Trends in
Endocrinology & Metabolism

Scientific Life

Nordic track: NIH dysfunction and my Helsinki recruitment

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National Institutes of Health aims to prioritize groundbreaking work that challenges existing views with rigor and reproducibility, and shows potential for translation. Increasingly, however, reviewers penalize applicants for novelty, critique of dogma, and for having work translated, while program officers are now guided to refuse review of proposals on forbidden topics. These practices have the potential to substantively degrade U.S. biomedical progress and played a role in my laboratory's move to Europe.

Career arc and observations on peer review

I am a quintessentially American biomedical scientist, born in Boston and educated through high school and college in New England. I moved to the San Francisco Bay Area to train in molecular biology and genetics at Chiron and the DNAX Research Institute [1] before earning my PhD in enzymology at Stanford [2]. I returned to Boston to conduct a postdoc in X-ray crystallography [3] and launched my independent research group at Jefferson in 1996. With two units of National Institutes of Health (NIH) funding, I moved from Jefferson to Dartmouth in 2003, and with two units of NIH funding plus a National Science Foundation grant, I moved to the University of Iowa in 2009, where I served as an endowed head of biochemistry. In 2020, I was recruited to City of Hope to serve as an endowed chair of diabetes and cancer metabolism.

In the last 7 years of writing research proposals, I earned funding from agencies as selective as the NIH, including the Gates Foundation, the State of California Tobacco-Related Disease Research Program (TRDRP), and the Waxman Foundation, but completely struck out at the NIH. I believe that the proposals I submitted in the past 7 years were more creative and had higher potential impact than those that had been funded by the NIH in my previous 23 years as an applicant.

Does the NIH really want us to discover things that can be translated?

At the dawn of the pandemic, I led a study that showed coronavirus infection disrupts the nicotinamide adenine dinucleotide (NAD) system via highly induced transcription of several members of the poly(adenosine diphosphate-ribose) polymerase superfamily and suggested that NAD-boosting with either nicotinamide or nicotinamide riboside might have antiviral activity [4]. This work was influential [5] and led to the conduct of multiple clinical trials for coronavirus disease recovery [6,7]. In response to a proposal to dissect the mechanisms by which NAD-boosting opposes viral replication, multiple reviewers lauded my contributions to the field, while another opined that since I have intellectual property (IP) in this space, I should not be NIH-supported to do the research. Such a comment flies in the face of the intent of the U.S. government to fund research that can be translated, as well as the public health statements of tens of thousands of NIH applicants, who claim that by working on their specific area of science, they may someday develop a drug or health intervention. When not checked as employing an inappropriate criterion, a single reviewer can tank a proposal in the face of the enthusiasm of multiple other reviewers.

Does the NIH really want us to keep the literature evidence-based?

After the NIH released a notice of funding opportunity (NOFO) for a project to harmonize methods for NAD quantification, I responded with a 'team of rivals' approach involving a collaboration with Anu Suomalainen and Madhuri Hegde, who had developed competing technologies, so that three investigators could compare methods and results against our gold-standard NAD quantification methodology [8]. As the NOFO called for the collection of data addressing human aging, I proposed using highly standardized skin shave biopsies to determine whether people with greater sun exposure and/or advanced years have a disturbed skin NAD system, and to assess whether an NAD-boosting strategy could accelerate wound healing from standardized biopsies in older or younger adults. The project was responsive, reasonable, and achievable within the timeline of the funding mechanism. Proposals were reviewed by a panel that included several individuals who had been active in sirtuin research, which I had recently critiqued [9]. Despite my qualifications and the responsiveness of my approach, a reviewer commented that they did not understand why I had critiqued resveratrol–sirtuin claims in the literature. In both of these cases, dismissive and nonscientifically grounded reviews led to my proposals not being discussed at study section. The score of 'not discussed' was remarkable given that, at the time of the NOFO, our lab had likely completed more quantitative NAD metabolome analyses than any other group using a fully calibrated stable-isotope internal standard approach [8].

Does the NIH really want us to conduct highly innovative research?

Five years ago, the Citrin Foundation—an organization that supports researchers to dissect and develop treatments for the rare disease citrin deficiency (CD), which combines metabolic dysfunction-

associated steatotic liver disease (MASLD) with sweet aversion, urea cycle dysfunction, and other distinct presentations [10], requested a meeting to encourage me to think about CD. I developed a theory that both the MASLD and the sweet aversion in CD could be explained by a mechanism involving a transcription factor I had never worked on, a hepatokine I had never worked on, and a mechanism no one had considered for how the transcription factor might be activated.

My proposals suggested that if my ideas were correct, we could explain a wide variety of basic and clinical data. The ideas polarized reviewers, with some championing my approaches as pioneering and others telling me to stay in my lane because they claimed that carbohydrate response element-binding protein (ChREBP) and fibroblast growth factor 21 (FGF21) experts understood these matters better than I did. Over the course of more than 3 years and seven NIH submissions, in which I presented increasingly substantive preliminary data, I received seven grant proposal rejections, some of which included reviews with scores as disparate as 2 (nearly perfect) and 8 (nearly meritless). Thanks to a mouse model [11] provided by the Citrin Foundation and the use of discretionary funding, my group demonstrated that glycerol-3-phosphate binding to ChREBP drives lipogenic transcription and FGF21 circulation in the mouse model of CD [12]. Seven NIH panels could have supported the first substantive NIH project on CD, but none did.

Having served on NIH panels during this period, I have seen plenty of great scores for projects that have solid but not groundbreaking aims. I believe that many U.S. colleagues agree that it has become nearly impossible to successfully propose a project that goes against the grain within a field.

Does the NIH really want to protect people against nicotine toxicology?

Building on work uncovering novel dimensions of nicotine toxicology that was supported by the State of California, I submitted a proposal to an NIH program in Tobacco Regulatory Science. After it was assigned to a study section but before review, NIH program officers informed me that my proposal could not be reviewed because the Tobacco Regulatory Science Program is funded by tobacco industry fees and governed by a rule that new vape ingredients such as 6-methyl nicotine cannot be investigated. They were unmoved when I made them aware that 6-methyl nicotine is a naturally formed alkaloid to which smokers have always been exposed [13].

Concluding remarks

Scientists operate within a peer review system, which asserts that developing IP capable of advancing to human testing [14,15] and challenging established dogma are its primary goals. However, if we remain passive when reviewers penalize those whose technologies have been developed and gatekeep against novel ideas or critiques of nonevidence-based claims in the literature, we risk stifling both innovation and scientific rigor. Furthermore, when NIH staff are compelled to enforce rules that designate particular problems in toxicology as off-limits, we expose the public to potentially severe hazards. The issues with peer review did not originate with the current administration in Washington. It was surprising, however, to witness the Secretary of Health and Human Services publicly endorse the safety of nicotine pouches precisely at a time when NIH staffers withdrew my grant proposal on the direct bronchial toxicology of nicotine and 6-methyl nicotine. It is also unclear how public health will benefit from large-scale grant cancellations [16] and policies that forbid certain topics, thereby preventing peer review. Would it not be wiser for fewer topics to be off-limits and to allow merit-based review to select the highest-impact research for funding from all submitted applications?

In the summer of 2025, Dr Suomalainen at the University of Helsinki invited me to give a keynote lecture at a conference on healthy aging, and after my lecture, I was walked into the dean's office to be recruited to Finland. I am told that they really value innovation in Finland, that they consider commercial investment and clinical testing to be signs of achievement, and that I can look forward to fresh perspectives on my research ideas in the coming months and years. Grateful to the Research Council of Finland for making my new position possible, and to the Sigrid Jusélius Foundation for their support of our work on nicotine, I will begin in Helsinki in July.

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Declaration of interests

I serve as the chief scientific advisor of Niagen Bioscience and NADMED, and I am a cofounder of Alphina Therapeutics and Juvenis.

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References

1. Brenner, C. *et al.* (1988) *CDC33* encodes mRNA cap-binding protein eIF-4E of *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* 8, 3556–3559
2. Brenner, C. and Fuller, R.S. (1992) Structural and enzymatic characterization of a purified prohormone-processing enzyme: secreted, soluble Kex2 protease. *Proc. Natl. Acad. Sci. U. S. A.* 89, 922–926
3. Brenner, C. *et al.* (1997) Crystal structures of HINT demonstrate that histidine triad proteins are GalT-related nucleotide-binding proteins. *Nat. Struct. Biol.* 4, 231–238

4. Heer, C.D. *et al.* (2020) Coronavirus infection and PARP expression dysregulate the NAD metabolome: an actionable component of innate immunity. *J. Biol. Chem.* 295, 17986–17996
5. Brenner, C. (2022) Viral infection as an NAD^+ battlefield. *Nat. Metab.* 4, 2–3
6. Altay, O. *et al.* (2021) Combined metabolic activators accelerates recovery in mild-to-moderate COVID-19. *Adv. Sci. (Weinh)* 8, e2101222
7. Wu, C.-Y. *et al.* (2025) Effects of nicotinamide riboside on NAD+ levels, cognition, and symptom recovery in long-COVID: a randomized controlled trial. *EClinicalMedicine* 89, 103633
8. Trammell, S.A. and Brenner, C. (2013) Targeted, LCMS-based metabolomics for quantitative measurement of NAD(+) metabolites. *Comput. Struct. Biotechnol. J.* 4, e201301012
9. Brenner, C. (2022) Sirtuins are not conserved longevity genes. *Life Metab.* 1, 122–133
10. Saheki, T. *et al.* (2020) AGC2 (citrin) deficiency—from recognition of the disease till construction of therapeutic procedures. *Biomolecules* 10, 1100
11. Saheki, T. *et al.* (2007) Citrin/mitochondrial glycerol-3-phosphate dehydrogenase double knock-out mice recapitulate features of human citrin deficiency. *J. Biol. Chem.* 282, 25041–25052
12. Tiwari, V. *et al.* (2025) Glycerol-3-phosphate activates ChREBP, FGF21 transcription and lipogenesis in citrin deficiency. *Nat. Metab.* 7, 2284–2299
13. Pankow, J.F. *et al.* (2025) Levels of the nicotine analog 6-methyl nicotine as a naturally formed tobacco alkaloid in tobacco and tobacco products. *Sci. Rep.* 15, 17945
14. McDermott, M.M. *et al.* (2024) Nicotinamide riboside for peripheral artery disease: the NICE randomized clinical trial. *Nat. Commun.* 15, 5046
15. Presterud, R. *et al.* (2024) Long-term nicotinamide riboside use improves coordination and eye movements in ataxia telangiectasia. *Mov. Disord.* 39, 360–369
16. Liu, M. *et al.* (2025) Characterization of research grant terminations at the National Institutes of Health. *JAMA* 334, 534–536