer.

(A start has been made with the PARP inhibitors)

An Important Challenge for the Next Generation of Biochemists:

Obtaining the information needed to accurately describe the mechanism of every type of protein machine in a cell.

This will require the **reconstitution of many hundreds of protein machines from their purified components**, so that the detailed chemistry of each machine can be deciphered through reactions studied in a test tube.

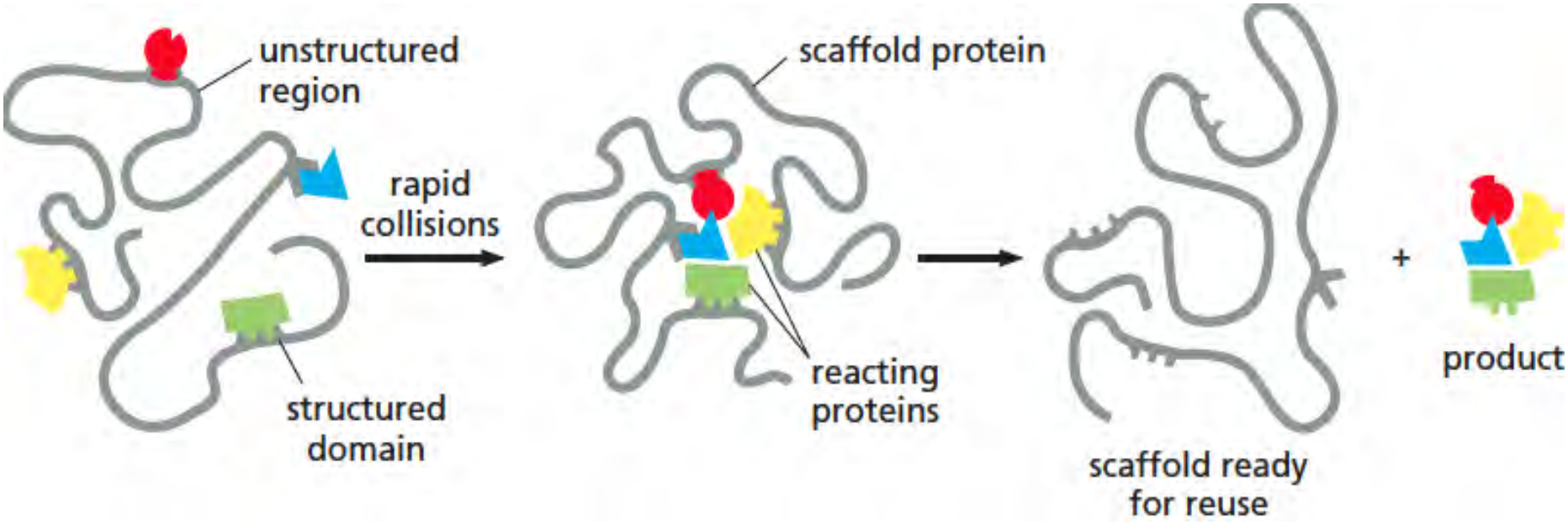
Two recent surprises for textbook authors (of many)

1). The recognition that extensive sets of **scaffolds** -- special protein and RNA molecules -- produce **biochemical sub-compartments** in the cell, without requiring a membrane.

2). The recognition that positive and negative feedback loops underlie nearly all cell chemistry, creating **complex networks of interactions;** these give rise to **emergent properties** that will require new computational methods to decipher.

Scaffold proteins

Intracellular compartmentation without membranes



A simple example: the whiskers on the actin-binding protein, **formin,** allow actin filaments to grow at rates faster than "diffusion controlled"

(from T. Pollard et al)

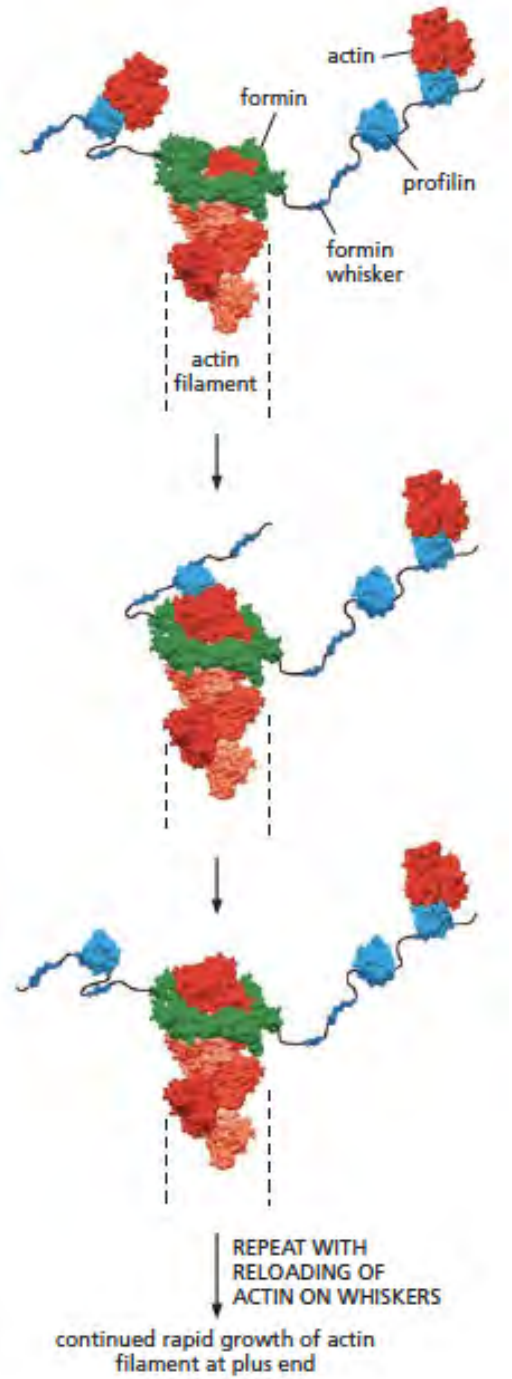
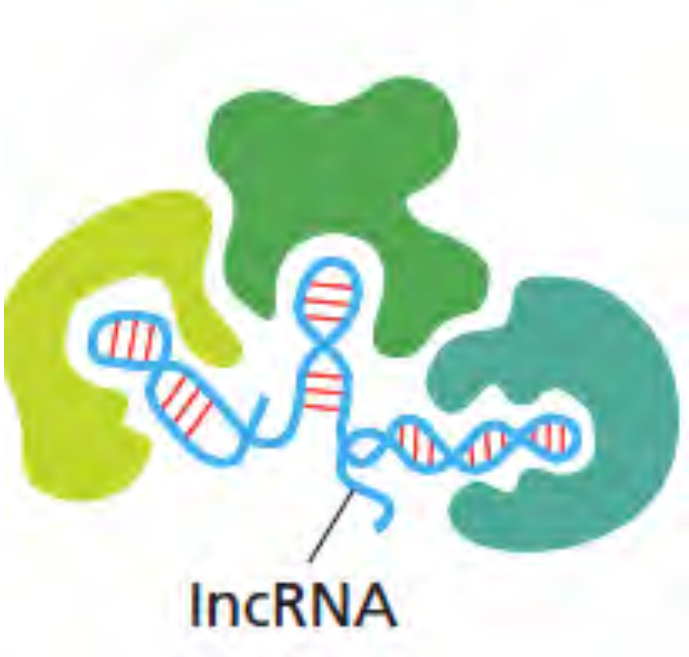


Figure 16-38 *Molecular Biology of the Cell* (© Garland Science 2008)

RNA scaffolds are also widely used in cells (thousands of long non-coding RNAS (*lnc RNAs*)

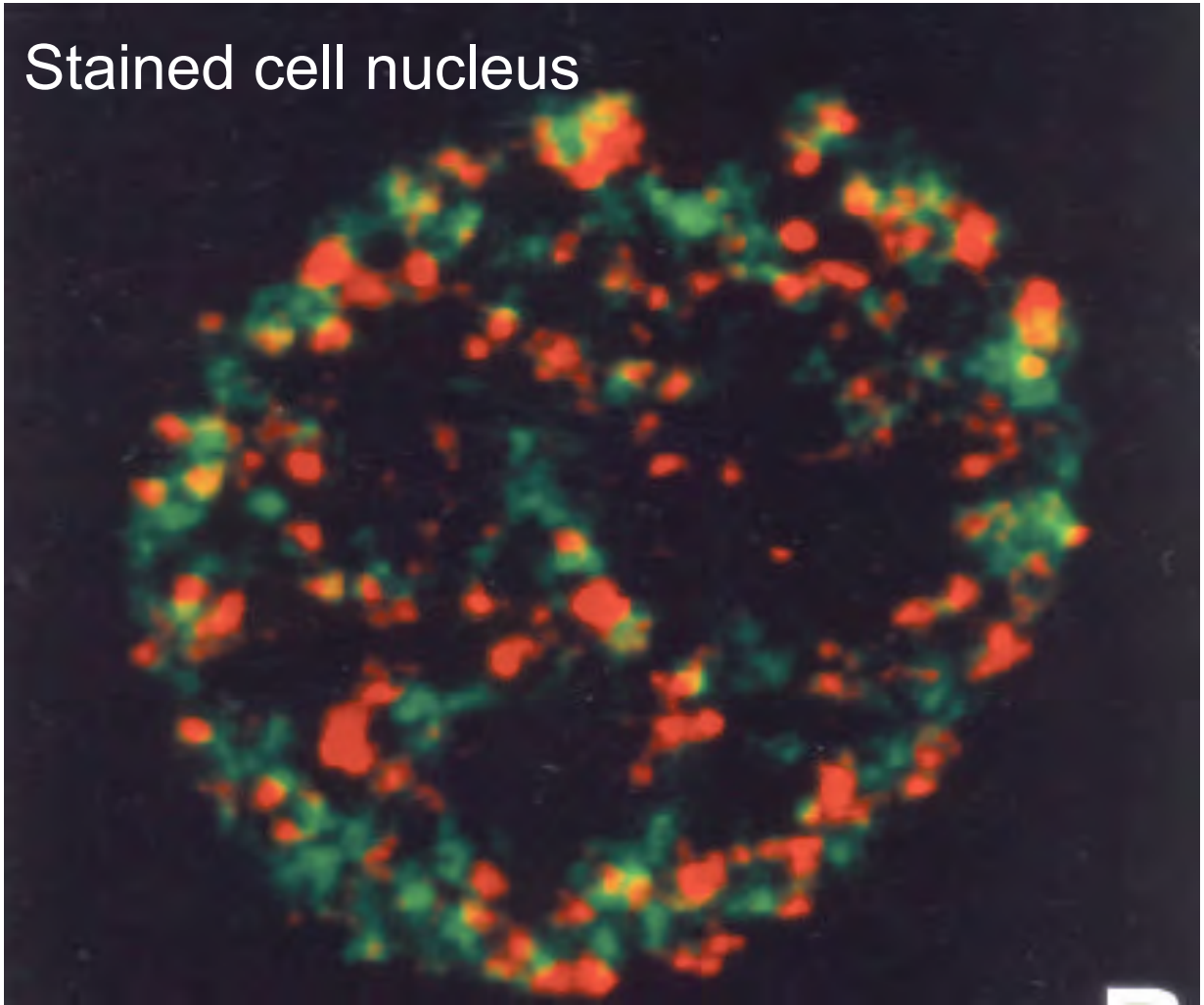


Scaffolds are involved in forming many different biochemical "factories" inside the cell

"liquid droplet aggregates"

Transcription factories RED

Replication factories GREEN



From D. G. Wansink, et al, 1994

What life is really like:

A cartoon from a review article

Protein scaffolds in the coupling of synaptic exocytosis and endocytosis

Volker Haucke[*§], *Erwin Neher*[‡] *and Stephan J. Sigrist*[§||]

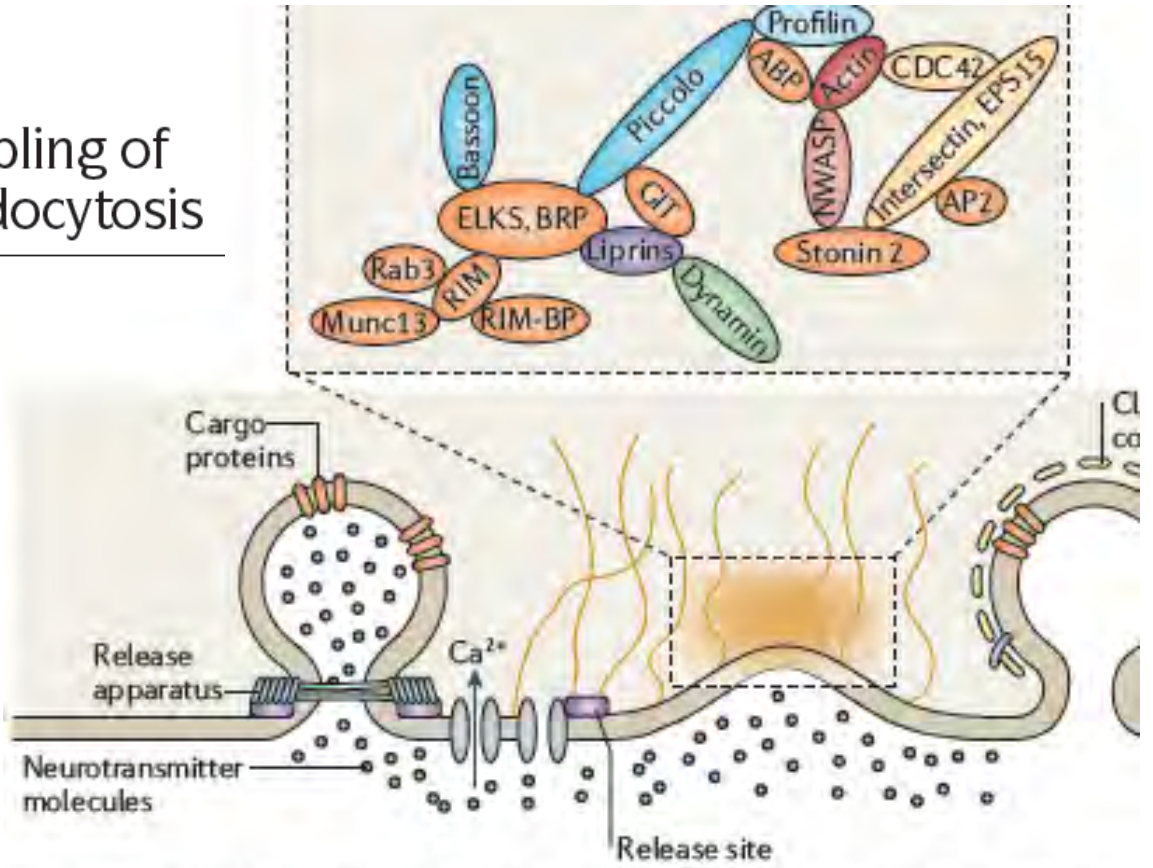


Figure 3 | **Scaffolds in exocytic–endocytic coupling.** Direct membrane contact between synaptic vesicles and the active zone. Tomographic slices that are 2.7 nm in

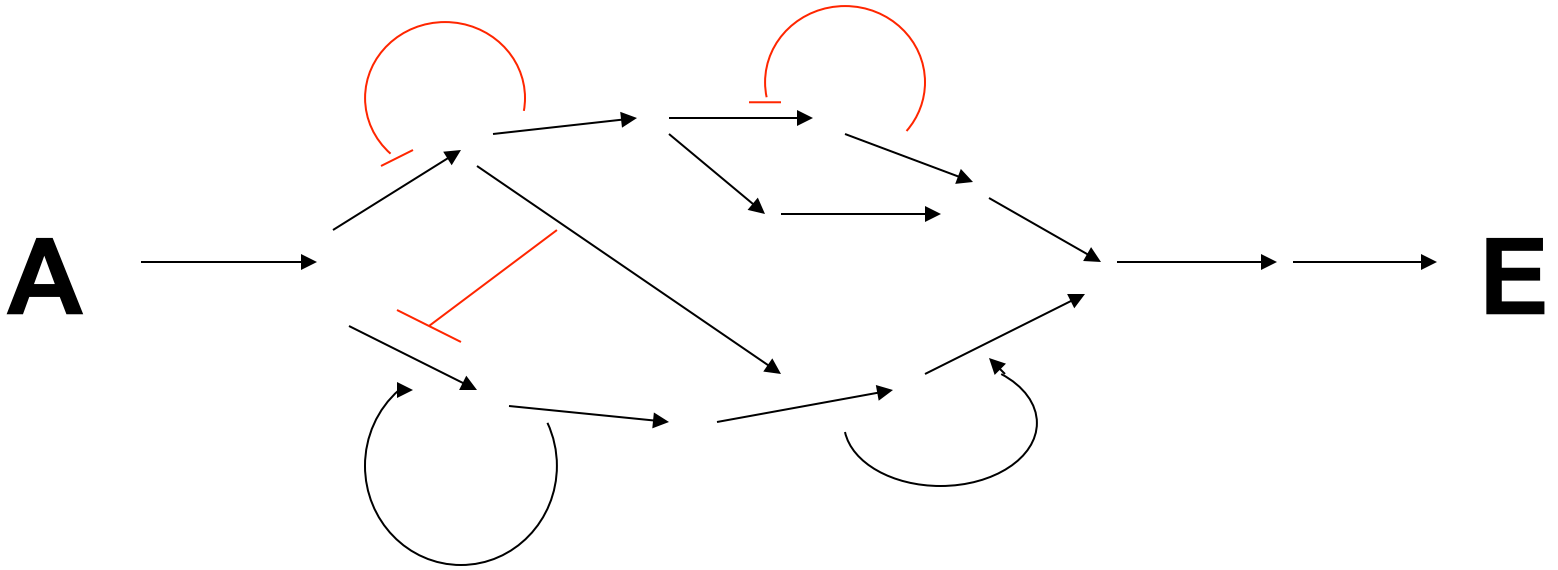
In conclusion, A CELL IS NOTHING LIKE A TEST TUBE!

Nearly everything is organized inside the cell by protein and RNA scaffolds

Emergent Properties

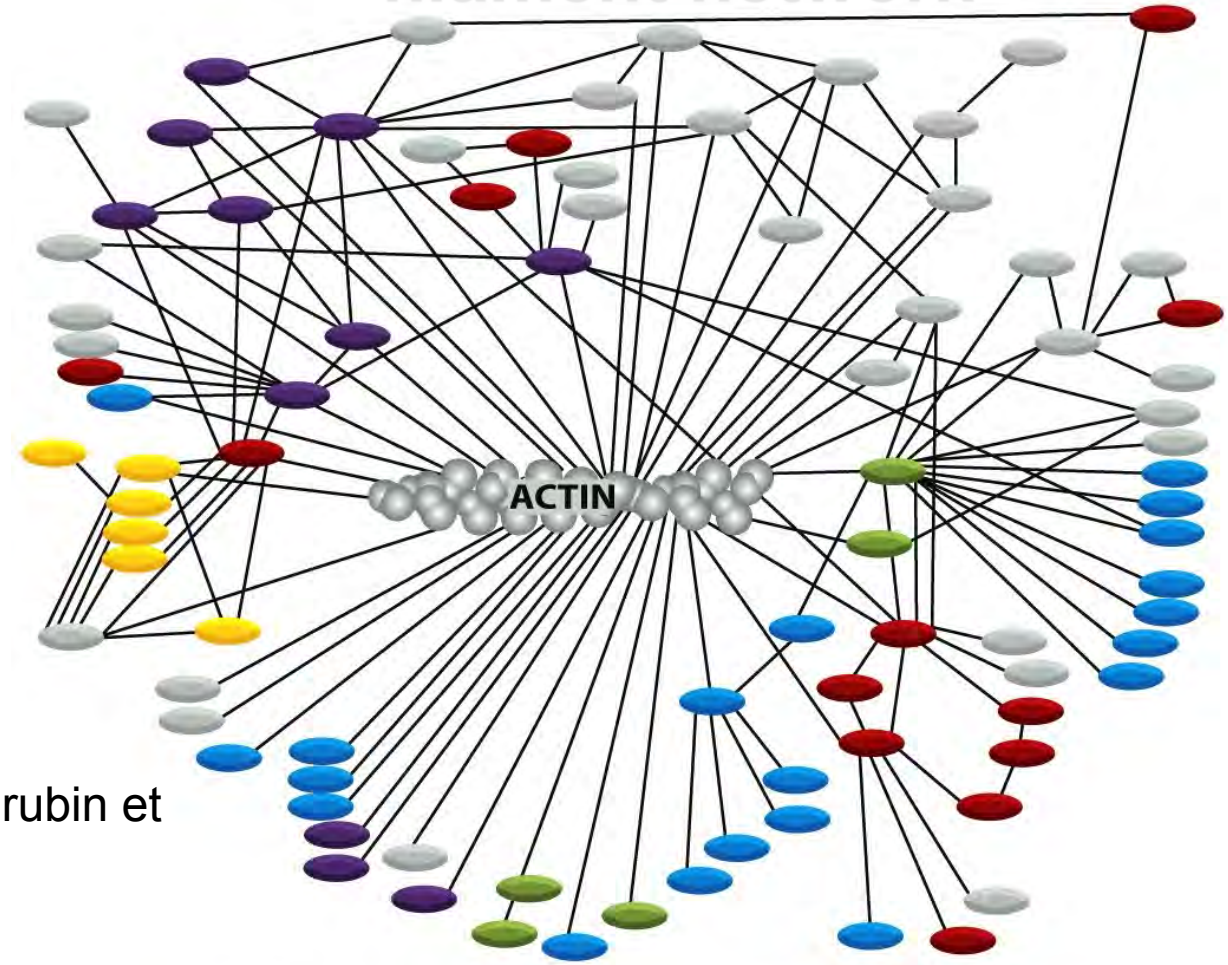
How nearly all of biology works

Feedback and feed-forward loops



There is no way to understand such pathways without mathematics

One example: the great complexity of the actin filament network



From D. Drubin et al.

Figure 16-18 *Molecular Biology of the Cell* (© Garland Science 2008)

As a consequence of such complexity

Even when we gain a **complete** knowledge of all of the molecules, protein machines, and molecular interactions in a cell, we will not be able to **understand** even the simplest of living cells.

Instead, life reflects the **emergent properties** that result from very complex networks of interactions.

My conclusion: It will probably take most of this century to gain a true understanding of how cells and organisms work

1. **Much more biochemistry** will be needed in purified systems that reconstitute biological systems.

2. Also needed: **new quantitative methods** for analyzing and understanding the enormous complexity of life's chemistry (**computer modeling/mathematics**).

Keeping science healthy

To keep science healthy we must all work to stimulate innovation

- In attempting to do so, it is important to recognize how new knowledge arises.
- To this end, the US National Academy of Sciences produced 20 8-page pamphlets with specific examples in the 1990's.

www.nasonline.org/publications/beyond-discovery

Timeline for Global Positioning System (GPS)

A Chronology of Selected Events in the Development of GPS.

This timeline of selected events emphasizes early research in physics, notably atomic clocks, that contributed to the development of the Global Positioning System and illustrates the value of such long-term basic research in the ultimate achievement of important benefits to society. It does not provide a complete portrait of the development of GPS.

1938-1940
I.I. Rabi invents molecular-beam magnetic resonance at Columbia University in 1938. He and his colleagues apply magnetic resonance to fundamental studies of atoms and molecules. Possibility of atomic clock to measure gravitational red shift is discussed. Rabi is awarded the Nobel Prize for this work in 1944.

1949
Norman Ramsey invents separated-oscillatory-field resonance method at Harvard University, for which he was awarded the Nobel Prize in 1989. Jerrold Zacharias proposes using Ramsey's method to create cesium-beam "fountain" clock that would be accurate enough to measure gravitational red shift.

1949
National Bureau of Standards operates atomic clock based on microwave absorption in ammonia gas. Work starts on cesium-beam atomic clock.

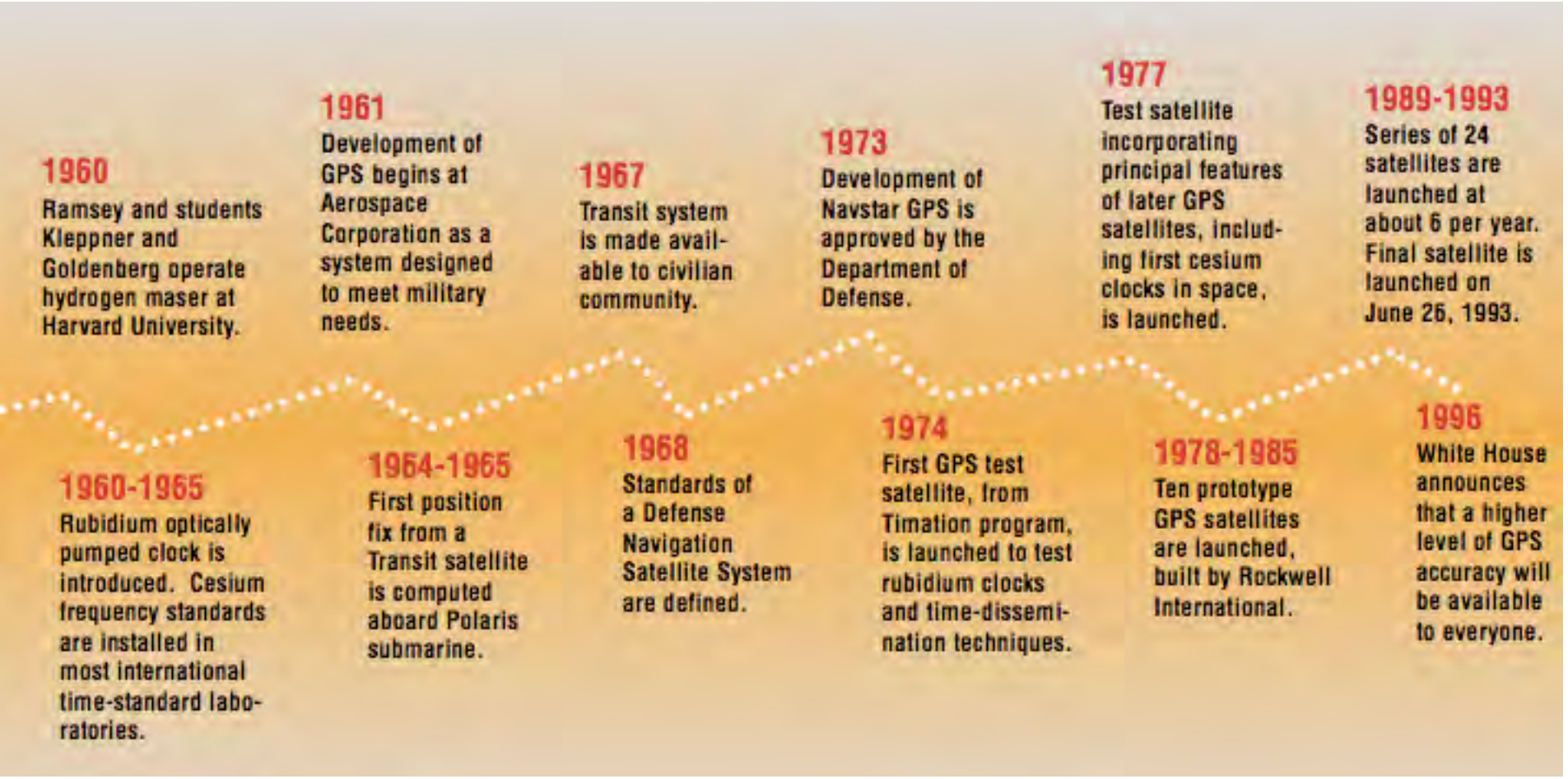
1954
Charles Townes at Columbia University demonstrates operation of the first maser based on emission of radiation from ammonia molecules. Townes shared the 1964 Nobel Prize in physics.

1954-1956
Zacharias and National Company develop the first self-contained portable atomic clock, the Atomichron.

1959
Albert Kastler and Jean Brossel, working in Paris and at MIT, develop methods of optical pumping. Kastler is awarded the Nobel Prize for this work.

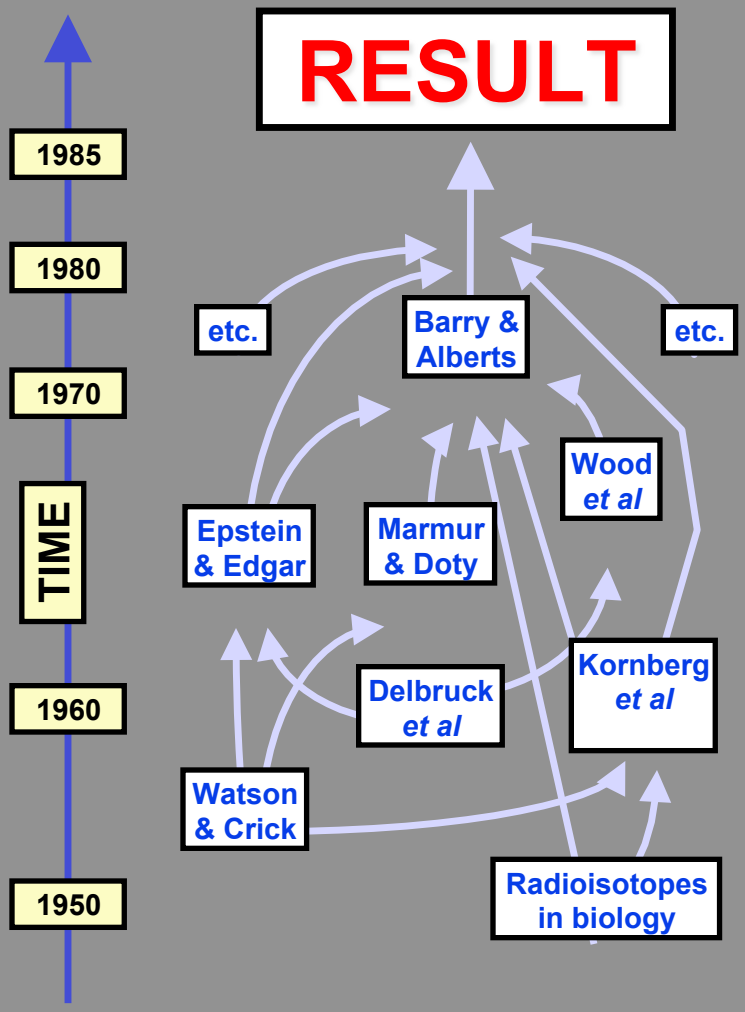
1957
Sputnik is launched in October by the Soviet Union. Satellite Doppler tracking is inaugurated at MIT Lincoln Laboratory and Johns Hopkins Applied Physics Laboratory (APL). Navy Transit program is started at APL in December.

Timeline continued

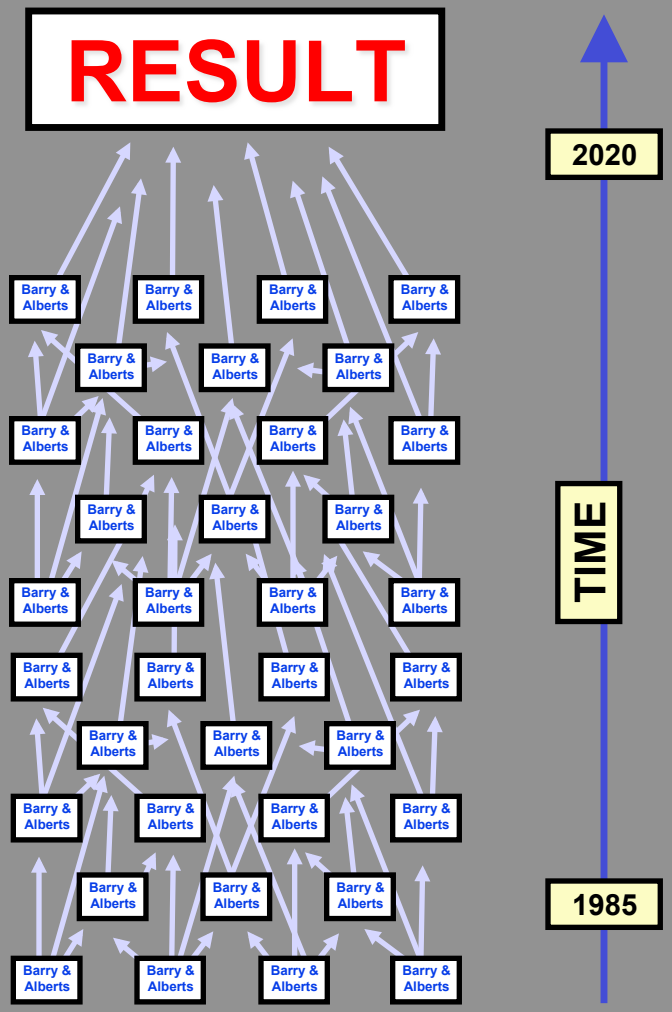


THE FUNDAMENTAL REASON FOR THE EXPLOSIVE GROWTH OF SCIENCE

100 units of knowledge
can be combined
in 100 times more ways
than can
10 units of knowledge



My field in 1950 - 1985



My field in 1985 - 2020

But there is a catch!

As knowledge grows, it becomes increasingly difficult to find the right combinations

The source of creativity in science

To create consists precisely in not making useless combinations and in making those which are useful and which are only a small minority.

Invention is discernment, choice… Among chosen combinations the most fertile will often be those formed of elements drawn from domains which are far apart. …

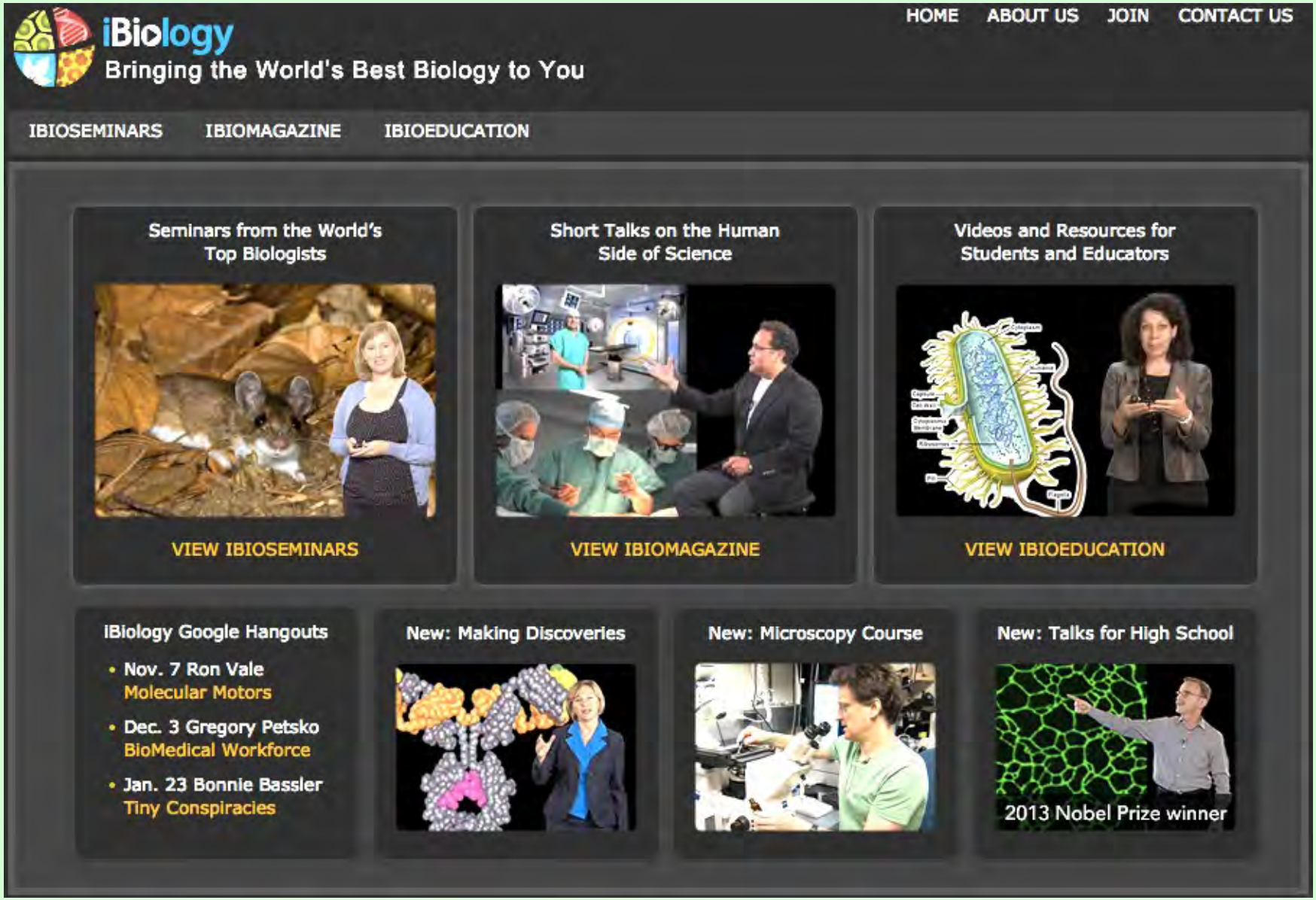
The true work of the inventor consists in choosing among these combinations so as to eliminate the useless ones.

Henri Poincaré

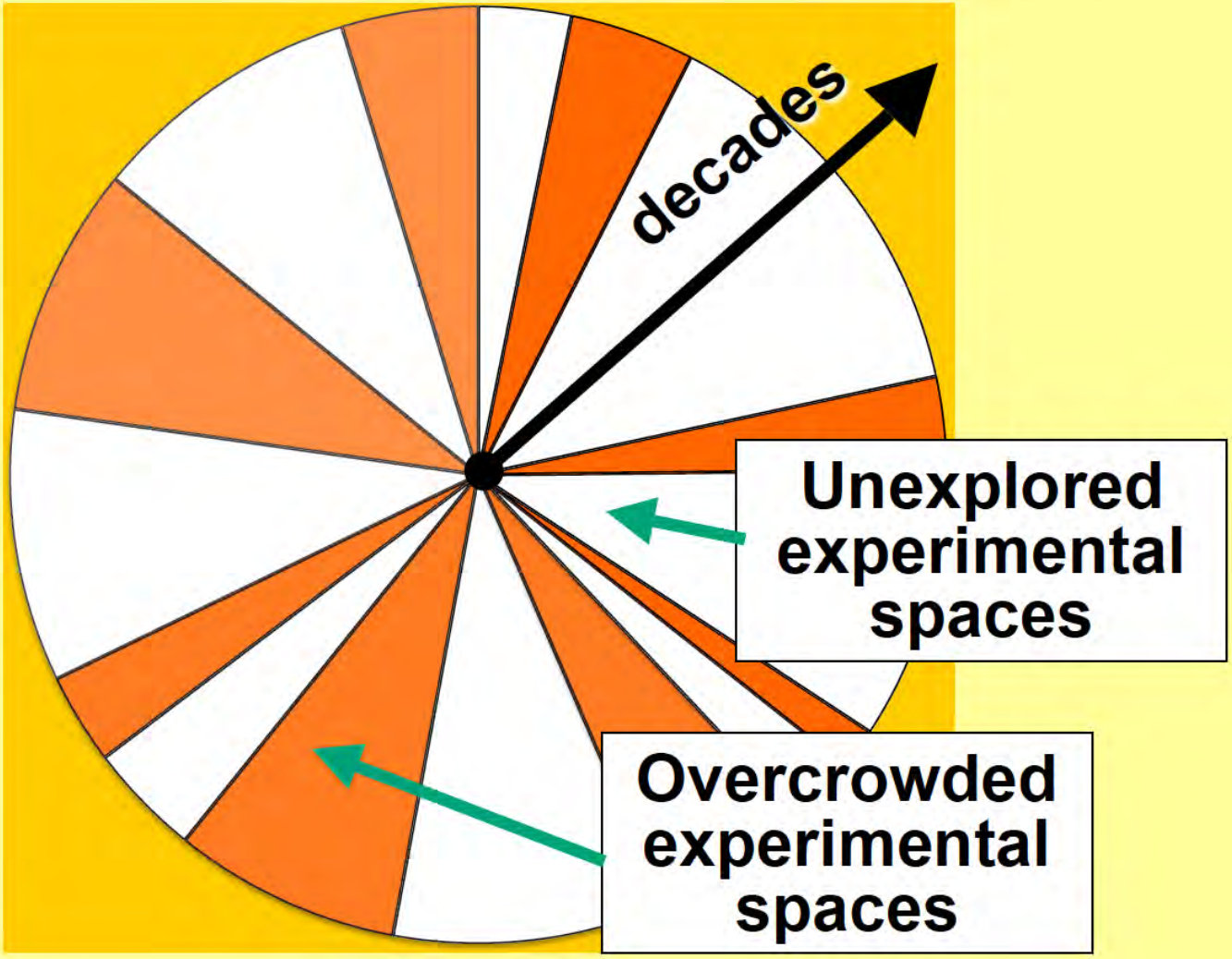
1908

A place to get new ideas for your research

www.ibiology.org



A major problem: the channeling of research topics due to “training inertia”



Unfortunately

Our present system for funding research strongly **discourages risk-taking**, preventing leaps into the "white spaces" where great new discoveries can be made.

A second problem

In the US, the National Institutes of Health (**NIH**) has been greatly overemphasizing "translational" biomedical research.

But with so many unknowns and so little understanding, **basic research on biological mechanisms** remains absolutely crucial for improving human health.

“The challenge in translational medicine is that scientists are trying to translate a text with the sophistication and depth of Shakespeare using a first-grader's vocabulary and experience”

EDITORIAL

H. Zoghbi, *Science* **339:** 250 (2013)

The Basics of Translation

Huda Y. Zoghbi is an investigator with the Howard Hughes Medical Institute; professor of Pediatrics, Molecular and Human Genetics, and Neuroscience at Baylor College of Medicine; and director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital in Houston, TX. E-mail: hzoghbi@bcm.edu.

THE PAST 20 YEARS HAVE WITNESSED GREAT ADVANCES IN UNDERSTANDING THE CAUSES OF MANY medical disorders, while also revealing how complex their pathogenesis can be. Hypertension, autism, and Alzheimer's disease have each proven to be a collection of disorders with multiple causes. Although the dream of personalized treatments has been realized for a few disorders, particularly in the field of cancer, the translation of scientific discoveries into effective treatments for other diseases has been much slower than expected. There are two main reasons for this fact: the complexity of human physiology, and our limited understanding of how the vast majority of genes, proteins, and RNAs work, irrespective of whether they are disease-associated or not.

Traditionally, such fundamental knowledge has come from untargeted, discovery-driven basic research. In recent years, however, the pressure to develop treatments at an ever more rapid pace has attenuated enthusiasm for deciphering the language of life. Science, like most human endeavors, is susceptible to fads and fashions driven by money and status; and today many highly qualified basic scientists feel compelled to jump on the “translational medicine” bandwagon. For quite some time, it has been apparent that biomedical research in the United States is more likely to get funded if it is tied to a practical outcome, such as a step toward a cure for some disor-

ONE EXAMPLE

149 of the 473 genes in a "minimal genome" are of unknown function!

Science, March 25, 2016

RESEARCH ARTICLE

SYNTHETIC BIOLOGY

Design and synthesis of a minimal bacterial genome

Clyde A. Hutchison III,[1*†] Ray-Yuan Chuang,[1†‡] Vladimir N. Noskov,[1] Nacyra Assad-Garcia,[1] Thomas J. Deerinck,[2] Mark H. Ellisman,[2] John Gill,[3] Krishna Kannan,[3] Bogumil J. Karas,[1] Li Ma,[1] James F. Pelletier,[4§] Zhi-Qing Qi,[3] R. Alexander Richter,[1] Elizabeth A. Strychalski,[4] Lijie Sun,[1||] Yo Suzuki,[1] Billyana Tsvetanova,[3] Kim S. Wise,[1] Hamilton O. Smith,[1,3] John I. Glass,[1] Chuck Merryman,[1] Daniel G. Gibson,[1,3] J. Craig Venter[1,3*]

We used whole-genome design and complete chemical synthesis to minimize the 1079–kilobase pair synthetic genome of *Mycoplasma mycoides* JCVI-syn1.0. An initial design, based on collective knowledge of molecular biology combined with limited transposon mutagenesis data, failed to produce a viable cell. Improved transposon mutagenesis methods revealed a class of quasi-essential genes that are needed for robust growth, explaining the failure of our initial design. Three cycles of design, synthesis, and testing, with retention of quasi-essential genes, produced JCVI-syn3.0 (531 kilobase pairs, 473 genes), which has a genome smaller than that of any autonomously replicating cell found in nature. JCVI-syn3.0 retains almost all genes involved in the synthesis and processing of macromolecules. Unexpectedly, it also contains 149 genes with unknown biological functions. JCVI-syn3.0 is a versatile platform for investigating the core functions of life and for exploring whole-genome design.

Cells are the fundamental units of life. The genome sequence of a cell may be thought deciphering the operating system of the cell was a daunting task.

tial genes. These results showed that it should be possible to produce a minimal genome that is smaller than any found in nature, but that the minimal genome would be larger than the common set of 256 genes. At that time, we proposed to create and test a cassette-based minimal artificial genome (*5*). We have been working since then to produce the tools needed to accomplish this. We developed methods to chemically synthesize the *M. genitalium* genome (*7*). However, *M. genitalium* grows very slowly, so we turned to the faster-growing *M. mycoides* genome as our target for minimization. We developed the method of genome transplantation, which allowed us to introduce *M. mycoides* genomes, as isolated DNA molecules, into cells of a different species, *M. capricolum* (*8*, *9*). In this process, the *M. capricolum* genome is lost, resulting in a cell containing only the transplanted genome. In 2010, we reported the complete chemical synthesis and installation of the genome of *M. mycoides* JCVI-syn1.0 [1,078,809 base pairs (bp) (*10*); hereafter abbreviated syn1.0). This genome was an almost exact copy of the wild-type *M. mycoides* genome, with the addition of a few watermark and vector sequences.

Genome reduction in bacteria such as *E. coli* and *B. subtilis* has previously been achieved by a series of sequential deletion events (*11*, *12*). After each deletion, viability, growth rate, and other phenotypes can be determined. In contrast to this approach, we set out to design a reduced genome, then build and test it. We initially designed a hypothetical minimal ge-

ANOTHER EXAMPLE: the importance of *Drosophila*

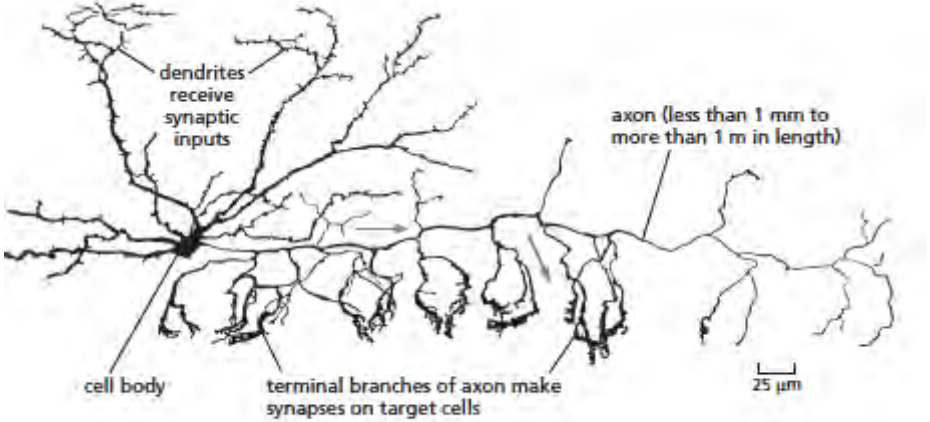
1. We are still far from understanding how cells work together to form and maintain tissues.

2. Many examples show that first working out a mechanism in *Drosophila* provides a shortcut to understanding humans.

3. Thus, in our textbook's 6th edition, the chapter on the development of tissues contains 50 references to *Drosophila*, four times more than the next most-cited organism.

Consider the human brain:

The ultimate **emergent property** is human consciousness

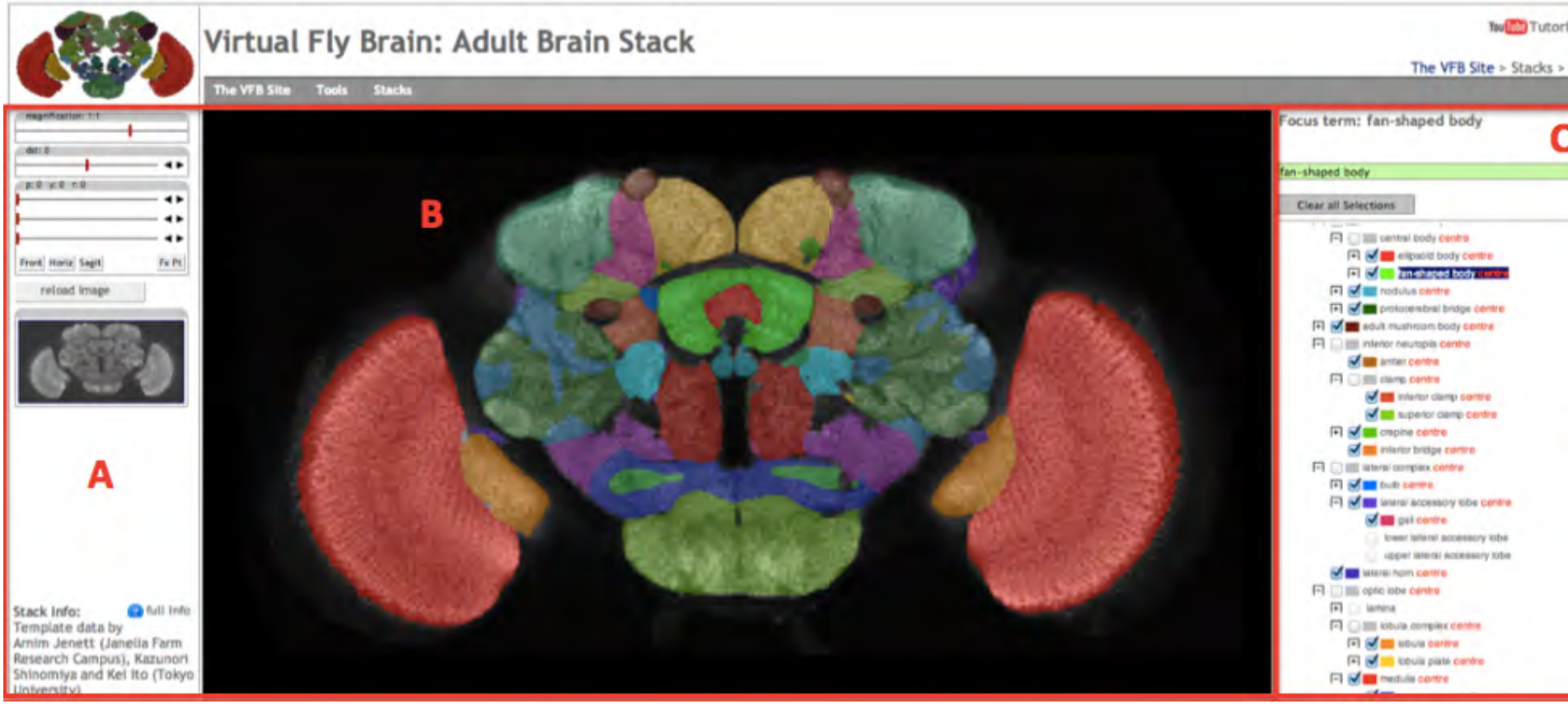


"A typical nerve cell, or neuron, has a structure unlike that of any other class of cells, with a long axon and branching dendrites, both of which make many synaptic connections to other cells.

The central challenge of neural development is to explain how the axons and dendrites grow out, find their right partners, and synapse with them selectively to create a neural network—an electrical signaling system—that functions correctly to guide behavior. The problem is formidable: **the human brain contains more than 100 billion neurons, each of which, on average, has to make connections with a thousand others, according to a regular and predictable wiring plan**."

Molecular Biology of the Cell, 6th Edition

The Drosophila brain contains about 100,000 neurons, a million times less than humans



1 millimeter

To understand cells, we also need new models!

OPEN ACCESS Freely available online

PLOS | BIOLOGY

The Kinase Regulator Mob1 Acts as a Patterning Protein for *Stentor* Morphogenesis

Mark M. Slabodnick*, J. Graham Ruby, Joshua G. Dunn, Jessica L. Feldman¤, Joseph L. DeRisi, Wallace F. Marshall*

Department of Biochemistry and Biophysics, University of California, San Francisco, California, United States of America

Abstract

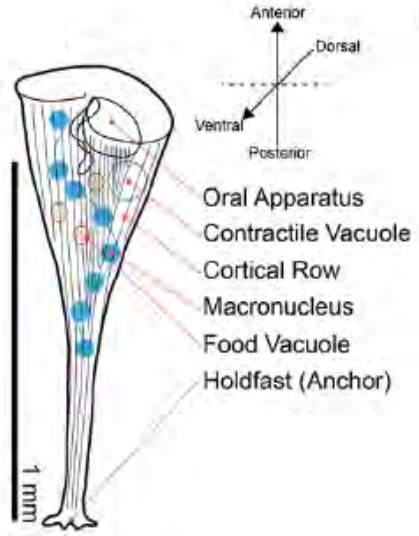
Morphogenesis and pattern formation are vital processes in any organism, whether unicellular or multicellular. But in contrast to the developmental biology of plants and animals, the principles of morphogenesis and pattern formation in single cells remain largely unknown. Although all cells develop patterns, they are most obvious in ciliates; hence, we have turned to a classical unicellular model system, the giant ciliate *Stentor coeruleus*. Here we show that the RNA interference (RNAi) machinery is conserved in *Stentor*. Using RNAi, we identify the kinase coactivator Mob1—with conserved functions in cell division and morphogenesis from plants to humans—as an asymmetrically localized patterning protein required for global patterning during development and regeneration in *Stentor*. Our studies reopen the door for *Stentor* as a model regeneration system.

Citation: Slabodnick MM, Ruby JG, Dunn JG, Feldman JL, DeRisi JL, et al. (2014) The Kinase Regulator Mob1 Acts as a Patterning Protein for *Stentor* Morphogenesis. PLoS Biol 12(5): e1001861. doi:10.1371/journal.pbio.1001861

Academic Editor: Elly M. Tanaka, Technische Universität Dresden, Germany

Received November 4, 2013; **Accepted** April 7, 2014; **Published** May 13, 2014

The ciliate *Stentor* is a giant single cell, with an intricately patterned plasma membrane that we do not understand



0.25 millimeter wide

What I hear repeatedly from even the most outstanding young scientists on the job market these days:

"Everybody tells me that I won't be able to get a research grant unless I work on **mouse or human** proteins/cells/tissues after my postdoc."

A call to action: *PNAS*, April 2014

PERSPECTIVE

Rescuing US biomedical research from its systemic flaws

Bruce Alberts[a], Marc W. Kirschner[b], Shirley Tilghman[c,1], and Harold Varmus[d]

[a]*Department of Biophysics and Biochemistry, University of California, San Francisco, CA 94158;* [b]*Department of Systems Biology, Harvard Medical School, Boston, MA 02115;* [c]*Department of Molecular Biology, Princeton University, Princeton, NJ 08540; and* [d]*National Cancer Institute, Bethesda, MD 20892*

Edited by Inder M. Verma, The Salk Institute for Biological Studies, La Jolla, CA, and approved March 18, 2014 (received for review March 7, 2014)

The long-held but erroneous assumption of never-ending rapid growth in biomedical science has created an unsustainable hypercompetitive system that is discouraging even the most outstanding prospective students from entering our profession—and making it difficult for seasoned investigators to produce their best work. This is a recipe for long-term decline, and the problems cannot be solved with simplistic approaches. Instead, it is time to confront the dangers at hand and rethink some fundamental features of the US biomedical research ecosystem.

graduate education | postdoctoral education | federal funding | peer review

By many measures, the biological and medical sciences are in a golden age. That fact, which we celebrate, makes it all the more difficult to acknowledge that the current system contains systemic flaws that are threatening its future. A central flaw is the long-held assumption that the enterprise will constantly expand. As a result, there is now a severe imbalance between the dollars available for research and the still-growing

DNA sequencing, sophisticated imaging, structural biology, designer chemistry, and computational biology—has led to impressive advances in medicine and fueled a vibrant pharmaceutical and biotechnology sector.

In the context of such progress, it is remarkable that even the most successful scientists and most promising trainees are increasingly pessimistic about the future of their chosen career. Based on ex-

doubling of the NIH budget ended, the demands for research dollars grew much faster than the supply. The demands were fueled in large part by incentives for institutional expansion, by the rapid growth of the scientific workforce, and by rising costs of research. Further slowdowns in federal funding, caused by the Great Recession of 2008 and by the budget sequestration that followed in 2013, have significantly exacer-

Launching a "**Rescuing Biomedical Research**" movement by expanding the "Gang of 4" to 16

Shirley Tilghman

Marc Kirchner

Harold Varmus

Nancy Andrews

Judith Kimble

Freeman Hrabowski

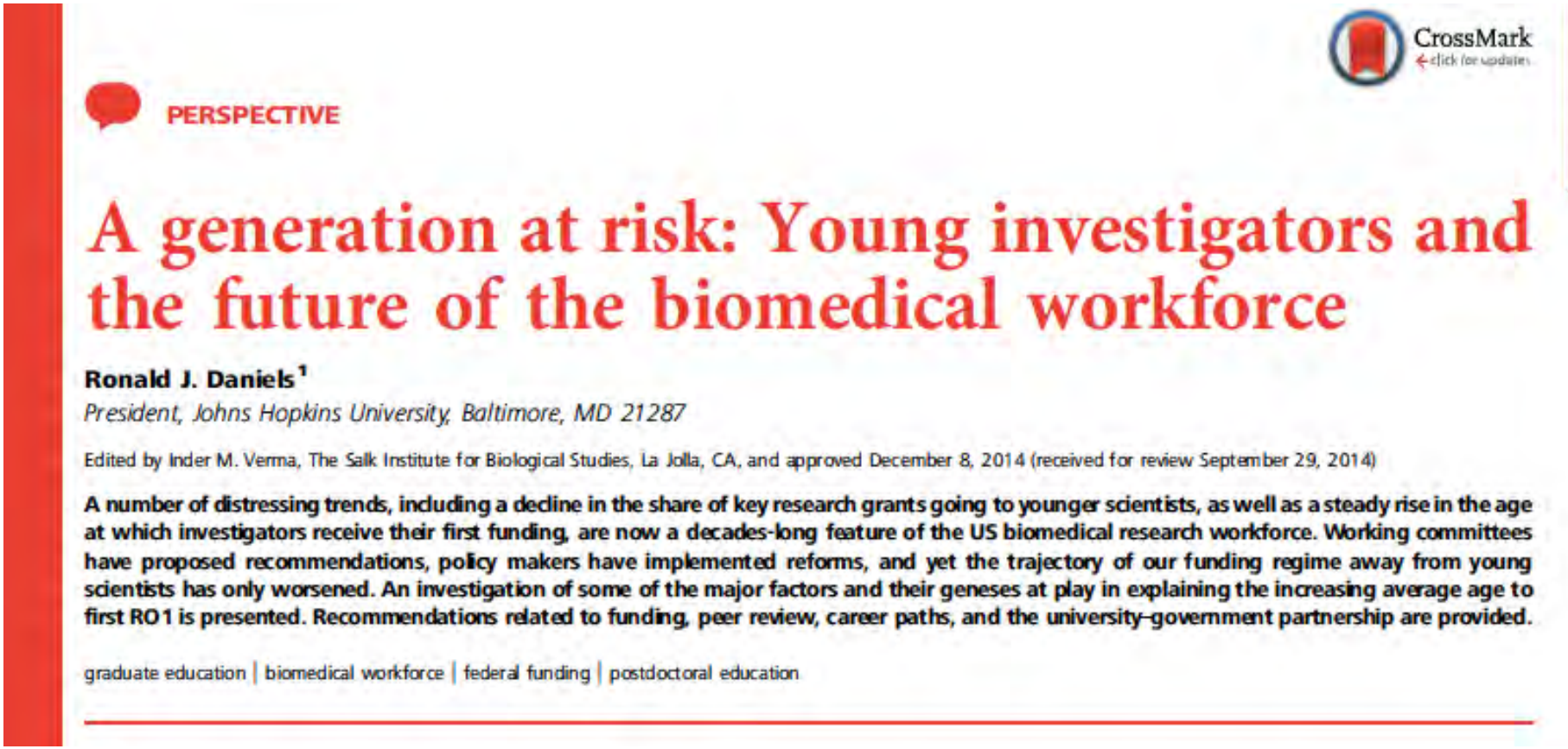
Daniel Colón-Ramos

Jessica Polka

Here, I can only highlight one more issue:

There have been very disturbing changes in the age distribution of independent researchers in the past 30 years

"The proportion of all grant funding awarded to scientists under the age of 36 has dropped from 5.6 percent in 1980 to 1.3 percent in 2012."



PERSPECTIVE

A generation at risk: Young investigators and the future of the biomedical workforce

Ronald J. Daniels[1]

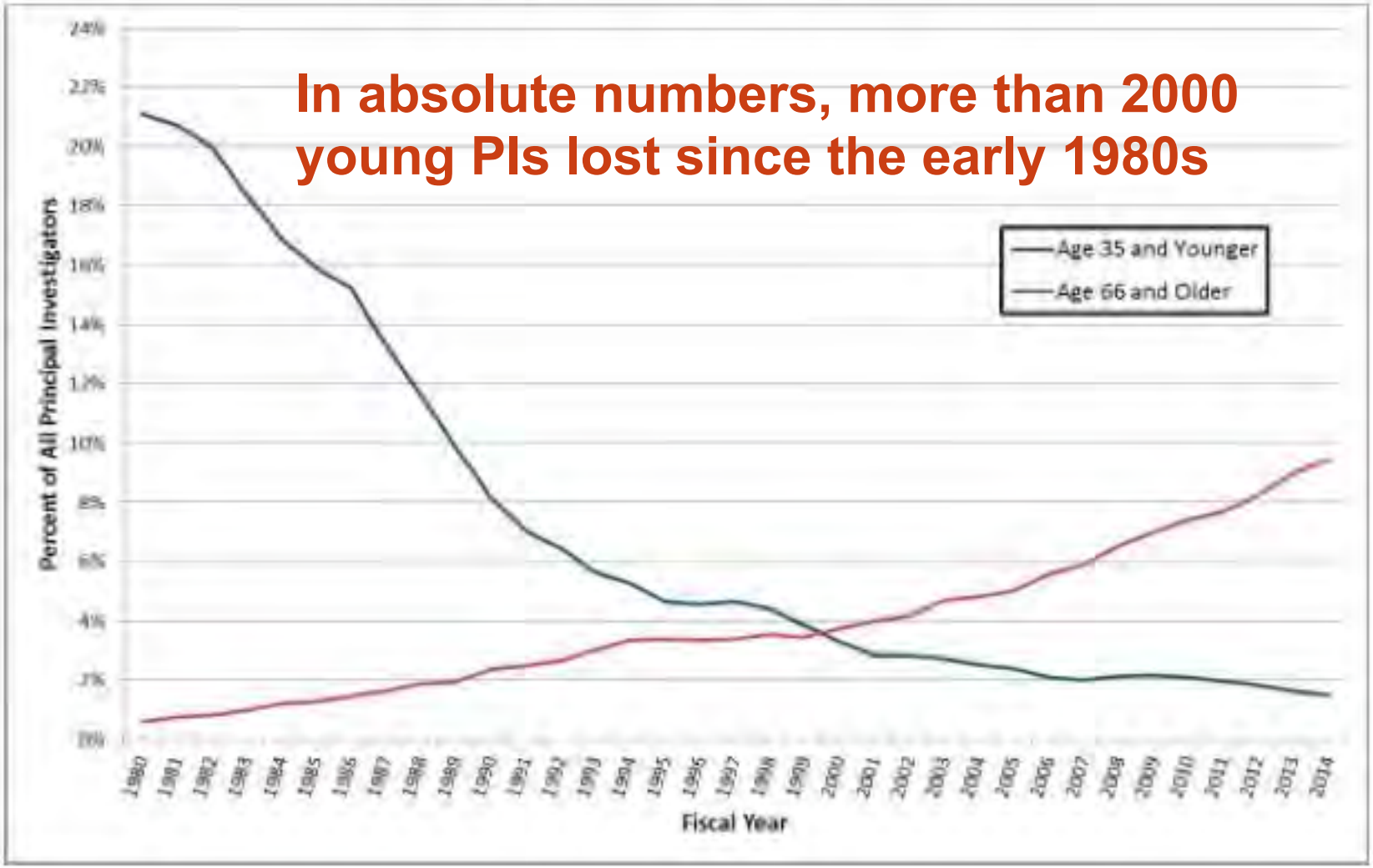
President, Johns Hopkins University, Baltimore, MD 21287

Edited by Inder M. Verma, The Salk Institute for Biological Studies, La Jolla, CA, and approved December 8, 2014 (received for review September 29, 2014)

A number of distressing trends, including a decline in the share of key research grants going to younger scientists, as well as a steady rise in the age at which investigators receive their first funding, are now a decades-long feature of the US biomedical research workforce. Working committees have proposed recommendations, policy makers have implemented reforms, and yet the trajectory of our funding regime away from young scientists has only worsened. An investigation of some of the major factors and their geneses at play in explaining the increasing average age to first RO1 is presented. Recommendations related to funding, peer review, career paths, and the university–government partnership are provided.

graduate education | biomedical workforce | federal funding | postdoctoral education

Percentage of NIH R01 Equivalent Principal Investigators of All Degrees: Age 35 and Younger vs. Age 66 and Older, Fiscal Year 1980 – 2014



The average age of an investigator receiving his or her first NIH R01 grant is 42 years!

A Question to Ponder

How successful would Silicon Valley be if nearly 99 percent of all investments went to innovators who were 36 years old or older?

What might be done to correct this problem?

Europe provides a model:

The European Research Council (ERC) was established in 2007.

The ERC holds an annual pan-European competition for young investigators who are "making the transition from working under a supervisor to being independent researchers in their own right**."** These **starting grants** are reserved for investigators with 2-7 years of experience since completion of PhD.

A crucial aspect of this ERC competition is that its **reviewing criteria specifically focus on novelty, interdisciplinarity, and high risk/ high gain research**. Each successful applicant is funded for 5 years, for a total of about 1,500,000 Euros.

Three separate ERC competitions are held, in which the investigators compete only with those at the same stage of their careers:

- Starting (2 to 7 years post PhD)
- Consolidator (7 to 12 years post PhD)
- Advanced (no limits)

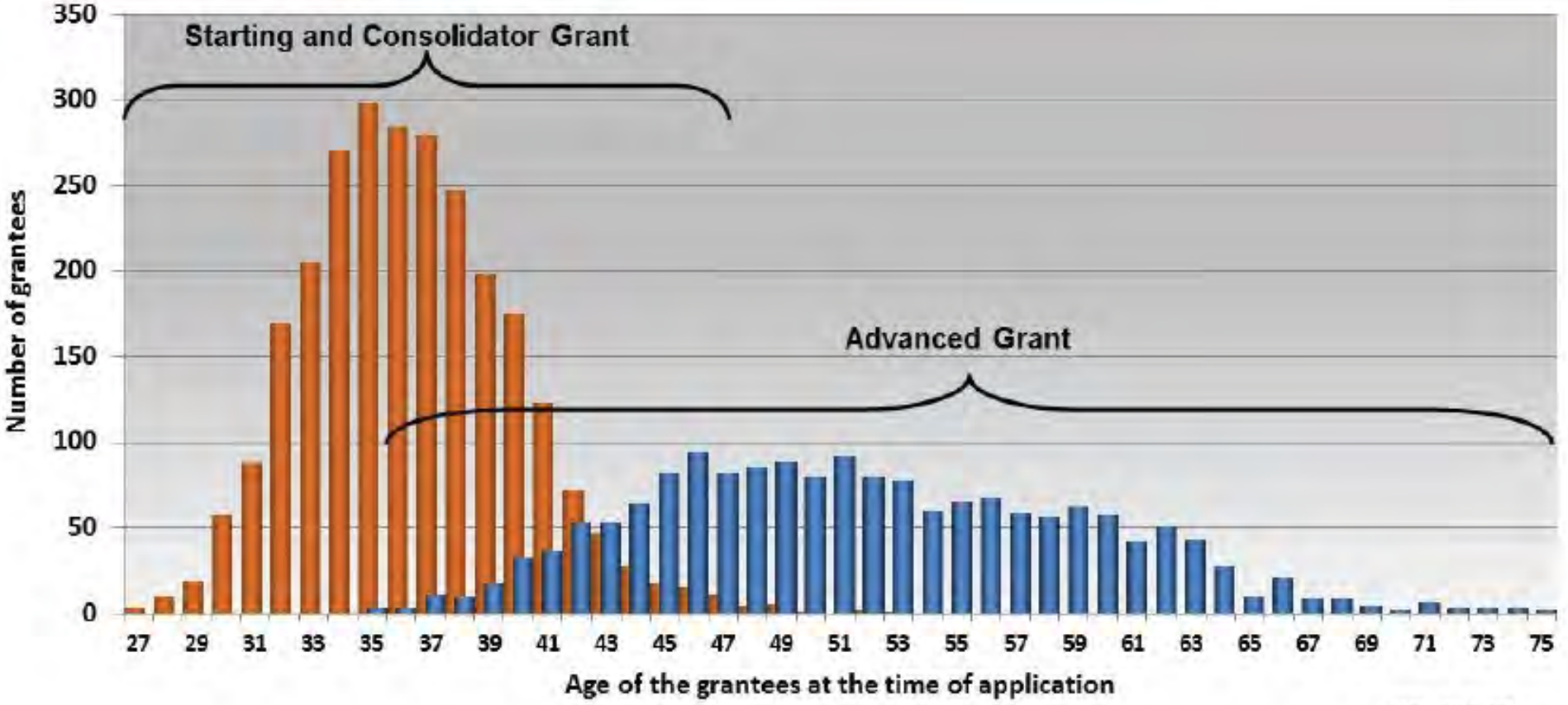
The total amount of funding for each group has been decided in advance, with about **57 percent of the money going to scientists who are within 12 years of their PhD**.

For 2015:

- 350 Starting Grants & 315 Consolidator Grants
- 280 Advanced Grants

ERC Grantees Age Distribution

European Research Council
Established by the European Commission



ERC 2007-2013

A proposal for the U.S.:

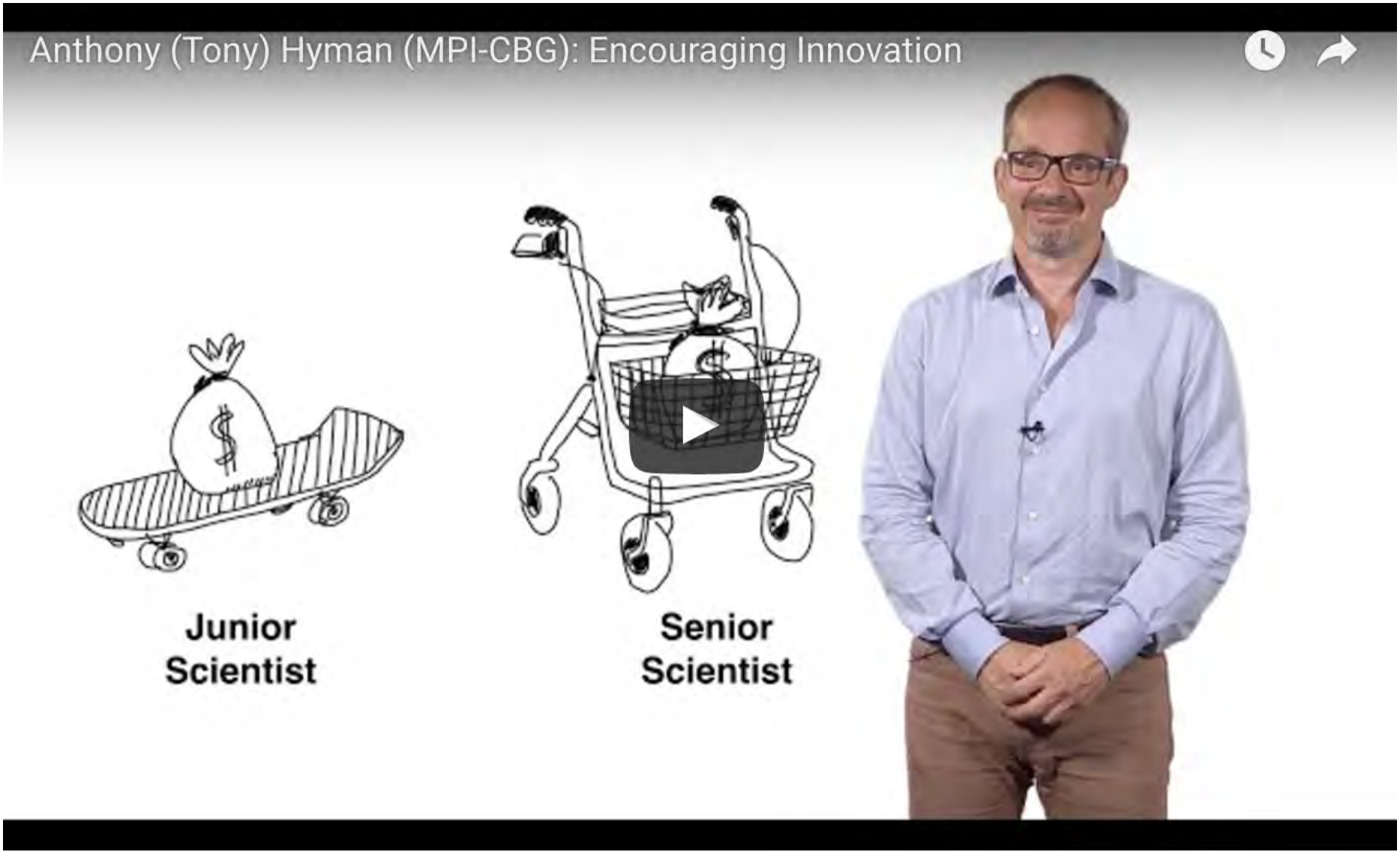
- Focus on generously funding the best young investigators within 7 years of their PhD, **committing enough funds to this new program to replace the 2000 independent investigators age 36 or younger who have been lost since the early 1980[1]s**.

- **Encourage ambitious aims** and do not require preliminary results.

- As for the ERC, review these applications using broad groups of outstanding investigators, to avoid the siloing effects of current NIH review groups.

- Consider including an interview at the final stage of selection, as does the ERC. Could such a program help to increase diversity?

See 13-min TALK BY TONY HYMAN, Encouraging Innovation, at
http://www.ibiology.org/ibiomagazine/encouraging-innovation.html



It will take a strong push from young scientists to generate such a change!

A need to support the new "**Future of Research**" (**FOR**) postdoc organizations

OPINION ARTICLE

REVISED Shaping the Future of Research: a perspective from junior scientists [v2; ref status: indexed, http://f1000r.es/4yc]

Gary S. McDowell[1*], Kearney T. W. Gunsalus[2*], Drew C. MacKellar[3], Sarah A. Mazzilli[4], Vaibhav P. Pai[1], Patricia R. Goodwin[5], Erica M. Walsh[6], Avi Robinson-Mosher[7], Thomas A. Bowman[8], James Kraemer[9], Marcella L. Erb[10], Eldi Schoenfeld[11], Leila Shokri[12], Jonathan D. Jackson[13], Ayesha Islam[14], Matthew D. Mattozzi[7], Kristin A. Krukenberg[3], Jessica K. Polka[3]

Author affiliations

[*] Equal contributors

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Abstract

The landscape of scientific research and funding is in flux as a result of tight budgets, evolving models of both publishing and evaluation, and questions about training and workforce stability. As future leaders, junior scientists are uniquely poised to shape the culture and practice of science in response to these challenges. A group of postdocs in the Boston area who are invested in improving the scientific endeavor, planned a symposium held on October 2nd and 3rd, 2014, as a way to join the discussion about the future of US biomedical research. Here we present a report of the proceedings of participant-driven workshops and the organizers' synthesis of the outcomes.

Corresponding authors: Kristin A. Krukenberg , Jessica K. Polka

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"…doing nothing is not an option. The stakes are enormous …"

Opinion: Addressing systemic problems in the biomedical research enterprise, PNAS, 2/17/2015

This website is designed to collect and organize input for solutions to problems such as those addressed in the April 2014 PNAS article entitled *Rescuing US biomedical research from its systemic flaws*, whose major points are briefly outlined here. Overseen by a Steering Committee that includes Nancy Andrews, Mary Beckerle, Jeremy Berg, Daniel Colón-Ramos, Ron Daniels, Rush Holt, Freeman Hrabowski, Tony Hyman, Judith Kimble, Jessica Polka, Joan Reede and Ron Vale — in addition to ourselves, the website seeks to organize, and begin to prioritize, the

UPCOMING EVENTS

See upcoming events, or submit an event to be listed >>

IBIOLOGY VIDEOS: THE BIOMEDICAL WORKFORCE

View full-size movie at iBiology.org >>

View iBiology Video Series: The Future of the Biomedical Workforce >>

AN EVEN BIGGER ISSUE: The image we want for science

What science should look like in school

Active learning in college biology class

TO SPREAD SCIENCE

We need to create **new career paths for PhD's**, recognizing the value of scientifically trained people in many professions

- These individuals are invaluable for connecting the scientific community to the very different cultures of government, pre-college education, law, the media, business, etc.

An example: California state Legislature's Science and Technology Policy Fellows

California state Legislature's Science and Technology Policy Fellows

To date, 6 classes of these fellows have finished their one-year terms.

When the first 10 fellows were initially offered to the Legislature, **it was hard to find places that wanted them.**

After this first year, attitudes changed completely. In fact, about half of the 60 graduates of this program have now been permanently hired in policy roles, 19 by the state Legislature

Both the Legislature's appreciation of scientists and its use of science for decision-making have dramatically improved!

TO SPREAD SCIENCE

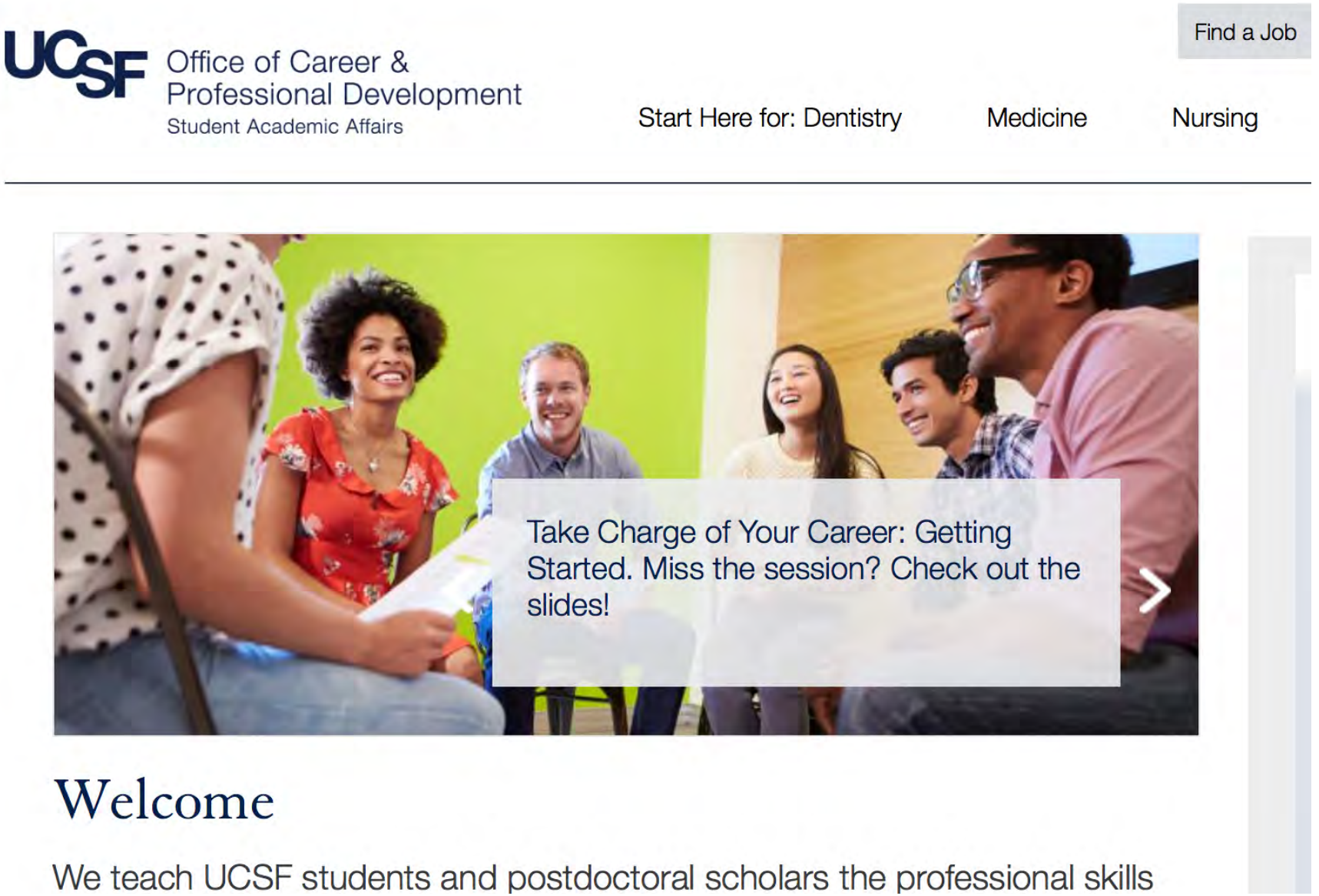
We need to create **new career paths for PhD's**, recognizing the value of scientifically trained people in many professions

Important questions

- How can we *improve career development* for graduate students?
- When should career training & mentoring occur?

A leading effort in this space

http://career.ucsf.edu/



The desired impact

1. **Change academic culture to value a diversity of career paths**
   1. "Non-traditional" careers become viewed as ***standard*** career paths that contribute greatly to the overall scientific enterprise.

   A broadening of what funding agencies consider to be a doctoral student's "successful outcome".

2. **Increase the attractiveness of advanced science education for students**

My favorite quote:

"The society of scientists is simple because it has a directing purpose: to explore the truth. Nevertheless, it has to solve the problem of every society, which is to find a compromise between the individual and the group. It must encourage the single scientist to be independent, and the body of scientists to be tolerant. From these basic conditions, which form the prime values, there follows step by step a range of values: dissent, freedom of thought and speech, justice, honor, human dignity and self respect.

Science has humanized our values. Men have asked for freedom, justice and respect precisely as the scientific spirit has spread among them."

Jacob Bronowski, Science and Human Values, 1956

Major retrospective ERC evaluation just completed
(199 completed grants analyzed by panels in detail)

Outcome by grant type

A higher proportion of the Advanced Grants evaluated in this exercise were awarded a grade A than Starting Grants (*Figure 2* and *Table 2*). When grades A and B are combined, however, a rather similar picture emerges for Starting Grants and Advanced Grants. There are no clear indications of differences between the two grant types in terms of the quality of the results obtained.

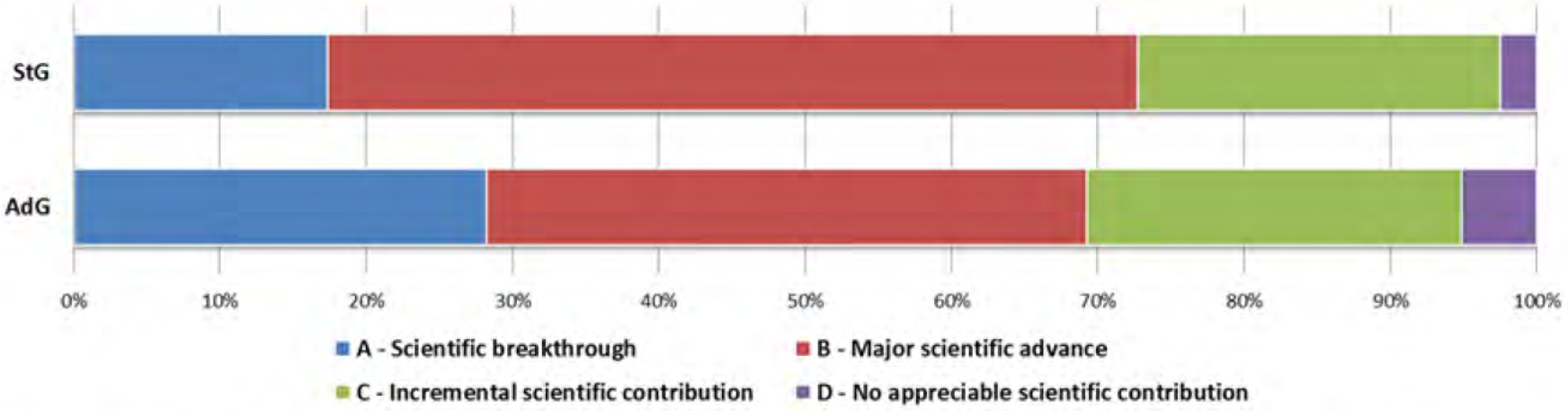


Figure 2: Overall grade attributed to projects by grant type. StG: Starting Grant; AdG: Advanced Grant.