WHAT MUST BE REJECTED AND WHAT MUST BE EMBRACED FOR CREATIVITY IN SCIENCE TO THRIVE?

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SUB-TITLE OF THIS TALK

LEARNING ABOUT BIOMEDICAL CREATIVITY FROM THE IMPORTANT DISCOVERIES OF THE PAST

TRUE CONFESSION

- I have read virtually no texts, watched no videos, attended no conferences, consulted no authorities on the subject of CREATIVITY
- This presentation is based on my own experiences as a researcher, my observations and my reading in the history of medicine and public health.
- I will lean heavily on the history of creative scientists in biomedicine and try to elucidate what made them creative

CREATIVITY IN BIOMEDICAL SCIENCE

- Creativity in the arts is different from creativity in science.
- And within science, creativity is not the same in basic science as it is in science that refers to itself as biomedical
- Once the term "medical" is allied to science, the resulting amalgam requires more than discovery for its own sake.
- Biomedical creativity requires impact on human lives, even if that impact is far in the future.

CONSTRAINT IN SCIENTIFIC CREATIVITY

- Every form of creativity is inevitably constrained by limits of time, energy and resources.
- But scientific creativity is additionally constrained by the circumstances required for observation or experiment, epidemiology especially so.
- The challenge of constraint is two-fold
  - First - is it a real constraint? Perhaps the constraint is in my thinking?
  - Second – can my creativity overcome real constraints?

CREATIVITY AND IMPACT

- Thus creative biomedical research is recognized by its impact on health.
- And the examples of creativity I will give today are not so much marked by brilliance, depth of scholarship, or even necessarily by imagination.
- They are marked by having created a measurable difference in health and survival.

SEVEN IDEAS/FORCES TO REJECT

1. That creativity starts with a tabula rasa or blank slate.
2. That there is a left brain (scientific rigor) and a right brain (scientific imagination)
3. Commercial interests/profit motive
4. The internalized voice of authority/convention/popularity
5. Overvaluation of your own field and your own expertise
6. Fads and fashions
7. Perfectionism

SEVEN CONCEPTS TO EMBRACE

1. The importance of asking the right question
2. A rigorous and critical understanding of what has been done before and using this information to formulate the question that now needs to be asked.
3. Capacity to borrow ideas from other fields of thought.
4. Welcoming apparent contradictions and surprising findings
5. Persistence
6. Patience
7. Courage

ELABORATING ON THE SEVEN FORCES TO REJECT

CREATIVITY: GENESIS OR SYNTHESIS?

- The first idea to reject is that scientific creativity comes from a blank slate and that the creative mind must be cleared of extraneous influences to identify the new and innovative.
- Yet the key element of scientific creativity is to discover just how our new ideas differ from what went before.
- This means that we have to know, and to know well, what has been done already
- In science, creativity is not so much creating something from nothing – *genesis*, but rather creating something new from the raw materials available to you - *synthesis*

STARTING FROM VOID OR FROM CHAOS?

- From a 19th century thinker:

"Invention, it must be humbly admitted, does not consist in creating out of void, but out of chaos; the materials must, in the first place, be afforded: it can give form to dark, shapeless substances, but cannot bring into being the substance itself."

Any idea who wrote this?

MARY SHELLEY

Frankenstein; or, The Modern Prometheus. (1818)

RIGHT BRAIN/LEFT BRAIN NONSENSE

- You have one brain! Do you use if for imagination or scientific rigor? You use if for both!

"Put off your imagination, as you put off your overcoat, when you enter the laboratory; but put it on again, as you do the overcoat, when you leave the laboratory. Before the experiment and between whiles let your imagination wrap you round; put it right away from yourself during the experiment itself, lest it hinder your observing power"

Claude Bernard, An Introduction to the Study of Experimental Medicine (1865)

- Imagination and scientific rigor need to be combined – each to be used when appropriate

THE PROFIT MOTIVE

- The aims of scientific research are not the aims of corporate business.
- Business interests can play a role in distributing and disseminating scientific discoveries, but historically biomedical science has ignored the profit motive until fairly recently.
- And it may be possible to leverage the business community for financial support for ideas
- Of the great many really important discoveries in biomedicine, it is hard to think of any that were stimulated by the profit motive.

SCIENTIFIC DISCOVERIES WITHOUT PROFIT

- The current trend to patent scientific technologies slows down scientific creativity and innovation

- No licensing fee has ever been paid for

  - The Petri dish. Developed in 1895 but with 88 mentions in pub med in 2021.

  - The Gram Stain. Developed in 1884 but with 769 pub med mentions in 2021.

- How would medical microbiology have fared had Gram and Petri charged royalties for use of their inventions?

AUTHORITY AND CONVENTION

"Knowledge is made by oblivion, and to purchase a clear and warrantable body of truth, we must forget and part with much we know."

Sir Thomas Browne, "Pseudodoxia Epidemica." 6th edition, 1672

I emphasize "we know" because it is our internalized conventions, the ideas we take for granted, that are most important to overcome

HOW DO WE DEAL WITH INTERNALIZED ASSUMPTIONS?

They become more and more evident as you challenge your thinking

- By discussions with others, especially others outside your field
- By reading extensively in the older literature to see what had been thought before
- By querying whether the constraints you encounter are real
- By honest self-assessment

OVERVALUING WHAT YOU HAVE BEEN TRAINED TO DO

- I often see scientists skeptical of research from arenas with which they are not familiar, and with a marked preference for research of the kind they are used to.
- Disciplinary prejudice is a great constraint on creativity, preventing scientists from reaching out to fields they are not familiar with that might help them achieve their goals.

FASHIONS AND FADS IN SCIENCE

- Science is full of fashions. Topics to study and approaches to research move in and out of favor.
- Popularity is often obtained through labelling that would make ad agencies proud
- Keep in mind that it is hard to be innovative by following the crowd

THE PERFECT IS THE ENEMY OF THE GOOD

John Snow once wrote, on a paper on the possible nutritional origins of rickets:

"The subject is capable of being decided by an exact numerical investigation, but I have thought it better to publish my inquiry in its present imperfect state, than to wait till I should be able to make such a complete research as I could wish, more especially as, by directing the attention of the profession to the question, it may be earlier decided."

ELABORATING ON THE SEVEN CONCEPTS TO EMBRACE

ASKING THE RIGHT QUESTION

- Nobelist Isidore Rabi was asked what made him such a good scientist.
- He answered that the mothers of most children he knew asked them after school if they had said something intelligent that the teacher had recognized.
- But his mother only wanted to know if he had asked the teacher a good question.

JOHN SNOW ASKED THE RIGHT QUESTION

- 19th century researchers of cholera etiology tended to focus on weather conditions, bad-smelling locations or eating habits, or else tried to identify the agent of cholera.
- But Snow bypassed those questions and asked as question no one else was asking:
- “What is the mode of communication of cholera?”
- All three of Snow’s books on cholera had “mode of communication” in the title.
- no other 19th century book in English on cholera in the Wellcome Historical Library Catalog has Mode of Communication in the title.

THE IMPORTANCE OF MODE OF COMMUNICATION

By asking about the mode of communication, Snow learned

- That the agent of cholera needed a period of incubation because exposure and onset of disease were separated by 24-48 hours
- That it must therefore be alive and capable of reproduction (he asserted that it was probably "something like a cell")
- That it entered the body by the mouth and left the body in feces, thus discovering the fecal-oral mode of communication
- That preventive measures must focus on having a clean water supply

IMMERSION IN THE LITERATURE

- The right question to ask emerges from knowing what has already been asked and answered, so that you know what question now most needs to be asked.
- Familiarity with the relevant literature can lead to the critical finding that allows you to move ahead.
- Walter Reed in 1900 allowed an infected *Aedes Aegypti* mosquito to bite a volunteer, producing yellow fever and showing how yellow fever is transmitted.
- Carlos Finlay, who first hypothesized that *Aedes Aegypti* was the vector of yellow fever, had been unable to do this. What did Reed know that Finlay did not?

THE CRITICAL PAPER

- In 1900, Dr. Henry Carter wrote a paper entitled:

  "A note on the interval between infecting and secondary cases of yellow fever from the records of the Yellow Fever at Orwood and Taylor, Mississippi, in 1898."

- Carter found that two to three weeks passed after an infected individual came to a small village before the second case occurred.
- Reed concluded that the agent of Yellow Fever had to develop over time inside the mosquito before the mosquito bite was infective.
- What did Reed do upon reading this paper?

REED'S CRUCIAL EXPERIMENT

- Reed abandoned his search for the organism of Yellow Fever and began to do human experiments attempting to create experimental yellow fever.
- Recognizing Carter's discovery, he avoided Finlay's error and kept the infected (because they had bitten a yellow fever patient) mosquitos alive for two weeks before having them bite the volunteer.
- Doing this enabled him to create experimental yellow fever and to prove that Aedes Aegypti was the vector.
- This critical discovery led to mosquito control measures in Havana that eradicated yellow fever.

A ROUTINE CASE SERIES

In 1970, a group of Boston gynecologists published a fairly standard case series describing vaginal cancer.

"*Data from 68 cases of primary carcinoma of the vagina are analyzed in detail. The tumors tend to occur beyond the fifth decade of life.*"

Herbst AL, Green TH, Ulfelder H:Primary carcinoma of the vagina. An analysis of 68 cases. Am J Obstet Gynec 1970; 106;210-218 (Jan 28)

BUT THREE MONTHS LATER HERBST PUBLISHED ANOTHER PAPER ON THE SAME CANCER

"Seven cases of adenocarcinoma of the vagina occurring in young women 15 to 22 years of age are reported."

Herbst AL, Scully RE: Adenocarcinoma of the vagina in adolescence. A report of 7 cases including 6 clear-cell carcinomas. Cancer 1970; 25:745-57 (April)

HERBST WONDERED WHAT TO DO NEXT

- As legend has it, he was discussing the problem of these surprising cases in young women in an elevator at the Massachusetts General Hospital.
- Overhearing the conversation, a neurologist, David Poskanzer, who had an MPH in epidemiology, said, “you need to do a case-control study”.

THIS WAS THE FINDING OF THE CASE-CONTROL STUDY

Pregnancy use of DES	Clear Cell Vaginal Adenocarcinoma	Matched control
YES	7	0
NO	1	32
	8	32

SOURCE: Herbst A, Ulfelder H, Poskanzer D: NEJM 1971; 285; 16 (April), 878

FDA ruled that DES is contraindicated in pregnancy in November, 1971

PERSISTENCE

- ...is not usually thought to be part of the creative process, but it is essential!
- Attributed to Thomas Alva Edison:

  "Genius is 1% inspiration

  and 99% perspiration"

- Repeatedly we see examples of major creative innovations in biomedical science that required great effort.

PERSISTENCE

- Ronald Ross suspected that the mosquito was the vector of malaria.
- But he had very little time available for research. He was a military doctor in India and his superiors disliked his interest in research
- He was transferred to a remote hill station where malaria was rare so as to reduce his capacity for research
- He almost had his microscope confiscated by the military authorities to prevent him from doing research.

PERSISTENCE

- Nevertheless he spent his free time examining mosquitos under the microscope, two hours per mosquito, looking for the plasmodium (identified by Laveran in 1880). He examined about a thousand mosquitos before he found his first plasmodium in a mosquito stomach.
- "*The work ... was ... so blinding that I could scarcely see afterwards, and the difficulty was increased by the fact that my microscope was almost worn out, the screws being rusted with sweat from my hands and forehead, and my only remaining eye-piece being cracked...*"
- This work won him the Nobel Prize in 1902

DREW WEISSMAN (co-developer of the mRNA technology used to create the COVID vaccine)

“The person who achieves his goal is the one that has faced frustration and dealt with it, understood it, and used it to their advantage. We repeatedly fell, were knocked down, ignored. And we kept getting up, and we didn’t give up.”

Speech accepting honorary degree, Drexel University, May, 2021

PATIENCE

- Robert Koch had never come across a germ that would not appear visible to the naked eye within 2-3 days after plating on media
- But nothing could be seen when he tried to culture the organism he had identified in the tissues of people with tuberculosis.
- The slow growing mycobacterium takes 2-3 weeks to show in culture. Koch's first successful tube showed no growth until the 20th day.

PATIENCE AS A FORM OF GENIUS?

“But Koch waited; though to anyone’s knowledge, there was nothing in past experience to suggest that the passing of time held the key....And in waiting, he won out. It was patience, and patience alone that saved the day for Koch.... Patience may indeed be exalted to genius”

Source: Allen K. Krause, introduction to a 1932 translation into English of Koch’s The Aetiology of Tuberculosis Berliner Klinische Wochenschrift 1882;15 (April 10).

COURAGE

- Needed to swim against the tide of convention
- Needed when all results seem to point in the wrong direction
- Needed when a great leap into the unknown is required

THE FIRST CARDIOVERSION

"The procedure was carefully developed by Bernard Lown and his associates who experimented first on animals and then on postoperative patients using a direct-current technique designed to avoid the vulnerable period. Their results, published in 1962, were soon accepted, and the procedure became a major therapeutic advance in the treatment of heart disease."

Silverman ME: Am J Cardiol 2004 Sep 15;94(6):751-2

The classic paper: Lown B, Amarasingham R, Newman J: New Method for Terminating Cardiac Arrhythmias. Use of Synchronized Capacitor Discharge. JAMA 1962; 182:548-555

COURAGE

- Remark made by Bernard Lown during rounds in the cardiology service of the Peter Bent Brigham Hospital, Boston, in 1971 after being queried about his experience developing cardioversion.
- "*You think we weren't scared when we first used the paddles? We were terrified!*"
- But nonetheless, Lown forged ahead

Bernard Lown MD, 1921-2021, RIP

MY RECOMMENDATIONS FOR CREATIVE BIOMEDICAL RESEARCH

IN FIVE PHASES

PHASE ZERO – SELF ASSESSMENT

1. What is your passion? What excites you about research?
2. How do you think? Are you visual (like Allen) or non-visual (like me)?
3. Do you require solitude for ideas to come to you (like Allen) or find yourself spinning ideas from being around colleagues (like me)?
4. What underlying assumptions do you have that get in the way of creativity?

PHASE ONE – BROWSING

1. Once you have found a topic that intrigues you, read all the literature you can find on the topic, looking for the papers that stimulate your thinking. Your response to what you read is your creativity at work.

2. Do not restrict yourself to recent papers! Chase references! Go back as close to the beginning as you can.

3. Search in fields different from yours that may have had to deal with similar problems

4. Look carefully for that nugget-of-gold paper – it may have been overlooked by others!

PHASE TWO – CONSOLIDATING IDEAS

1. As your ideas begin to form, test them out on colleagues, especially colleagues from other fields
2. Never listen to criticism that is unconstructive, such as “that’ll never work”. If you’ve really done your homework in the library, you know you are past that stage.
3. All new ideas should be treated as infants. They don’t know how to walk yet, let alone run! Sadly many good ideas are strangled in the cradle by critics.
4. Listen to nourishing, trustworthy criticism that acknowledges the value of your effort and can suggest amendments and improvements.

PHASE THREE – GIRDING FOR THE STRUGGLE

1. Recognize that you must invest a great deal of yourself to make a contribution to biomedical science.
2. You will have to seek funding to pursue your ideas.
3. Getting funded is a long, hard process, full of discouragement and rejection.
4. All successful scientists can paper their walls with the rejection letters they have received from review panels and journals.

PHASE FOUR – GETTING HELP

1. As the project matures, recognize your limitations
2. You may need to acquire a new skill or new knowledge
3. You may need to bring in a collaborator
4. You may need a trusted mentor or advisor, especially in the tough moments
5. Be open to change of course - You may need to adapt as you learn more about your subject matter

ABOVE ALL
ENJOY YOURSELF!

NOW – LET'S DISCUSS

EXTRAS

AND SOMETHING ELSE LOWN SAID

“As a historic footnote—it needs be noted that research funds for the early stages of this endeavor were refused by the National Institute of Health and publication of the first manuscript was rejected, the reviewer opined that the technology had ‘little clinical relevance.”

Lown B: Defibrillation and cardioversion. *Cardiovascular Research*, 2002; 55:220–224

Bernard Lown (1921 – 2021)

A recent paper in Nature explores, using machine learning methods, especially creative periods (which the authors call "hot streaks") in art, cinema and science.

Liu L, Dehmamy N, Chown J et al: Understanding the onset of hot streaks across artistic, cultural, and scientific careers. Nature Communications 12, 5392, 9/13/2021

WHICH IS MORE IMPORTANT
EXPLORATION OR EXPLOITATION?

EXPLORATION engages individuals in experimentation and search beyond their existing or prior areas of competency. It is more risky but it may increase the likelihood of stumbling upon a groundbreaking idea through unanticipated combinations of disparate sources.

EXPLOITATION allows individuals to build knowledge in a particular area and to refine their capabilities in that area over time. A conservative strategy, it may stifle originality and limit an individual’s ability to consistently produce high-impact work.

THEIR CONCLUSION

- The shift from exploration to exploitation is characteristic of the onset of a creative period. Exploration, as a risky, variance-enhancing strategy, increases one's chances of stumbling upon new, potentially groundbreaking ideas
- The subsequent exploitation behavior allows the individual to focus, develop knowledge and capabilities in that focal area, and build out discoveries further.
- Not all explorations are fruitful, and exploitation in the absence of promising new ideas may not be productive.
- Both exploration and exploitation are necessary.

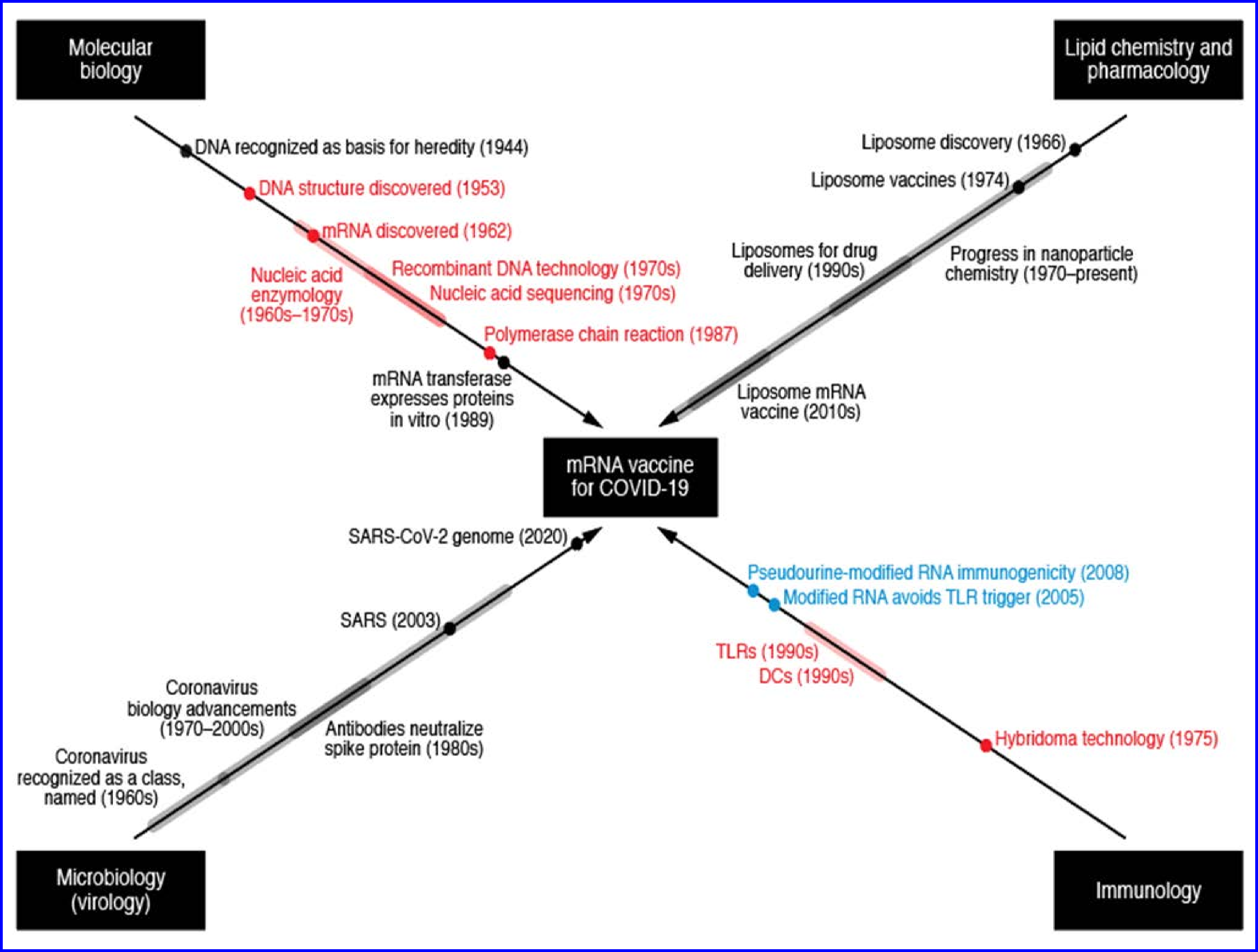
CREATIVE SYNTHESIS:
THE SEVERAL STRANDS OF SCIENCE THAT LED TO THE mRNA VACCINE

Courtesy of Arturo Casadevall

The mRNA vaccine revolution is the dividend from decades of basic science research.

Journal of Clinical Investigation

2021; Sep 24:e153721


Molecular biology
Lipid chemistry and pharmacology
DNA recognized as basis for heredity (1944)
DNA structure discovered (1953)
mRNA discovered (1962)
Nucleic acid enzymology (1960s–1970s)
Recombinant DNA technology (1970s)
Nucleic acid sequencing (1970s)
Polymerase chain reaction (1987)
mRNA transferase expresses proteins in vitro (1989)
Liposome discovery (1966)
Liposome vaccines (1974)
Liposomes for drug delivery (1990s)
Progress in nanoparticle chemistry (1970–present)
Liposome mRNA vaccine (2010s)
mRNA vaccine for COVID-19
SARS-CoV-2 genome (2020)
SARS (2003)
Coronavirus biology advancements (1970–2000s)
Antibodies neutralize spike protein (1980s)
Coronavirus recognized as a class, named (1960s)
Pseudourine-modified RNA immunogenicity (2008)
Modified RNA avoids TLR trigger (2005)
TLRs (1990s)
DCs (1990s)
Hybridoma technology (1975)
Microbiology (virology)
Immunology