Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful. "Negative" is actually a misnomer, and

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2 $\times$ 2 table, one gets PPV = $(1 - \beta)R/(R$

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Corollary 1: The smaller the studies conducted in a scientific field, the less likely the research findings are to be true.

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Corollary 2: The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.

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Corollary 3: The greater the number and the lesser the selection of tested relationships in a scientific field, the less likely the research findings are to be true.

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Corollary 4: The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true.

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Corollary 5: The greater the financial and other interests and prejudices in a scientific field, the less likely the research findings are to be true.

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Corollary 6: The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true.

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Why Most Published Research Findings Are False

Most Research Findings Are False
for Most Research Designs
and for Most Fields

Claimed Research Findings
May Often Be Simply Accurate
Measures of the Prevailing Bias

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How Can We Improve the Situation?

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Cargo Cult Science

by RICHARD P. FEYNMAN

In the South Seas there is a Cargo Cult of people. During the war they saw airplanes land with lots of good materials, and they want the same thing to happen now. So they've arranged to make things like runways, to put fires along the sides of the runways, to make a wooden hut for a man to sit in, with two wooden pieces on his head like headphones and bars of bamboo sticking out like antennas—he's the controller—and they wait for the airplanes to land. They're doing everything right. The form is perfect. It looks exactly the way it looked before. But it doesn't work. No airplanes land.

So I call these things Cargo Cult Science, because they follow all the apparent precepts and forms of scientific investigation, but they're missing something essential, because the planes don't land.

https://calteches.library.caltech.edu/51/2/CargoCult.htm

nature medicine

A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

Vineet D Menachery[1], Boyd L Yount Jr[1], Kari Debbink[1,2], Sudhakar Agnihothram[3], Lisa E Gralinski[1], Jessica A Plante[1], Rachel L Graham[1], Trevor Scobey[1], Xing-Yi Ge[4], Eric F Donaldson[1], Scott H Randell[5,6], Antonio Lanzavecchia[7], Wayne A Marasco[8,9], Zhengli-Li Shi[4] & Ralph S Baric[1,2]

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The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS)-CoV underscores the threat of cross-species transmission events leading to outbreaks in humans. Here we examine the disease potential of a SARS-like virus, SHC014-CoV, which is currently circulating in Chinese horseshoe bat populations[1]. Using the SARS-CoV reverse genetics system[2], we generated and characterized a chimeric virus expressing the spike of bat coronavirus SHC014 in a mouse-adapted SARS-CoV backbone. The results indicate that group 2b viruses encoding the SHC014 spike in a wild-type backbone can efficiently use multiple orthologs of the SARS receptor human angiotensin converting enzyme II (ACE2), replicate efficiently in primary human airway cells and achieve *in vitro* titers equivalent to epidemic strains of SARS-CoV. Additionally, *in vivo* experiments demonstrate replication of the chimeric virus in mouse lung with notable pathogenesis. Evaluation of available SARS-based immune-therapeutic and prophylactic modalities revealed poor efficacy; both monoclonal antibody and vaccine approaches failed to neutralize and protect from infection with CoVs using the novel spike protein. On the basis of these findings, we synthetically re-derived an infectious full-length SHC014 recombinant virus and demonstrate robust viral replication both *in vitro* and *in vivo*. Our work suggests a potential risk of SARS-CoV re-emergence from viruses currently circulating in bat populations.

The emergence of SARS-CoV heralded a new era in the cross-species transmission of severe respiratory illness with globalization leading to rapid spread around the world and massive economic impact[3,4]. Since then, several strains—including influenza A strains H5N1, H1N1 and H7N9 and MERS-CoV—have emerged from animal populations, causing considerable disease, mortality and economic hardship for the afflicted regions[5]. Although public health measures were able to stop the SARS-CoV outbreak[4], recent metagenomics studies have identified sequences of closely related SARS-like viruses circulating in Chinese bat populations that may pose a future threat[1,6]. However, sequence data alone provides minimal insights to identify and prepare for future prepandemic viruses. Therefore, to examine the emergence potential (that is, the potential to infect humans) of circulating bat CoVs, we built a chimeric virus encoding a novel, zoonotic CoV spike protein—from the RsSHC014-CoV sequence that was isolated from Chinese horseshoe bats[1]—in the context of the SARS-CoV mouse-adapted backbone. The hybrid virus allowed us to evaluate the ability of the novel spike protein to cause disease independently of other necessary adaptive mutations in its natural backbone. Using this approach, we characterized CoV infection mediated by the SHC014 spike protein in primary human airway cells and *in vivo*, and tested the efficacy of available immune therapeutics against SHC014-CoV. Together, the strategy translates metagenomics data to help predict and prepare for future emergent viruses.

The sequences of SHC014 and the related RsWIV1-CoV show that these CoVs are the closest relatives to the epidemic SARS-CoV strains (**Fig. 1a,b**); however, there are important differences in the 14 residues that bind human ACE2, the receptor for SARS-CoV, including the five that are critical for host range: Y442, L472, N479, T487 and Y491 (ref. 7). In WIV1, three of these residues vary from the epidemic SARS-CoV Urbani strain, but they were not expected to alter binding to ACE2 (**Supplementary Fig. 1a,b** and **Supplementary Table 1**). This fact is confirmed by both pseudotyping experiments that measured the ability of lentiviruses encoding WIV1 spike proteins to enter cells expressing human ACE2 (**Supplementary Fig. 1**) and by *in vitro* replication assays of WIV1-CoV (ref. 1). In contrast, 7 of 14 ACE2-interaction residues in SHC014 are different from those in SARS-CoV, including all five residues critical for host range (**Supplementary Fig. 1c** and **Supplementary Table 1**). These changes, coupled with

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Zhengli Shi,
The Wuhan “Bat Woman”

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A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

30 March 2020 Editors' note, March 2020: We are aware that this article is being used as the basis for unverified theories that the novel coronavirus causing COVID-19 was engineered. There is no evidence that this is true; scientists believe that an animal is the most likely source of the coronavirus.

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COVID ~~VACCINES~~

Experimental injections that force prolonged transgenic expression of a newly engineered cytotoxic protein

A layperson encounter, on the “modified” RNA world

Abstract

A chance conversation with a nonscientist about the mRNA-COVID vaccines, conveyed here, reminded the author of our enduring responsibility to accurately portray science to the public.

Pederson T. A layperson encounter, on the "modified" RNA world. Proc Natl Acad Sci U S A. 2021 Nov 16;118(46)

A layperson encounter, on the “modified” RNA world

“This struck me as a perfect storm of an educated, reasonably informed nonscientist being led astray by how the media often doesn’t get it quite right, though we all recognize that too much detail can be narcoleptic.”

Pederson T. A layperson encounter, on the "modified" RNA world. Proc Natl Acad Sci U S A. 2021 Nov 16;118(46)

A layperson encounter, on the “modified” RNA world

“I told my friend what the doping was, using lay terms. He listened thoughtfully and then I came in with my final shot: nature is full of RNA that is “doped,” and even DNA is as well. These chemical modifications are not done by mad scientists but by the very biological systems in which these RNAs and DNAs reside, using their own enzymes.”

Pederson T. A layperson encounter, on the "modified" RNA world. Proc Natl Acad Sci U S A. 2021 Nov 16;118(46)

A layperson encounter, on the “modified” RNA world

“He left somewhat convinced and hopefully is now vaccinated.”

Pederson T. A layperson encounter, on the "modified" RNA world. Proc Natl Acad Sci U S A. 2021 Nov 16;118(46)

A layperson encounter, on the “modified” RNA world

Competing Interests

Competing interest statement: T.P. owns stock in Moderna Therapeutics Inc.

Pederson T. A layperson encounter, on the "modified" RNA world. Proc Natl Acad Sci U S A. 2021 Nov 16;118(46)

Modifications in an Emergency: The Role of N1-Methylpseudouridine in COVID-19 Vaccines

“The chemical components of mRNA vaccines are pleasantly unremarkable”

...

“the non-natural RNA nucleobase N1-methylpseudouridine”

“it is important to gently push back on the narrative that this process was hurried, which may invite skepticism.”

Nance KD, Meier JL. Modifications in an Emergency: The Role of N1-Methylpseudouridine in COVID-19 Vaccines. ACS Cent Sci. 2021 May 26;7(5):748-756.

The Critical Contribution of Pseudouridine to mRNA COVID-19 Vaccines

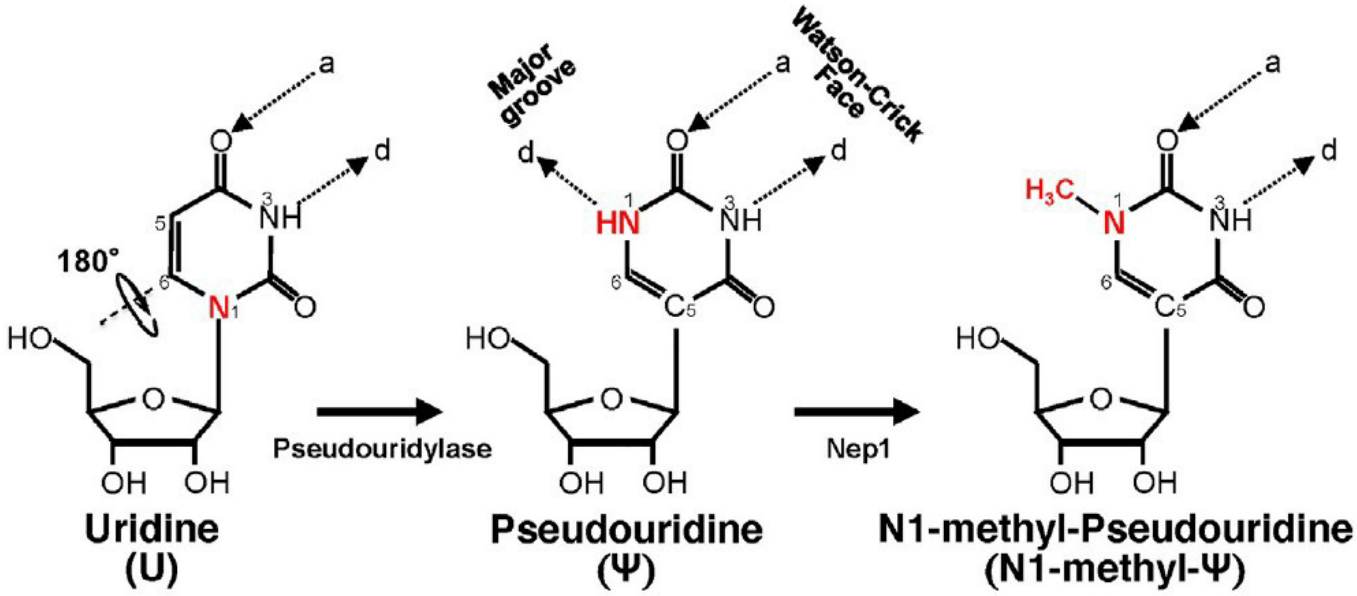
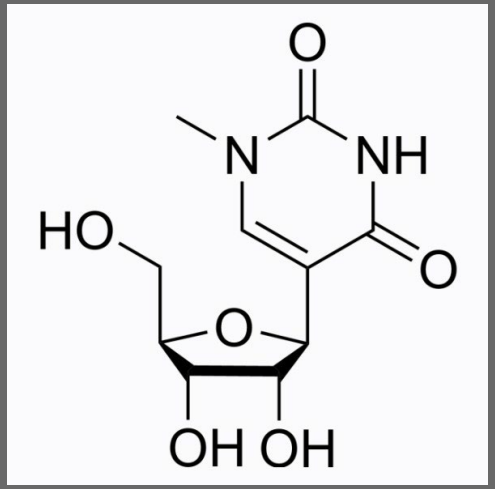


FIGURE 1 | Schematic representation of U-to-Ψ isomerization and additional N1 methylation. Ψ is a rotational isomer of uridine, in which the N-C glycosidic bond is substituted with the C-C bond. The isomerization reaction also creates an extra hydrogen bond donor (-N1H). Ψ can be further methylated at the N1 position by Nep1 (an N1-specific Ψ methyltransferase) to generate N-methyl-Ψ. d, hydrogen bond donor; a, hydrogen bond acceptor.

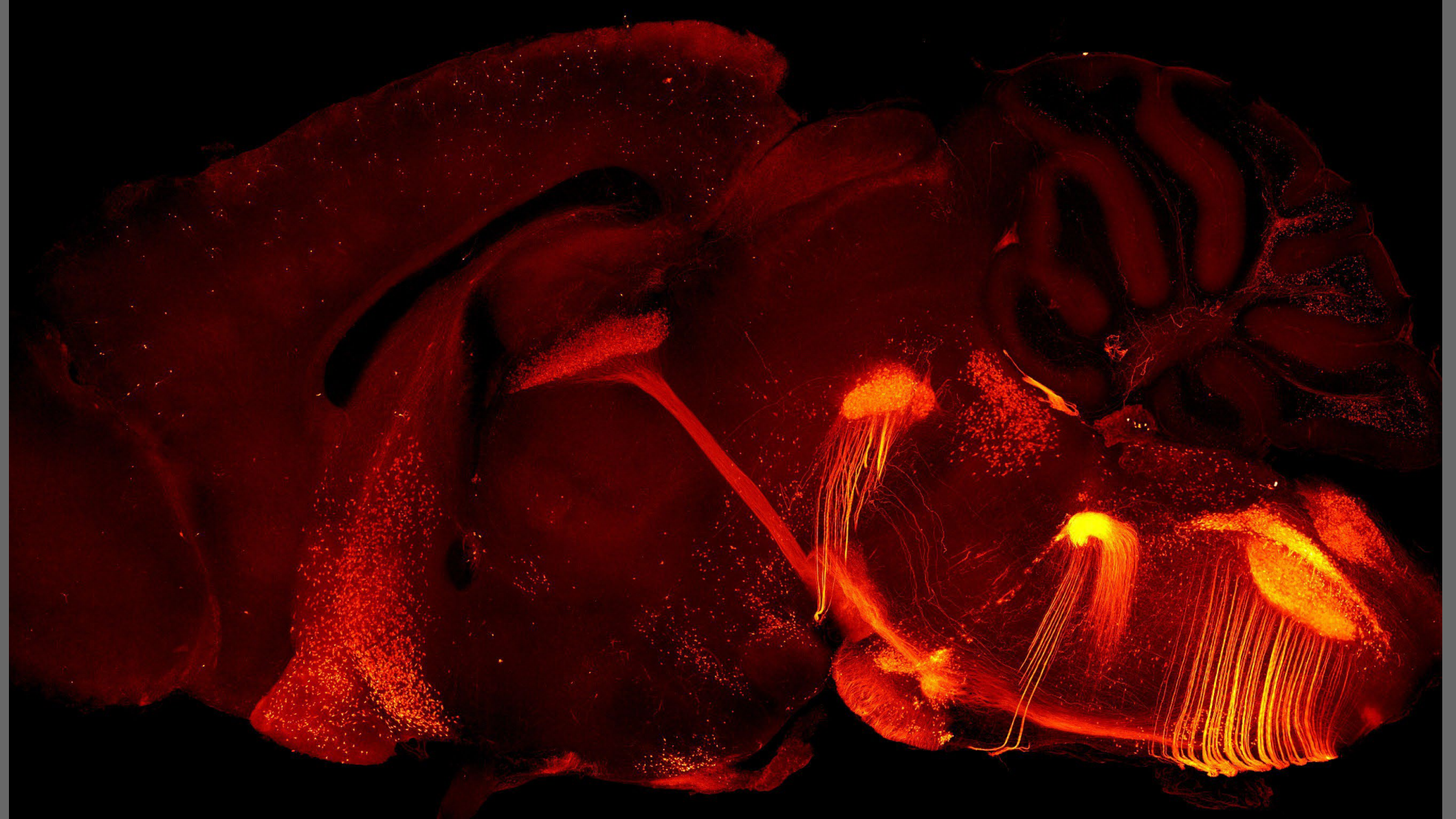
Morais P, Adachi H, Yu YT. The Critical Contribution of Pseudouridine to mRNA COVID-19 Vaccines. Front Cell Dev Biol. 2021 Nov 4;9:789427.

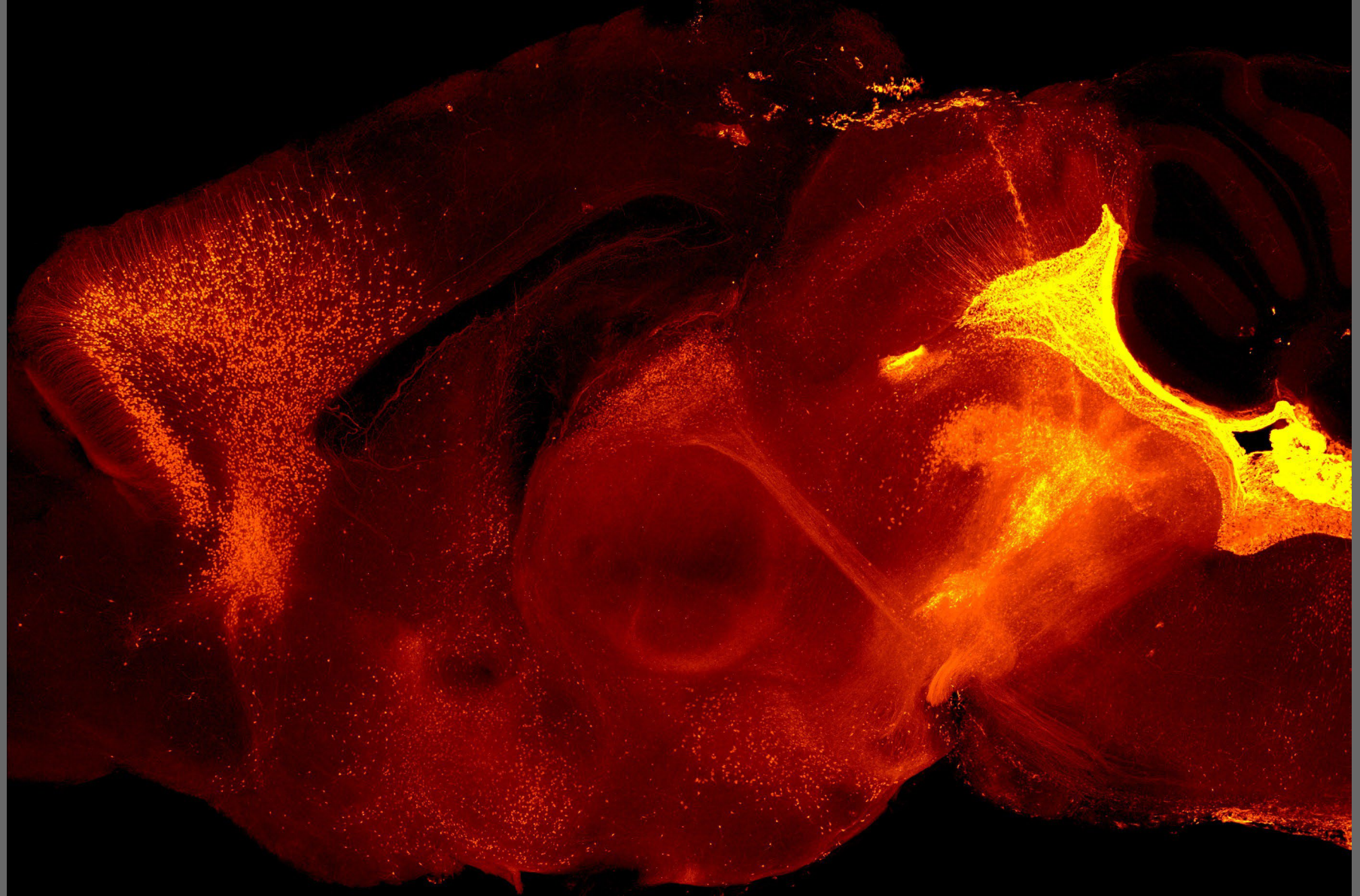
N1-methylpseudouridine



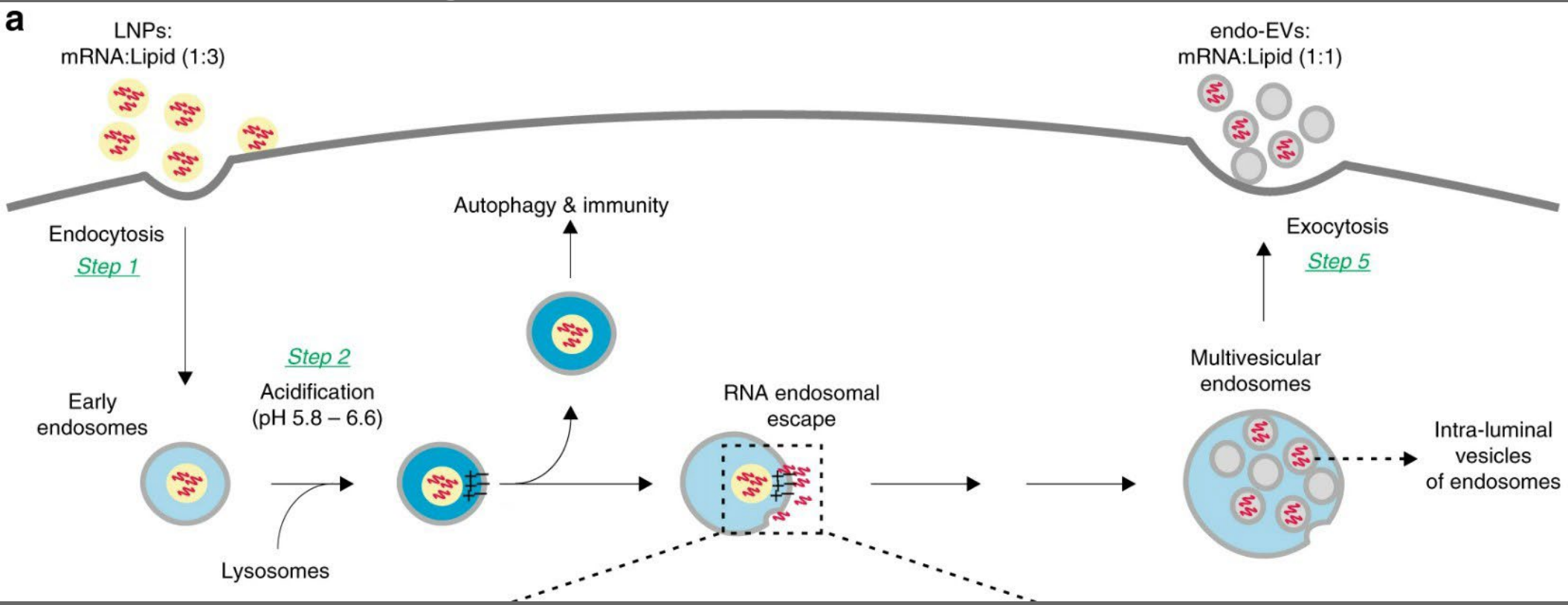
N1-methyl-Ψ-mRNA

M1ΨmRNA:LNP experimental injections





Linkage between endosomal escape of LNP-mRNA and loading into EVs for transport to other cells



A hypothetical mechanism explaining the fate of LNP endosomes

Maugeri M, Nawaz M, Papadimitriou A, Angerfors A, Camponeschi A, Na M, Hölttä M, Skantze P, Johansson S, Sundqvist M, Lindquist J, Kjellman T, Mårtensson IL, Jin T, Sunnerhagen P, Östman S, Lindfors L, Valadi H. Linkage between endosomal escape of LNP-mRNA and loading into EVs for transport to other cells. Nat Commun. 2019 Sep 24;10(1):4333.