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Творчість та оригінальність є ключовими елементами в медичних дослідженнях: Нобелівська премія Каталін Каріко та Дрю Вайсмана з фізіології та медицини 2023 року – нещодавній приклад

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Протягом принаймні століття предметом частої дискусії було, що є першочергово важливим для досягнень у біомедичних дослідженнях: оригінальність/творчість чи складні методи/обладнання. Ми пропонуємо короткий історичний огляд, в якому аргументуємо важливість творчості, оригінальності та наполегливості. Зокрема, найкращим реальним прикладом цього є нагорода Нобелівської премії з фізіології та медицини 2023 року, присуджена докторам Каталін Каріко та Дрю Вайсману за винахід та розробку вакцини на основі мРНК проти COVID-19. Каталін Каріко мала наукову мету використовувати мРНК для лікування раку, але коли була оголошена структура SARS-CoV-2, вона змінила свої інтереси на розробку вакцини на основі мРНК проти нового вірусу. Однак, оскільки молекула мРНК відома своєю нестабільністю та схильністю до легкого руйнування за умов внутрішньоклітинного введення, вона об'єдналася з доктором Вайсманом, який працював над методами доставки молекул мРНК в клітину. Ця творча співпраця з оригінальними ідеями розробки вакцини ілюструє те, що інші творчі вчені, такі як Олександр Флемінг, Ганс Сельє, Леон Попєльскі та Джеймс Блек відкрили у своїх наукових галузях. Сумною частиною цієї історії є те, що лише двоє з цих вчених отримали в нагороду Нобелівську премію.

Ключові слова: дослідження, наука, Нобелівська премія з фізіології та медицини, COVID-19, вакцина, Каталін Каріко, Дрю Вайсман, Август Кекуле, Леон Попєльскі, Джеймс Блек, Олександр Флемінг, Ганс Сельє.

Creativity and originality are key elements in medical research: Recent illustration by the 2023 Nobel Prize in Physiology or Medicine to Katalin Kariko and Drew Weissman

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For at least a century, an often-debated topic is what is of primary importance to make breakthrough in biomedical research: originality/creativity or sophisticated methods/equipment. We present here a short historical overview arguing about the importance of creativity, originality, and persistence. Namely, the best living example of this is the 2023 Nobel Prize in Physiology or Medicine awarded to Drs. Katalin Kariko and Drew Weissman for the invention and development of mRNA-based vaccine against COVID-19. Katalin Kariko had a life-long obsession to use mRNA for cancer therapy, but when the structure of SARS-CoV-2 was announced, she shifted her interest to develop an mRNA-based vaccine against the new virus. But since the mRNA molecule is notoriously unstable and easily degraded if injected intracellularly, she teamed up with Dr. Weissman who was working on techniques to deliver mRNA molecules intracellularly. This creative teamwork with original ideas of vaccine development illustrates what other creative scientists, like Alexander Flemming, Hans Selye, Leon Popielski and James Black discovered in their fields. The sad part of the story is that only two of these scientists got the Nobel Prize.

Keywords: Research, science, Nobel Prize in Physiology and Medicine, COVID-19, vaccine, Katalin Kariko, Drew Weissman, August Kekulé, Leon Popielski, James Black, Alexander Fleming, Hans Selye

*This article was inspired by recent 2023 the Nobel prize in Physiology or Medicine to Katalin Kariko and Drew Weissman

Introduction

A long-standing and often sharp discussion in biomedical sciences usually concentrates on emphasizing the importance of methods and sophisticated, often very expensive instruments, vs. creativity and originality... We again emphasize here that our analysis is focused only on medical research, since in other fields of science, like physics and astronomy, the importance of instruments is a top priority. Namely, the stunning discoveries and images about our universe unraveled by the new James Webb Space Telescope could not have been achieved without huge financial investments and technical achievements.Another two components, almost prerequisites, leading to big discoveries are chance and persistence...

The history of science is full of these illustrations, for better or worse, one of the earliest being the story of «the nineteenth-century chemist August Kekulé claimed to have pictured the ring structure of benzene after dreaming of a snake eating its own tail» (Fig.1) [1].

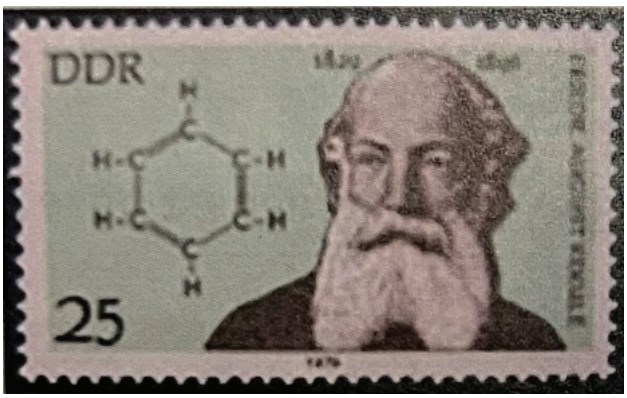

Figure 1. Chemist August Kekulé visualized the ring structure of benzene in 1865

In 1901, Leon Popielski's research unveiled the existence of a «peripheral reflex center» that regulated gastric secretion by peripheral humoral processes. Fast forward to the 1960s and early 1970s, Sir James W. Black significantly expanded upon Popielski's model regarding histamine's impact on gastric secretion. His groundbreaking work led to the development of a new category of antisecretory drugs known as H2 receptor antagonists. Among these drugs cimetidine became this orally active H2 receptor blocker used for the treatment of gastroduodenal ulcers. Hence, Black received the Nobel Prize in Physiology and Medicine in 1988. Namely, his studies solidified the crucial role of histamine in stimulating gastric acid secretion, but Popielski's original research stands as a testament to the transfer of fundamental studies into clinical applications [2].

Alexander Fleming's discovery of penicillin is also a good example, i.e., «in 1928, he noticed that a fungus, *Penicillium notatum*, had contaminated a culture plate of *Staphylococcus aureus* bacteria he had accidentally left uncovered. The fungus had created bacteria-free zones wherever it grew on the plate» [3]. The other stunning related fact is, as Hans Selye described, that 16 other microbiologists missed the importance of this chance observation [4]... Persistence, i.e., not giving up after a chance observation plays a role here also in the penicillin story: Fleming «found that *P. notatum* proved extremely effective even at very low concentrations, preventing *Staphylococcus aureus* growth even when diluted 800 times, and was less toxic than the disinfectants used at the time». All this resulted in «mass production process, and Howard Florey and Ernst Chain shared the 1945 Nobel Prize in Medicine with Alexander Fleming for their role in creating the first mass-produced antibiotic» [3].

The story of mRNA COVID-19 vaccine development, based on persistence, obsession-like focus, by Dr. Katalin Kariko is a perfect example of continuation of this historic trend. Namely, as she described in many interviews during the last few years, and as summarized in recent short review in Science [5], she was obsessed by creating an mRNA-related anti-cancer vaccine. She started her research carrier at the University of Szeged in Hungary, continued at the University of Pennsylvania (U. Penn) in Philadelphia, USA. Very soon she realized, as we all who worked on RNA extraction realized, mRNA molecules are very unstable, since they are destroyed by enzymes in living cells, or even extracellularly. It was by chance that at a copy machine in the corridors of U. Penn. she met another scientist Dr. Drew Weissman, who was working on delivering sensitive molecules into cells. After that they worked together, and navigating through multiple technological and personal challenges, they managed to achieve a safe and effective delivery of mRNA molecules in living cells (Fig.2).

Figure 2. Drs. Katalin Kariko (on left) and Drew Weissman (on right; adapted from Science, Oct 6, 2023 [5])

As much as 'focus, focus' on your original goals and projects is important, as we all learned in our early research carrier, Drs. Kariko & Weissman realized that when the first structure of SARS-Co-2 was announced and the need for rapid vaccine development became obvious, they shifted their interest from cancer vaccines to develop an mRNA-based vaccine for the prevention of COVID-19. This was a critical decision, since the COVID-19 pandemic started with panic and chaos as there was no effective drug for prevention and treatment [5]. And with the technological help from two major companies (Bio N 'Tech, Moderna and Pfizer), indeed they managed to develop and mass-produce this vaccine. This was the fastest developed vaccine in the history of medicine, since the other 'rapidly developed vaccine (that took 'only' about 3 years.

In summary, the 2023 Nobel Prize in Physiology or Medicine illustrates and reconfirms the primary importance of originality, creativity, and focused persistence in biomedical research. As Hans Selye summarized in the motto at the entrance of his institute [7]:
«Neither the prestige of your subjects and
The power of your instruments
Nor the extent of your planning
Can substitute for
The originality of your approach and
The keenness of your observation»

Thus, let's learn from these great scientists, irrespective if they got the highest prize in research or not (e.g., Selye and Popielski never got). Another interesting and related closing remark is that Katalin Kariko often mentioned in interviews and in her recently reviewed book "Breaking through: My life in sciences" (8) that she was attracted to medical research after reading the Hungarian translation of Selye's book "The stress of life", originally published in 1956. Hence, we can indeed learn from creative, accomplished scientists!

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