The Problems and Challenges in Biomedical Sciences: Keeping Science Healthy

Duke University
Durham, NC
May 17, 2016

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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

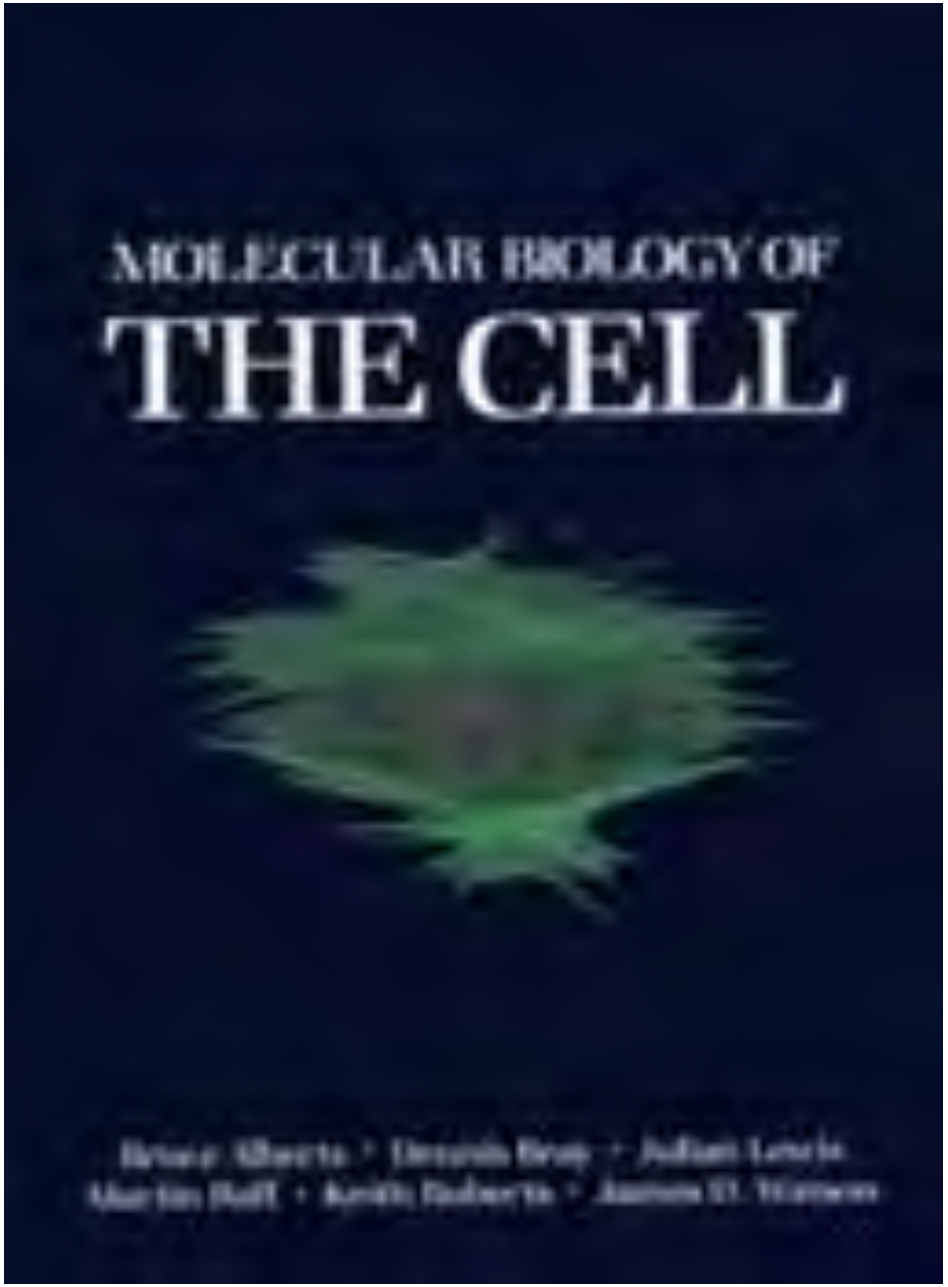
How it all started

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 <u>very</u> <u>much</u> 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.

Adding Two Younger Authors, 4th edition

Newest authors are Karen Hopkin, David Morgan, and Rebecca Heald

Sandy Johnson Peter Walter

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.

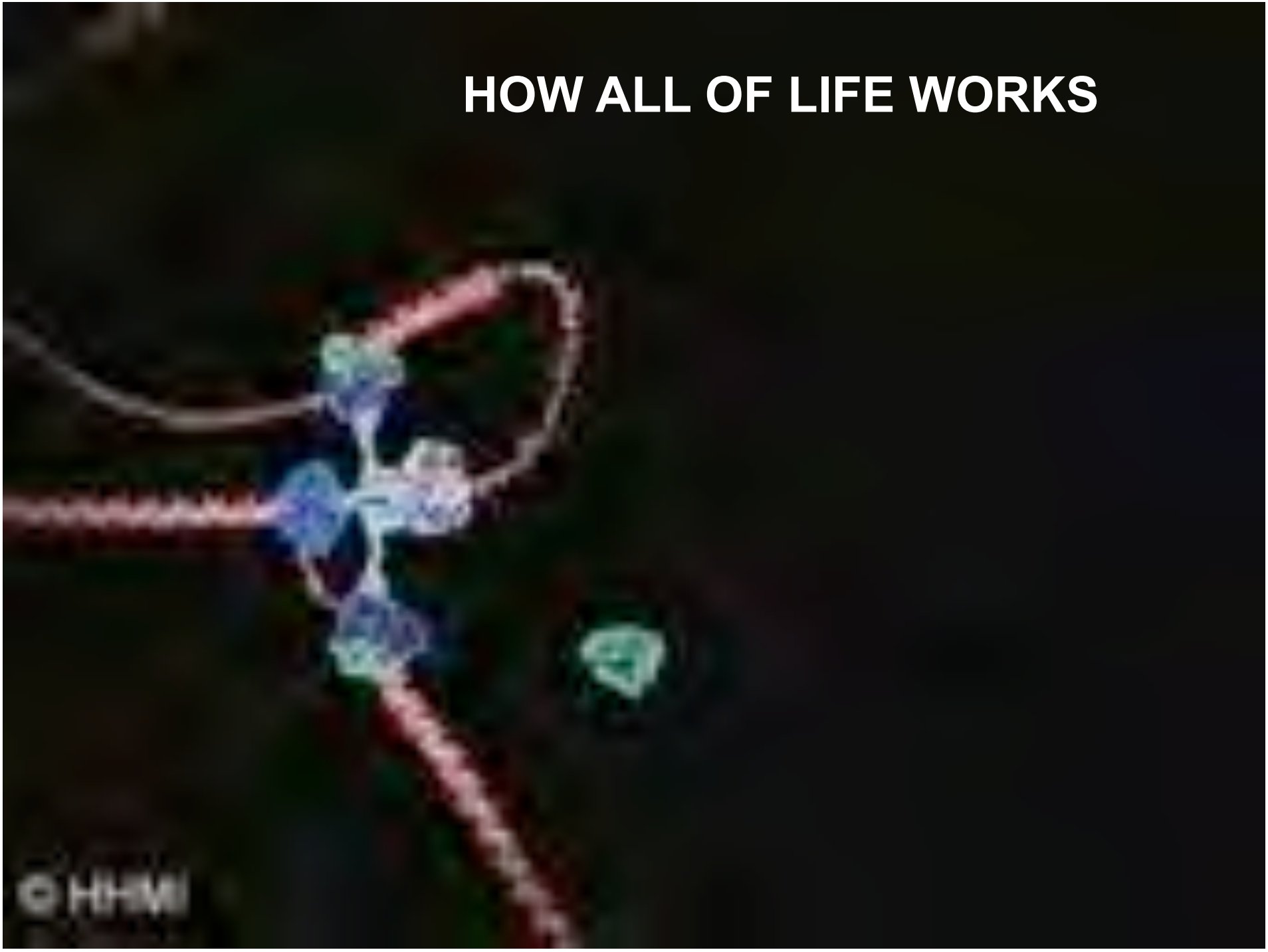
THIS IS ALL WRONG!

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



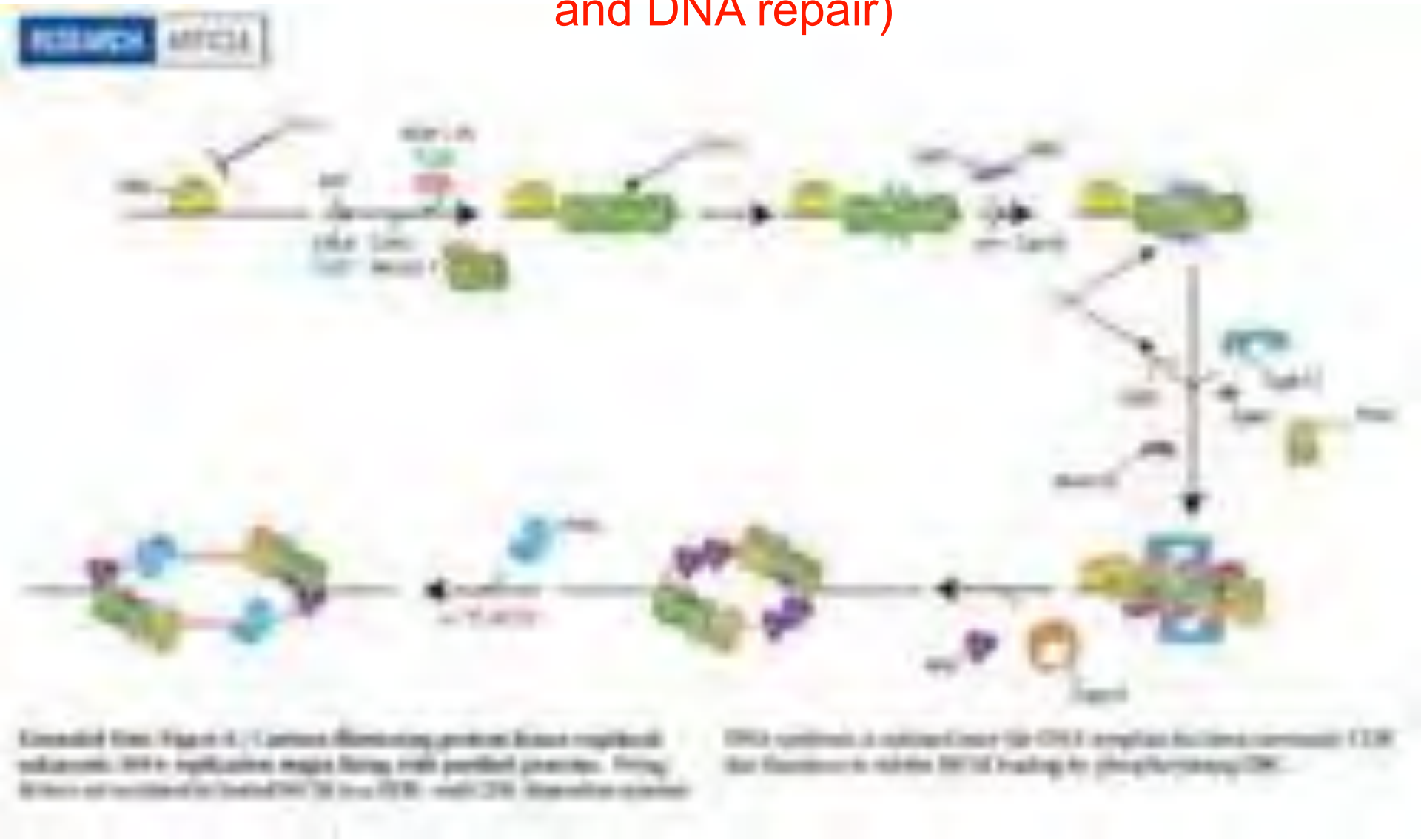
A Recent Breakthrough

ARTICLE

Regulated eukaryotic DNA replication origin firing with purified proteins

This is only the tip of the iceberg!

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



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.

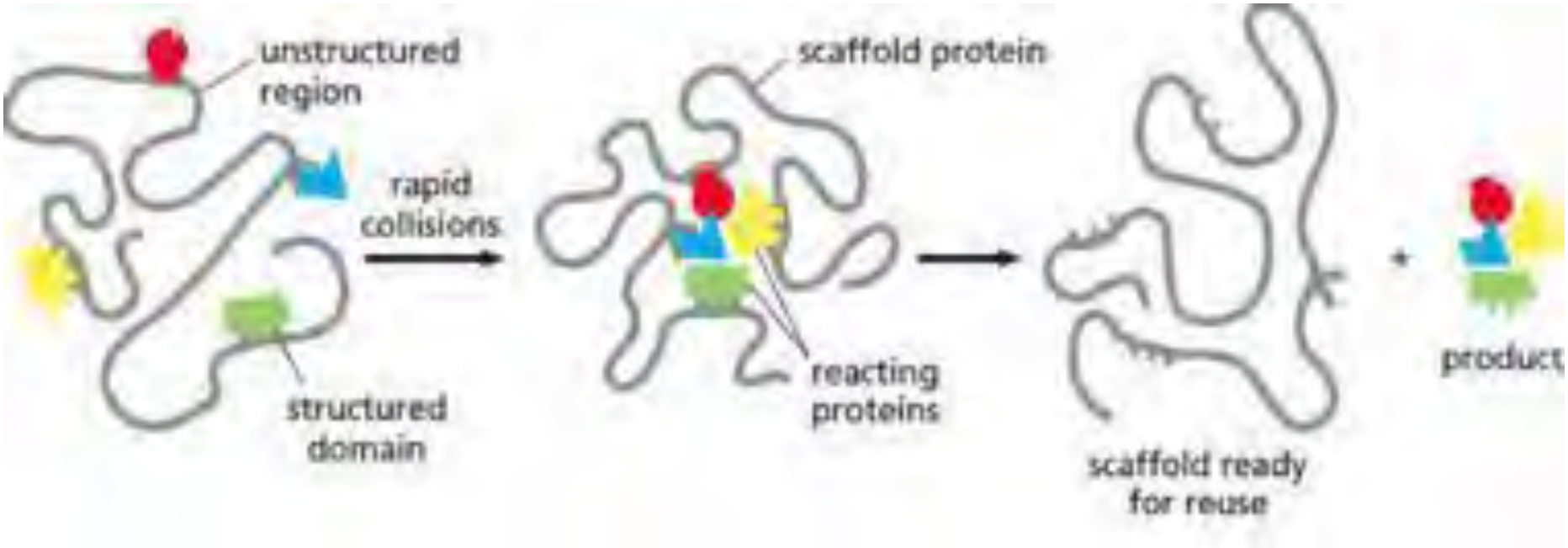
Two recent surprises for textbook authors (of many)

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)

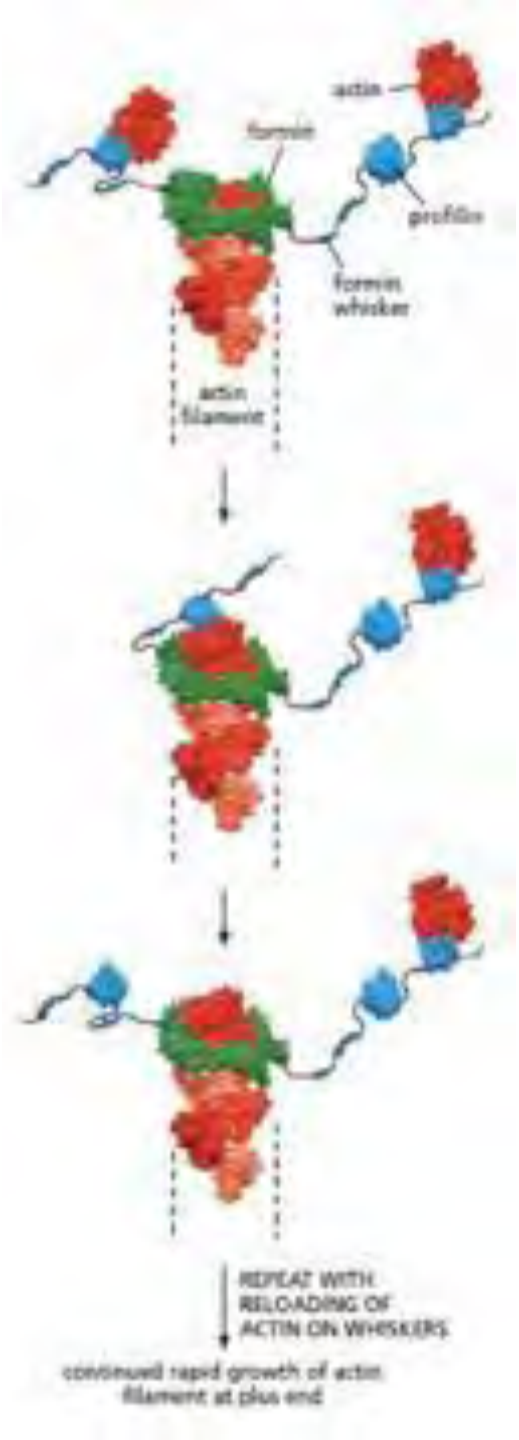


Figure 16-38 *Molecular Biology of the Cell* (© Garland Science 2008)

More complex scaffolds. *Science* 332: 680-686 (2011)

Scaffold Proteins: Hubs for Controlling the Flow of Cellular Information

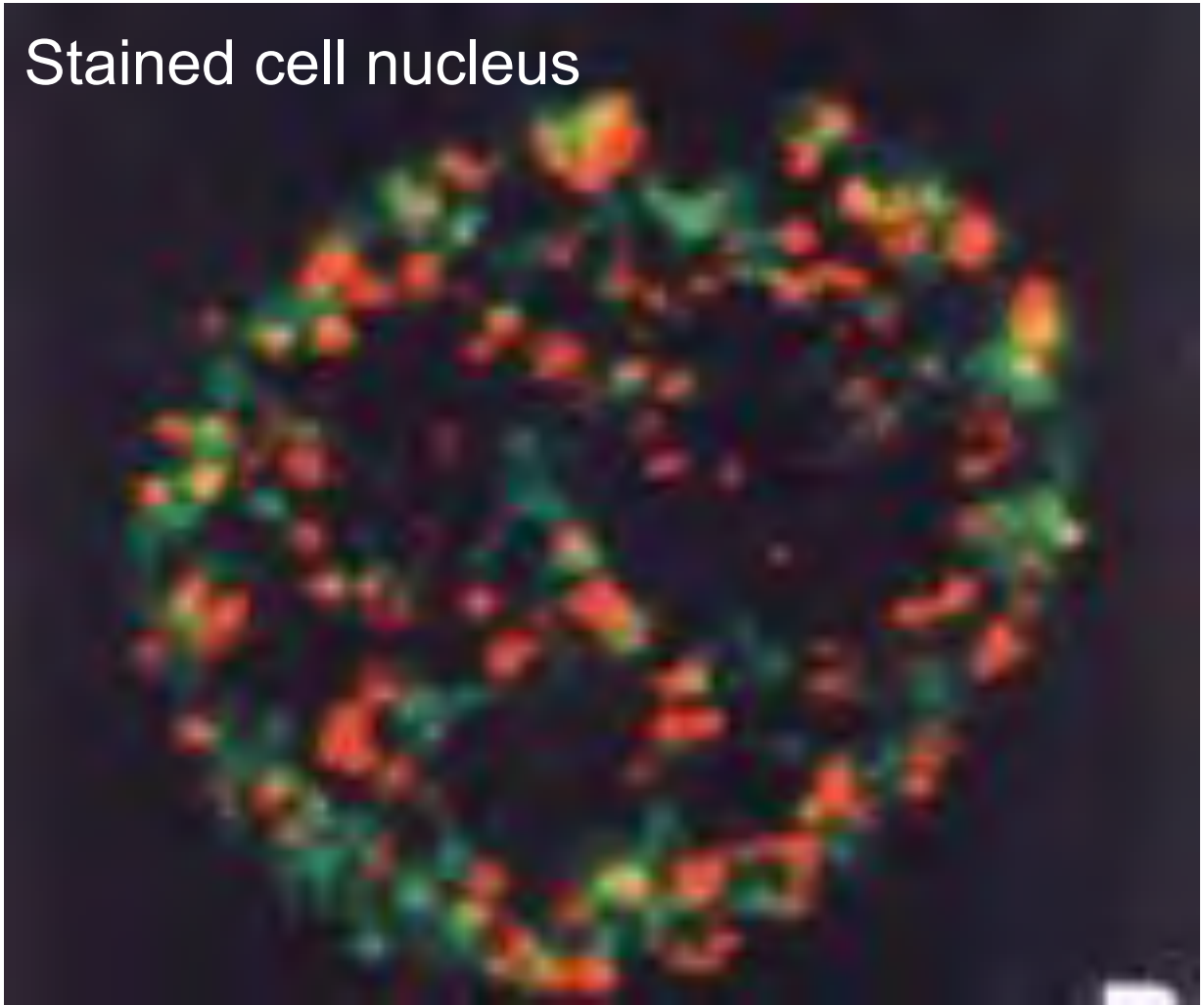
RNA scaffolds are also widely used in cells (thousands of long non-coding RNAS (*lnc RNAs*)

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

"liquid droplet aggregates"

Transcription factories RED

Replication factories GREEN



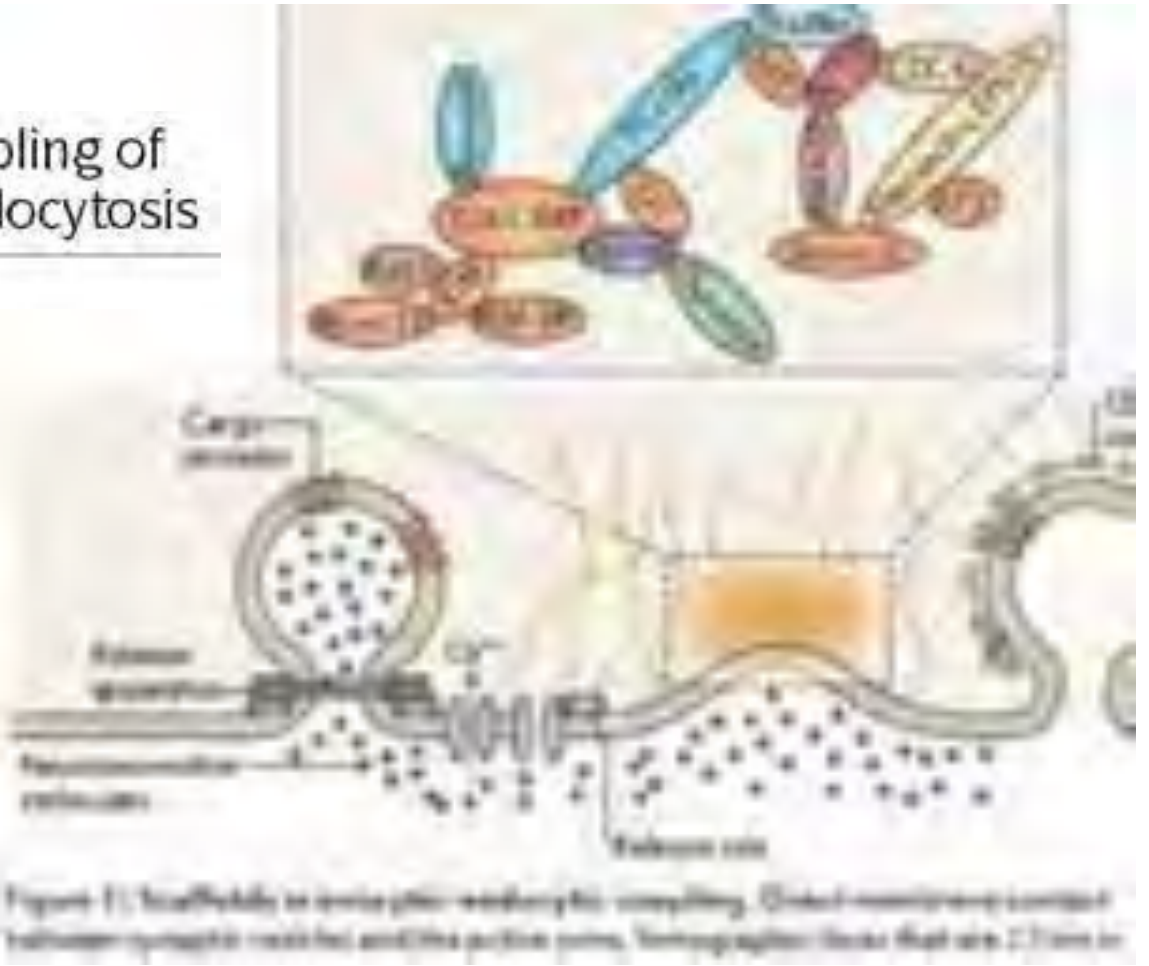
From D. G. Wansink, et al, 1994

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‡



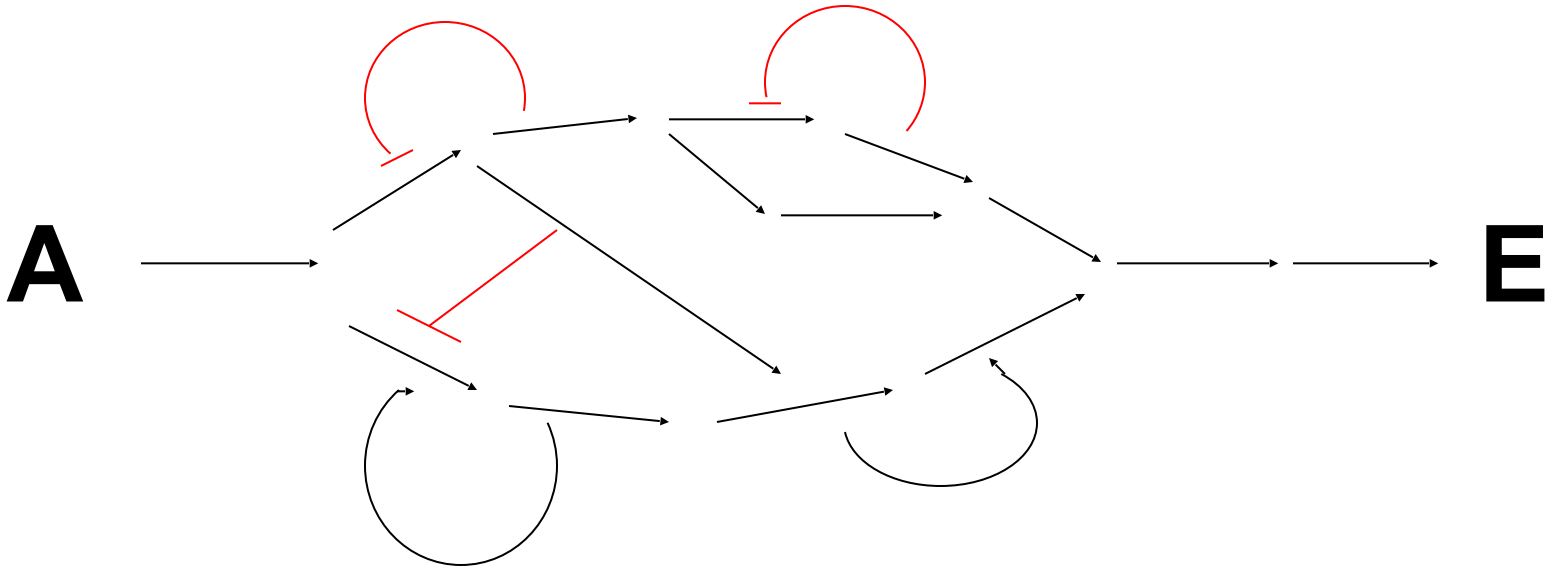
In conclusion, A CELL IS NOTHING LIKE A TEST TUBE!

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.

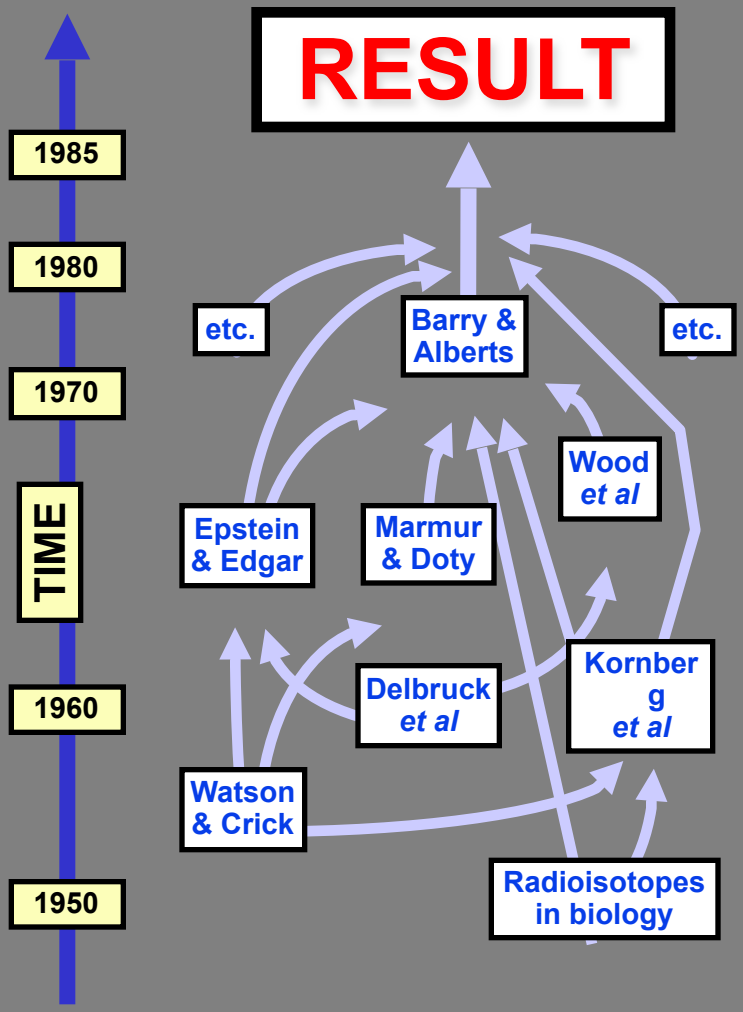
www.nasonline.org/publications/beyond-discovery

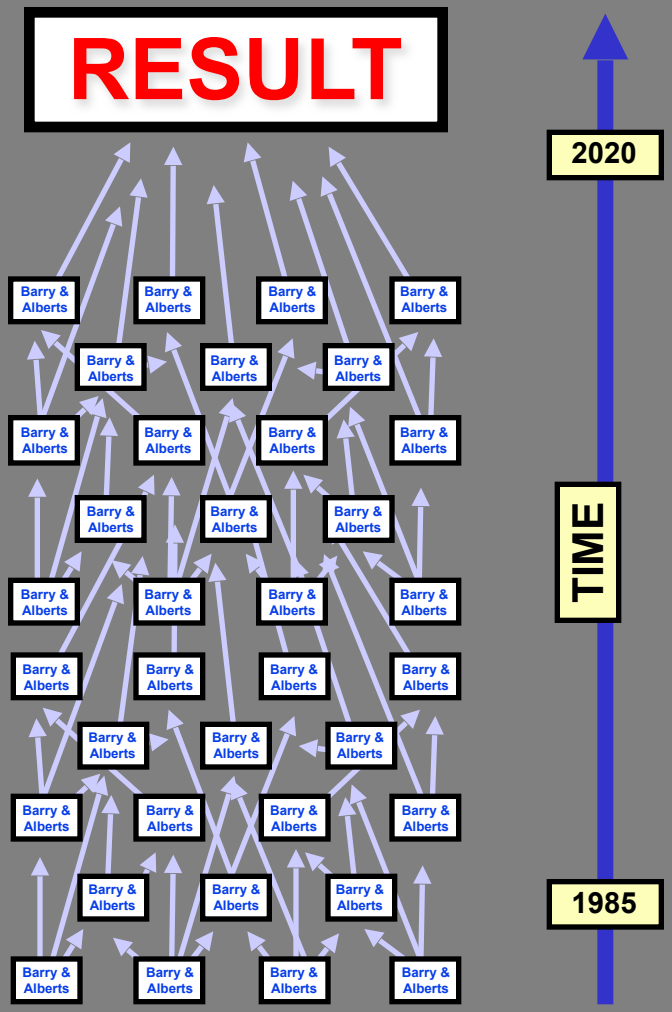
Timeline for Global Positioning System (GPS)

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.

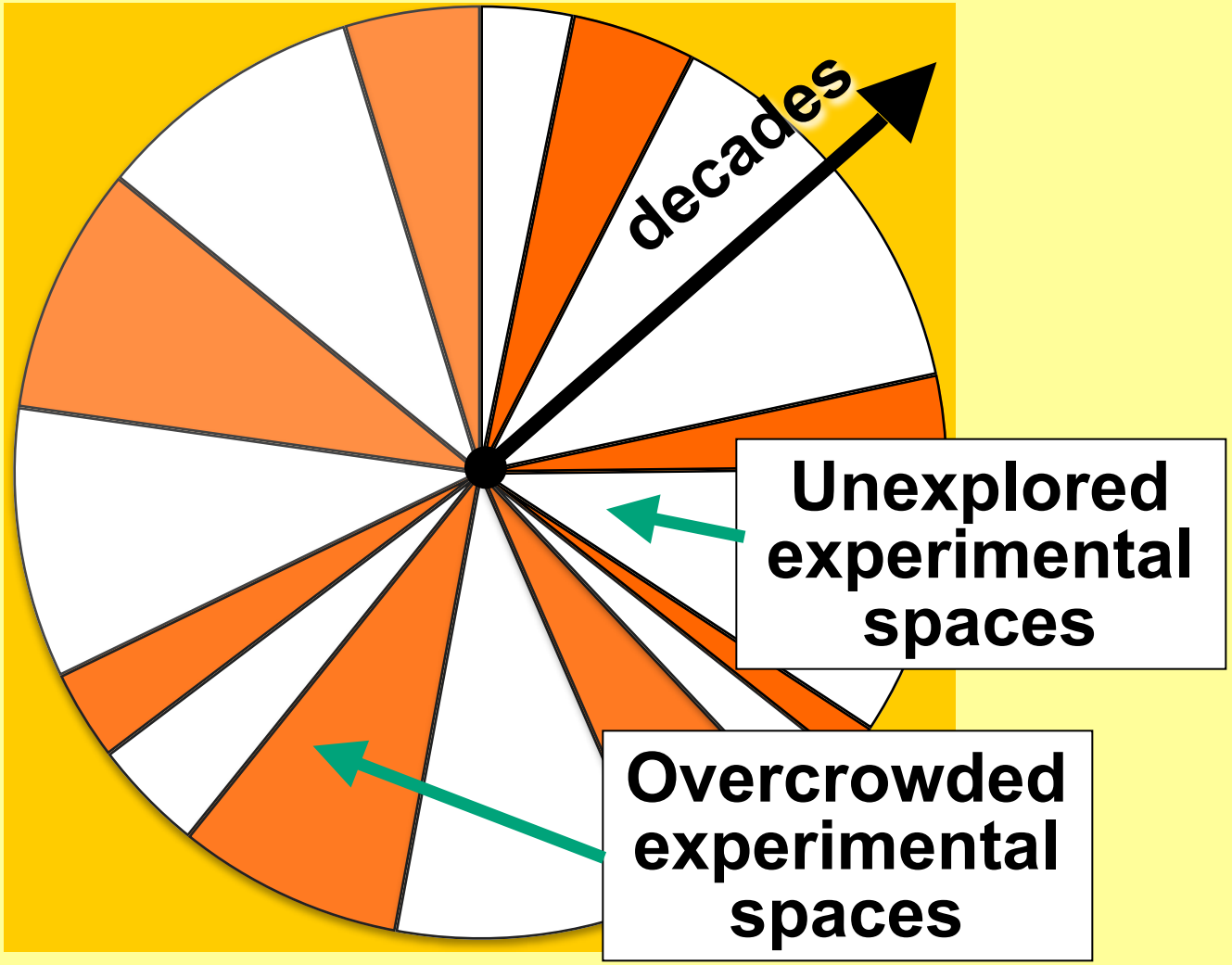
Henri Poincaré

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

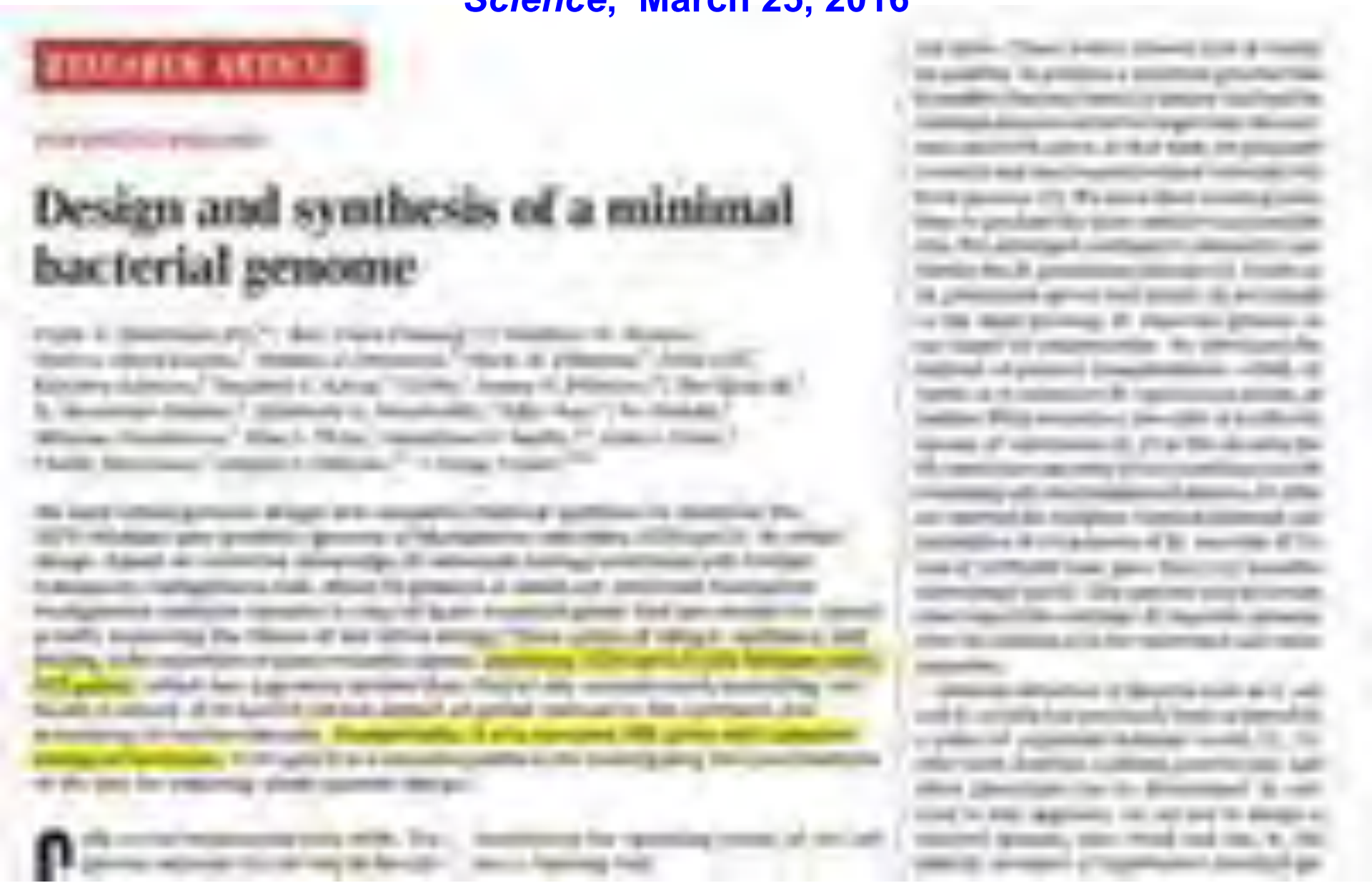
H. Zoghbi, *Science* **339:** 250 (2013)

The Basics of Translation

ONE EXAMPLE

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

***Science*, March 25, 2016**



RESEARCH ARTICLE

Design and synthesis of a minimal bacterial genome

ANOTHER EXAMPLE: the importance of *Drosophila*

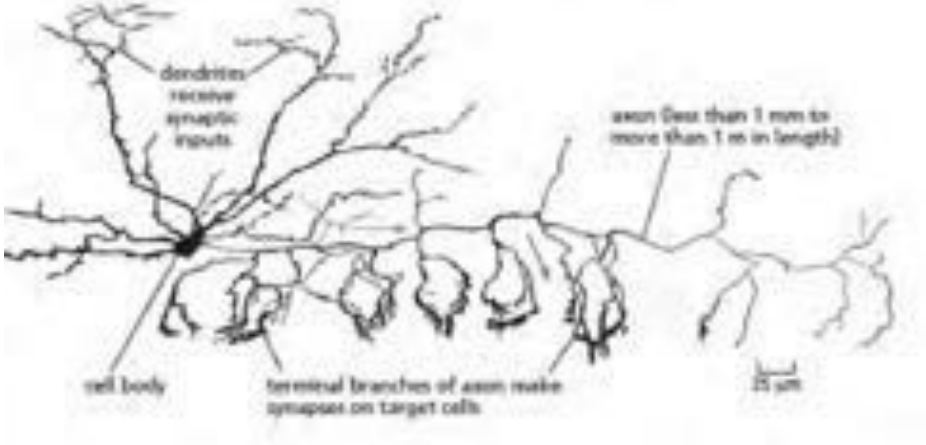
1. **We are still far from understanding how cells work together to form and maintain tissues.**

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

Current Biology 21, 1–11, January 11, 2011 ©2011 Elsevier Ltd All rights reserved DOI 10.1016/j.cub.2010.11.056

Article

Three-Dimensional Reconstruction of Brain-wide Wiring Networks in *Drosophila* at Single-Cell Resolution

Ann-Shyn Chiang et al., Taiwan

Results: To assemble this map, we deconstructed the adult *Drosophila* brain into approximately 16,000 single neurons and reconstructed them into a common standardized framework to produce a virtual fly brain. We have constructed a mesoscopic map and found that it consists of 41 local processing units (LPUs), six hubs, and 58 tracts covering the whole *Drosophila* brain. Despite individual local variation, the architecture of the *Drosophila* brain shows invariance for both the aggregation of local neurons (LNs) within specific LPUs and for the connectivity of projection neurons (PNs) between the same set of LPUs. An open-access image database, named FlyCircuit, has been constructed for online data archiving, mining, analysis, and three-dimensional visualization of all single neurons, brain-wide LPUs, their wiring diagrams, and neural tracts.

7 of 100,000 neurons

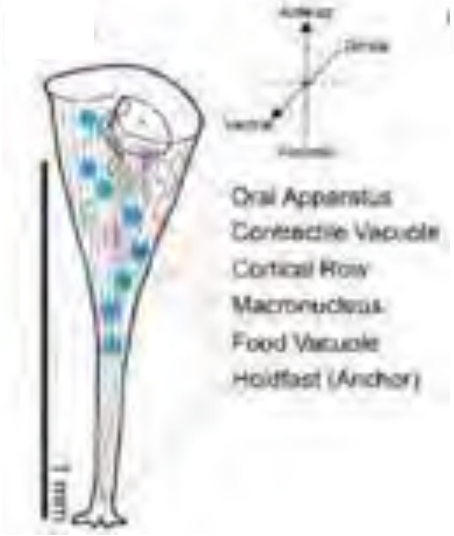
Recently published in the journal *Genetics*

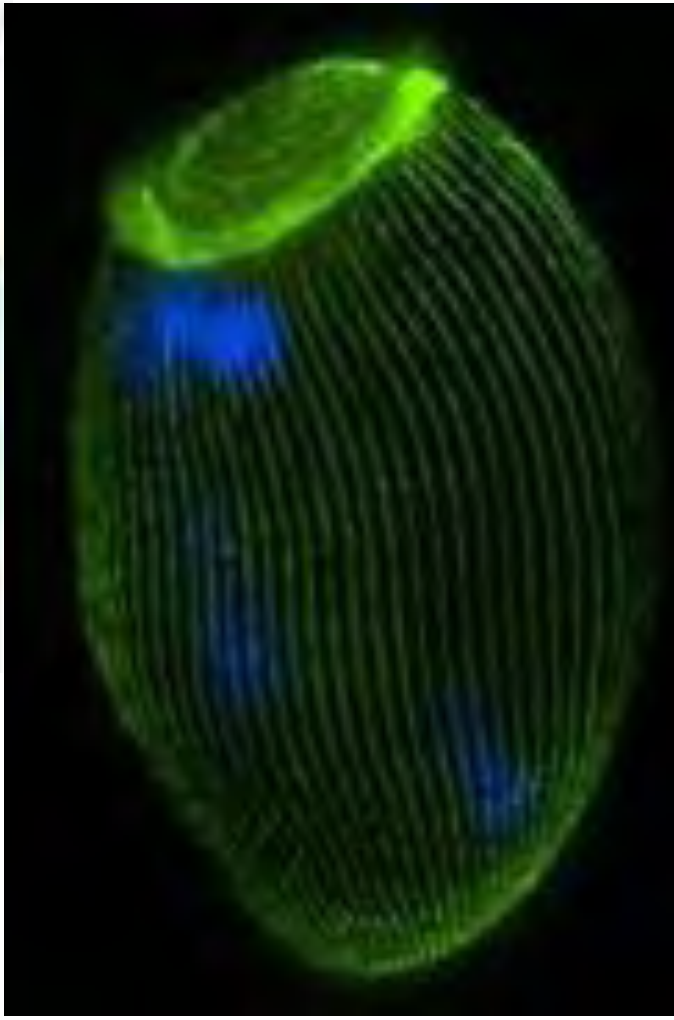
The mutant phenotypes for thousands of fly genes with human homologues can be at least partially rescued by a cDNA clone of the human gene

But there has been a <u>30 percent drop</u> in US NIH support for *Drosophila* research in the past 5 years, compared to a 15 percent drop overall.

To understand cells, we also need new models!

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

Rescuing US biomedical research from its systemic flaws

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:

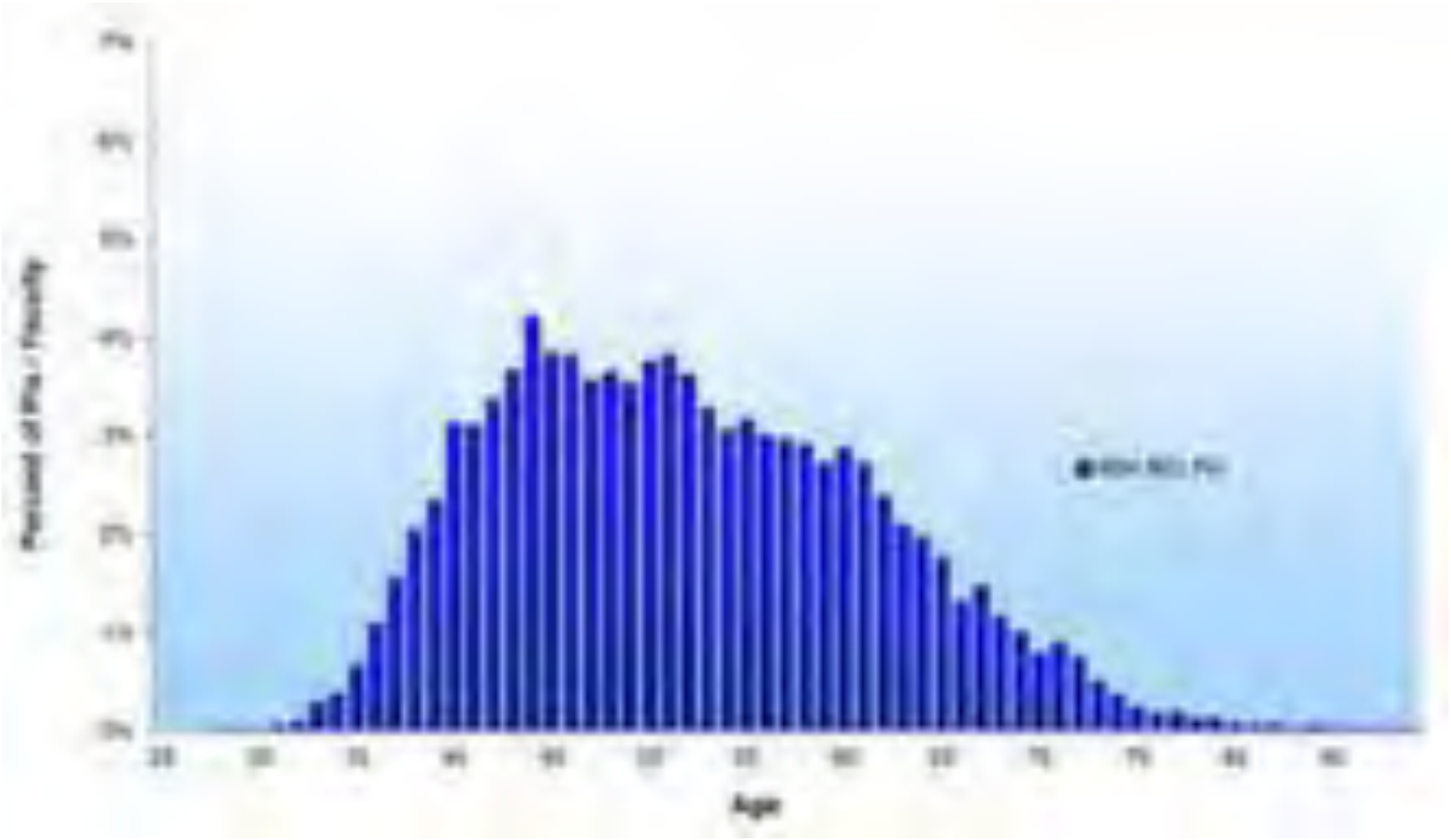
There have been very disturbing changes in the age distribution of independent researchers in the past 30 years

"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

The current distribution of U.S. Principal Investigator (PI) ages



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 up to 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:

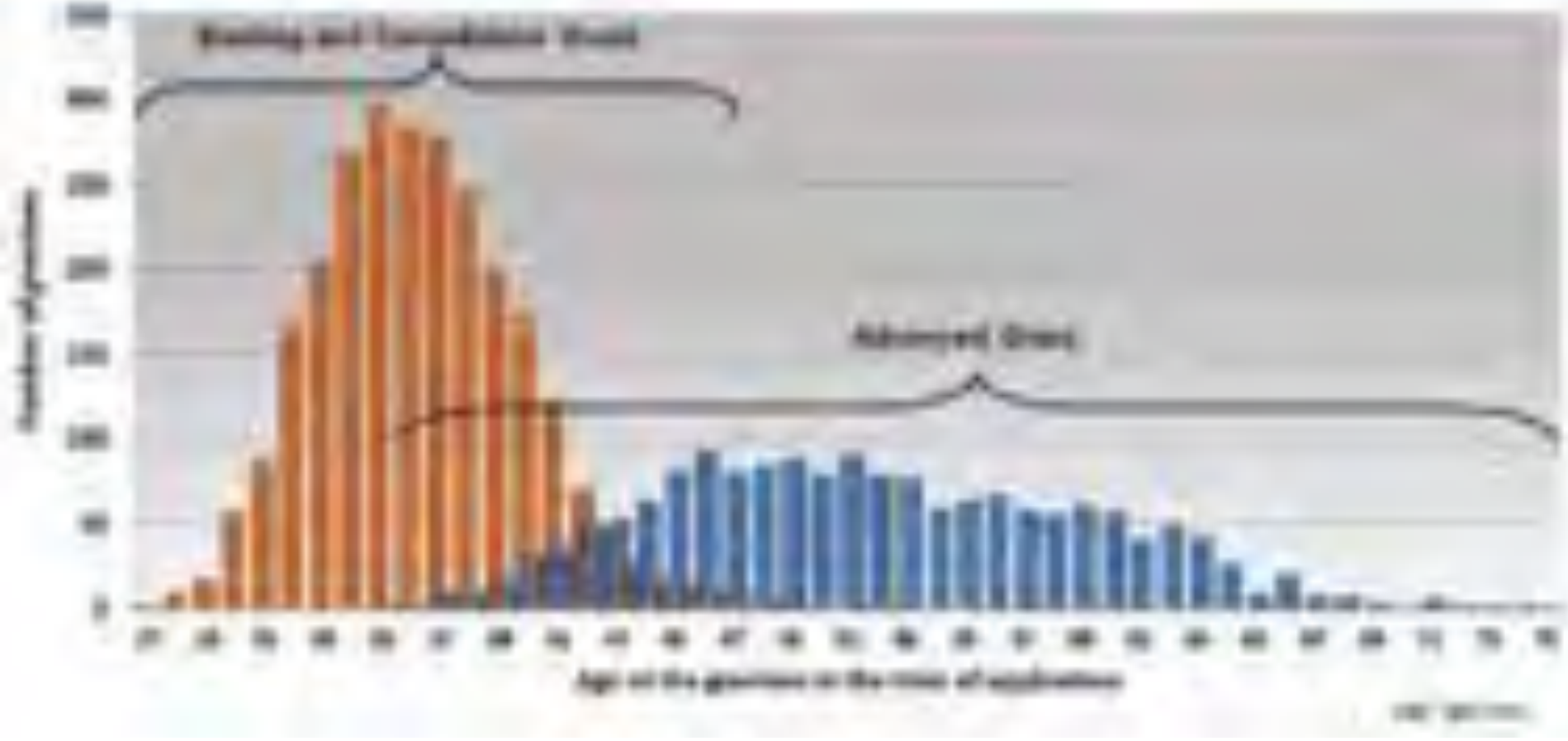
- Starting (2 to 7 years post PhD)
- Consolidator (7 to 12 years post PhD)
- Advanced (no limits)

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

For the current 5 year period:

- Starting Grants 2.0 billion Euro
- Consolidator Grants 2.7 billion Euro
- Advanced Grants 3.5 billion Euro

ERC Grantees Age Distribution



A broad expertise on each ERC review group avoids the silos typical of many US reviews:

For Life Sciences, the reviewing is carried out panels composed of outstanding scientists grouped into the following 9 broad scientific areas:

- Molecular & Structural Biology & Biochemistry
- Genetics, Genomics, Bioinformatics & Systems Biology
- Cellular and Developmental Biology
- Physiology, Pathophysiology & Endocrinology
- Neurosciences & Neural Disorders
- Immunity & infection
- Diagnostic Tools, Therapies & Public Health
- Evolutionary, Population & Environmental Biology
- Applied Life Sciences & Biotechnology

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?

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

http://rescuingbiomedicalresearch.org

AN EVEN BIGGER ISSUE: The image we want for science

Creating a scientific temper:
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

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