

# Funding Risky Research

Paula Stephan

Georgia State University and NBER

Funders' Forum

October 11, 2021

# Overview

---

- Speed with which Covid-19 vaccines were developed and their high-performance underscore importance of science
- Especially case for vaccines based on mRNA
  - Enabled identification of a vaccine with high efficacy in less than 3 months after virus was sequenced
  - Holds huge promise for future of vaccines and medicine more broadly
- Raises questions
  - Is funding for research sufficiently supportive of key breakthroughs?
  - Does system of science funding encourage sufficient risk taking?



# Plan of Presentation

- Briefly discuss Katalin Karikó, key mRNA researcher, and problems she faced getting funding for research
- Set out framework for thinking about why funding agencies may eschew funding risky research
- Interventions/experiments agencies could consider enacting if they wish to encourage risk taking;

# Messenger RNA

- Technology used by Pfizer-BioNTech and Moderna to develop first two vaccines against Covid 19 to obtain FDA approval
- Discovered in 1961; synthesized in test tube in early 1980s;
- By early 1990's recognized that mRNA could be used to turn human bodies into medicine-making factories
- But faced critical problems: In vitro-transcribed mRNA, when delivered to animals, could either be destroyed as body fielded an immune response before reaching its target, or worse yet, cause serious side effects (Sahin et al. 2014).



# Katalin Karikó

- Determined to find a way to make synthetic mRNA non-inflammatory applicable to treat human diseases
- Held soft-money position at University of Pennsylvania Med School beginning late 1980's
- Submitted more than 20 grants, many to NIH. *"Every night I was working: grant, grant, grant,"* recounts Karikó. *"And it came back always no, no, no."*
- Inability to support her research on grants resulted in her being taken off faculty position at Penn
- In 1995 she accepted non-faculty position, *"more like a post-doc position"* at University of Pennsylvania without prospect of advancing



# Katalin Karikó cont.

- Met Drew Weissman, MD PhD immunologist, recently arrived from NIH, at photocopying machine in 1997
- Realized they shared an interest in developing synthetic mRNA vaccine against HIV
- Started working together on mRNA research
- Work supported on a Weissman non-related NIH grant
- Breakthrough came when they recognized that uridine was nucleoside in mRNA that provoked human immune system
- Published results in *Immunity* after rejected by several top journals; now highly cited but few citations in first few years



# Commercialization

- Resulting patents licensed exclusively to CellScript by University of Pennsylvania.
- CellScript sublicensed to BioNTech and Moderna

# After Seminal Publication

- Karikó continued to have problems getting funding; Weissman more successful although had number turned down
- In 2013 Karikó became a Senior Vice President of BioNTech

# What Could Have Been? No counterfactual

- No way to know what would have happened if Karikó's early applications for funding had not been turned down
  - Perhaps mRNA-based vaccines would have been available for Swine Flu in 2009
  - Perhaps she would have given up, were it not for casual meeting with Weissman
- Do know that her early proposals not funded, and University moved her out of soft-money faculty position
  - Could reflect failure in her proposals to address problem of immune system response
  - Could reflect risk aversion on part of review panels, that considered area too risky to be "fundable"
  - *"People were not interested in mRNA. The people who reviewed the grants said mRNA will not be a good therapeutic, so don't bother."* Weissman
- Example does show that early-funding of designer mRNA research, now considered a promise of future medicine, was difficult

# Raises Question of Risk Aversion in Funding Scientific Research

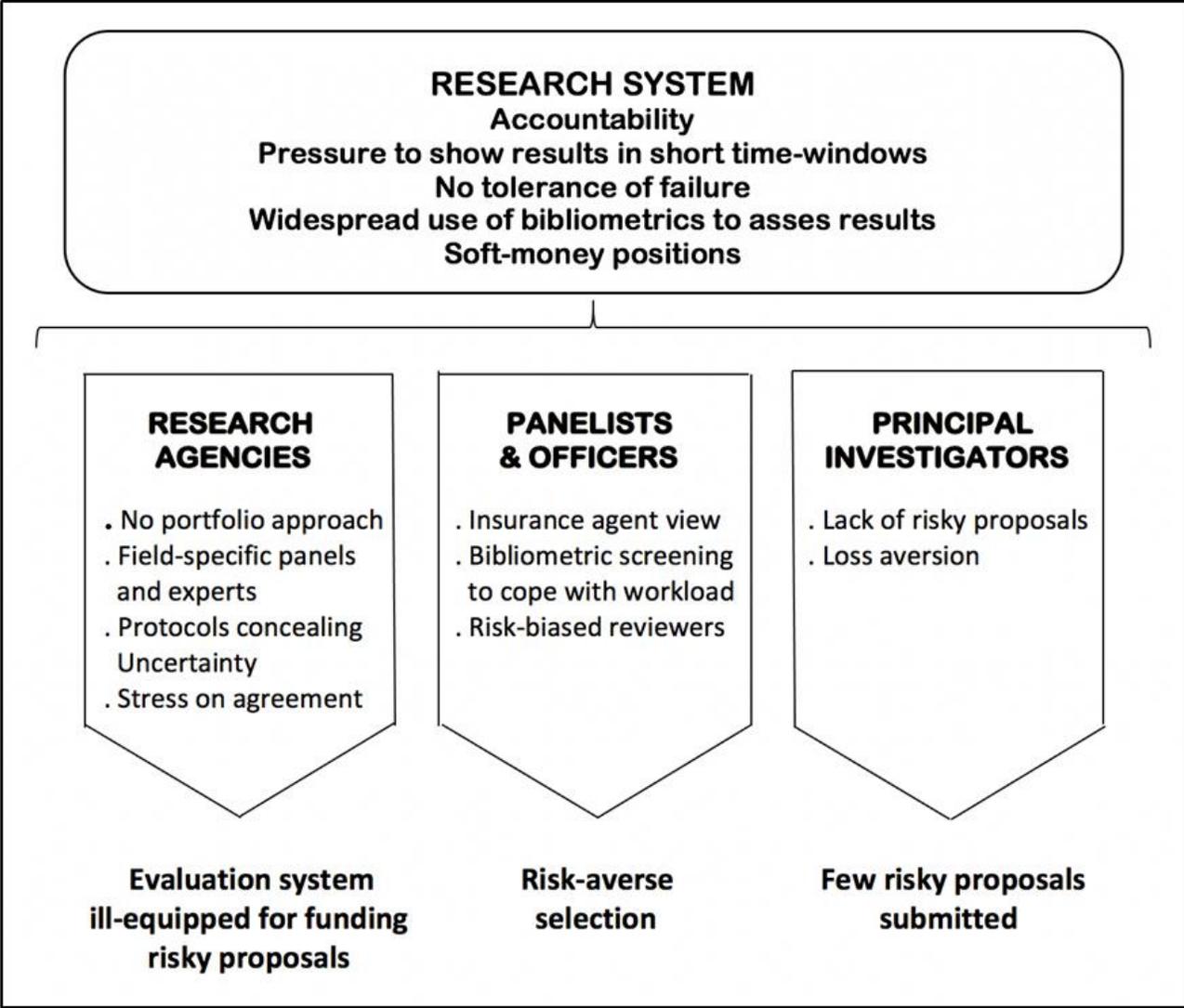
- Is there evidence that it exists?
- If so, why?
- Possible remedies?

# Raises Question of Risk Aversion in Funding Scientific Research

- Is there evidence that it exists?
- Yes: some evidence that risk aversion exists among funders
  - Veugelers et al (ERC)
  - Boudreau et al (2016) experiments Harvard Medical School
  - SGER study NSF (Wagner and Alexander)
  - Carayol & Lanoe (2019) French ANR bias against novel research

# Why Funding Agencies May Avoid Funding Risky Research: Hypotheses

- Bias against risky research in overall research system
- Bias against risky research among players within research funding system
  - Principal Investigators
  - Research Agencies
  - Panelists



# Panelists and Research Officers

- Aware that future of program depends upon not “coming up empty handed”
- Place emphasis on “what can go wrong” rather than “what can go right”
- Fuels heavy emphasis on preliminary results as necessary condition for funding
- In essence, research is “de-risked” before it funded
- Karikó rejections included comments such as “insufficient preliminary data”

# Research Agencies: hypotheses concerning risk aversion

- Panels lack portfolio approach—choose proposals one by one rather than thinking of overall portfolio; akin to buying stocks one-by-one without reference to what is in portfolio. Choices are correlated implying that portfolio is overly conservative
- Interdisciplinary bias of panels (interdisciplinary research has a riskier profile; Boudreau et al show less likely to be chosen); most panels are discipline based
- Peer review provides little room for uncertainty; reviewers provide only one score—conceals uncertainty. In evaluating risky research, outcomes of interest can be expected to be in the tails and single-point estimate may have little meaning.
- Practice of seeking consensus among panel members may induce bias against risky research

# Panelists and Research Officers *continued*

- Heavy workload leads panelist to screen on readily available bibliometrics—ERC panel member has 137 proposals to screen on first call
- Bibliometrics in short run are biased against risky research
- Journal Impact Factor—which is frequently looked at—negatively correlated with risk (Wang et al)



# These are but hypotheses as to why system appears risk averse

- If goal is to encourage risk taking, there is a need to see what types of practices work and what types of practices do not work
- Experiments offer an important way to gain insight into this issue
- Funding organizations regularly fund researchers to run experiments
- But they have been hesitant to consider running experiments themselves

# Moving Forward

- Funders need to take some risk so we can learn how to take on more risk
- Consider at a minimum running pilot study experiments
- Examples:
  - Experiments concerning scoring and aggregation practices used by panels
  - Experiments concerning disciplinary composition of panels
  - Experiments concerning how funders can take a portfolio approach
  - Experiments concerning funding in stages

# Questions? Comments

- [pstephan@gsu.edu](mailto:pstephan@gsu.edu)

# Funding Risky Research

Chiara Franzoni, Paula Stephan & Reinhilde Veugelers

NBER WORKING PAPER 28905

