ERC Scientific Seminar - How, when and why science fails to correct itself?

Frédérique Bordignon, Y J Erden, Raphaël Lévy

NanoBubbles: how, when and why science fails to **correct** itself?

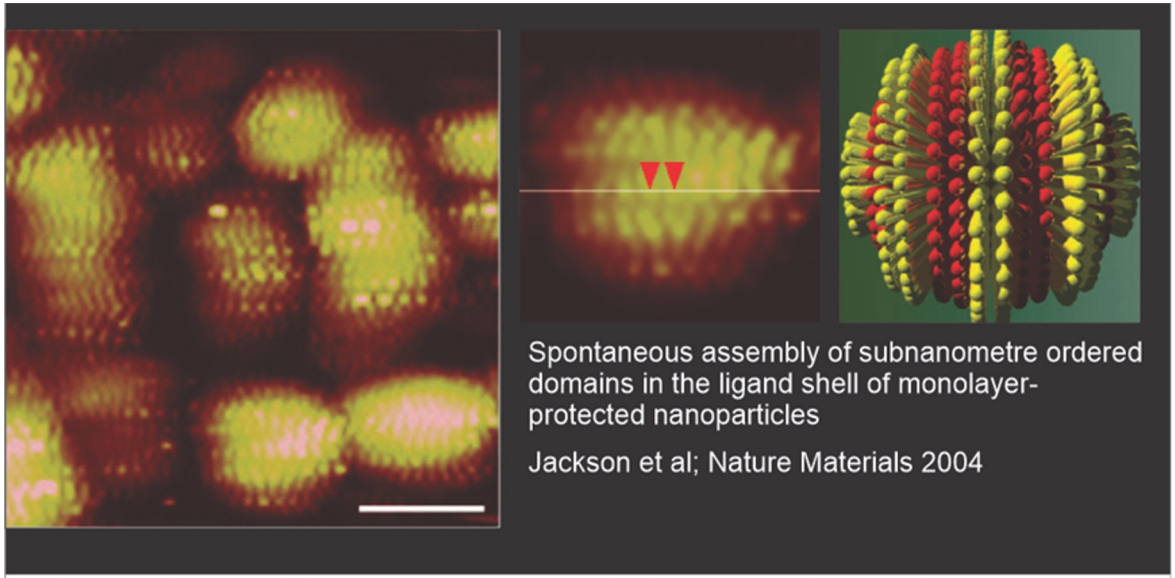
Frédérique Bordignon, Y. J. Erden, Raphaël Lévy

ERC Scientific Seminar
July 8th, 2022

The beginning of the story…

First attempt at “correcting science”: the stripy nanoparticles controversy

2004



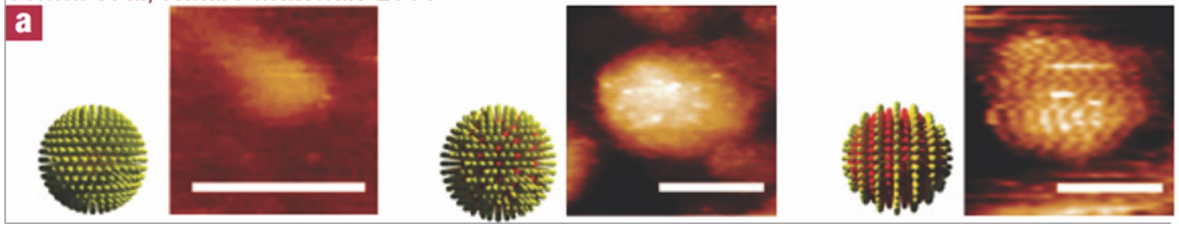
Spontaneous assembly of subnanometre ordered domains in the ligand shell of monolayer-protected nanoparticles

Jackson et al; Nature Materials 2004

2008

Surface-structure-regulated cell-membrane penetration by monolayer-protected nanoparticles

Verma et al; Nature Materials 2008



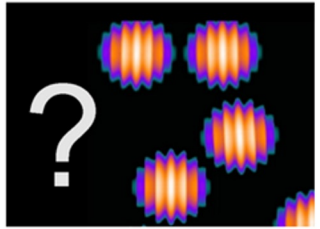
Stripy Nanoparticles Revisited

Submitted 2009

Three years to publish a “revisited” article? let’s blog

2012

STRIPY NANOPARTICLES REVISITED



Challenging published results is an onerous but necessary task. Today, our article entitled **Stripy Nanoparticles Revisited** has been published in *Small*, three years after its initial submission to this journal (3/12/09) and about three and a half years after the first submission (to Nature Materials, 21/07/09).

As its title indicates, the article challenges the evidence for the existence and properties of “stripy” nanoparticles. The stripy nanoparticle hypothesis was first

Search …

My Tweets

COMMENTS

Raphaël Lévy on What Proportion of Scientific…

Raphaël Lévy on What

Whose job is it to correct science? Are blogs an appropriate place?

physicsfocus

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SCIENCE & TECHNOLOGY

BIG TUSSLE OVER TINY PARTICLES

In peer-reviewed papers and on blogs, researchers argue over the existence of **STRIPED COATINGS** on nanoparticles

LAUREN K. WOLF, C&EN WASHINGTON

AS TRUTH SEEKERS, scientists often challenge one another's work and debate over the details. At the first-ever interna-

gory detail the various aspects of the controversy. Stellacci, who refuses to engage in these discussions, says he feels as though

ARE FLAWS IN PEER REVIEW SOMEONE ELSE'S PROBLEM?

By Philip Moriarty O

Neuroskeptic

« Psychiatrists From Another Dimension (Part 2)

Medical Journal Apologizes "For The Distress Caused" By A Paper »

Postpublication "Cyberbullying" and the Professional Self

Neuroskeptic | January 27, 2014 4:47 pm

67

article in *Science* has been getting a lot of attention this week:

ano-Imaging Feud Sets Online Sites Sizzling

e 'stripey nanoparticles' debate, which I covered a few weeks

n 2004, Francesco Stellacci and his colleagues published a paper

NEWS&ANALYSIS

MATERIALS SCIENCE

Nano-Imaging Feud Sets Online Sites Sizzling

Scientific controversies often sort themselves out as new data roll in. But a decade-old dispute in nanoscience shows no sign of letting up. Researchers on both sides are claiming that recently published papers settle the debate in their favor, while one is charging his opponents with resorting to an

spot signatures consistent with Stellacci's stripes seals the deal, says Biscarini, a chemist and expert in scanning microscopy. "In my mind the controversy is over."

Stellacci's critics—chiefly U.K.-based STM experts Raphaël Lévy of the University of Liverpool and Philip Moriarty of the

what kids that commit suicide go

Instead of engaging in such "

and unprofessional" conduct, h

skeptics should go through th

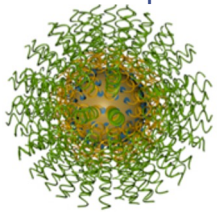
channels of peer review and pu

data in journals so the scientific p

work through the issues.

Second attempt at “correcting science”: the spherical nucleic acid controversy

A body of work published (mostly) by Chad Mirkin, Northwestern University, in 50+ scientific articles in top journals from **2006**.

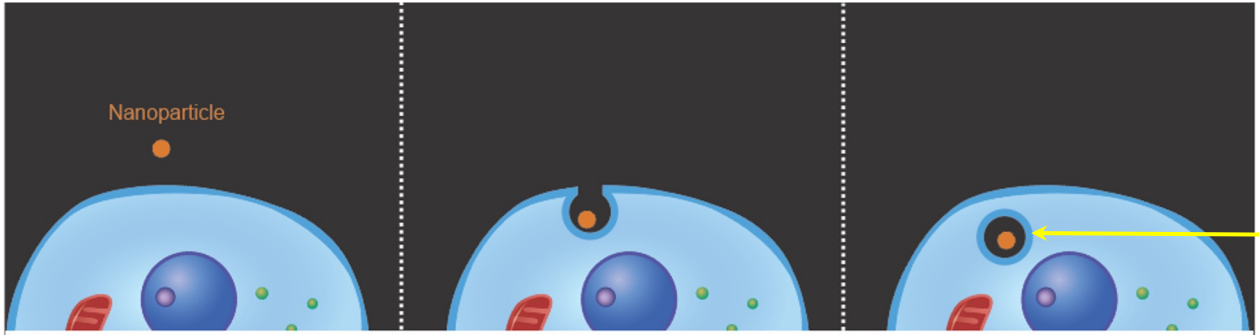


Expression “Spherical nucleic acids” coined in **2012**; gold nanoparticles with DNA strands attached to the gold core

The basis of several companies, scientific prizes, millions of dollars of research grants, cell biology research reagents advertised and sold worldwide for several years as well as clinical trials.

What is the problem?

Established knowledge: nanoparticles enter cells but end up in vesicles inside the cell

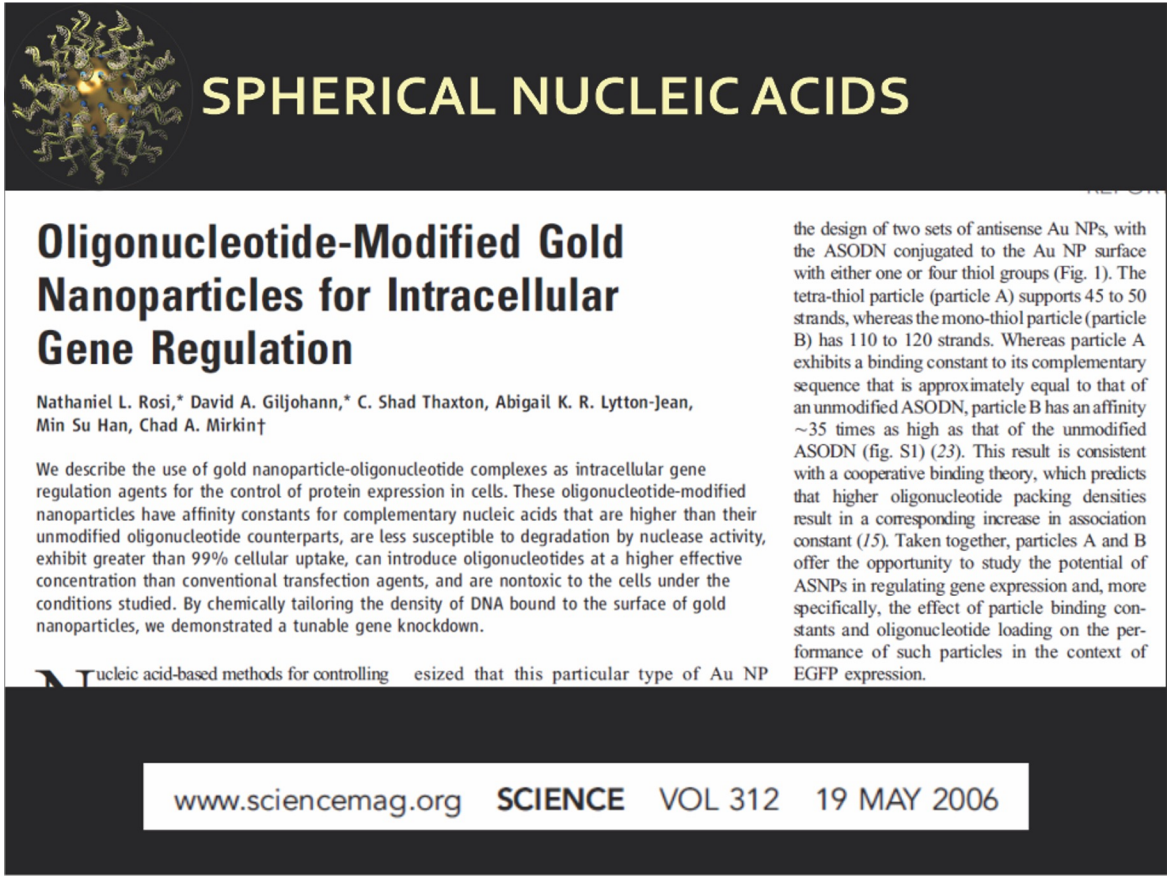


As Dales has pointed out (3), virus entry by phagocytosis, or during pinocytosis, might simply be a special example of the general method whereby cells in a wide variety of normal situations take up particulate objects. But under normal conditions phagocytosis is usually directed to the concentration of assimilated material in membrane-bounded vacuoles or inclusions connected with digestive disposal processes (7, 8), and for infection by ingested virus

In 1963, the mechanism of entry of nanoparticles into cells is already well established knowledge.

1963

Second attempt at “correcting science”: the spherical nucleic acid controversy



SPHERICAL NUCLEIC ACIDS

Oligonucleotide-Modified Gold Nanoparticles for Intracellular Gene Regulation

Nathaniel L. Rosi,* David A. Giljohann,* C. Shad Thaxton, Abigail K. R. Lytton-Jean, Min Su Han, Chad A. Mirkin†

We describe the use of gold nanoparticle-oligonucleotide complexes as intracellular gene regulation agents for the control of protein expression in cells. These oligonucleotide-modified nanoparticles have affinity constants for complementary nucleic acids that are higher than their unmodified oligonucleotide counterparts, are less susceptible to degradation by nuclease activity, exhibit greater than 99% cellular uptake, can introduce oligonucleotides at a higher effective concentration than conventional transfection agents, and are nontoxic to the cells under the conditions studied. By chemically tailoring the density of DNA bound to the surface of gold nanoparticles, we demonstrated a tunable gene knockdown.

Nucleic acid-based methods for controlling

esized that this particular type of Au NP

the design of two sets of antisense Au NPs, with the ASODN conjugated to the Au NP surface with either one or four thiol groups (Fig. 1). The tetra-thiol particle (particle A) supports 45 to 50 strands, whereas the mono-thiol particle (particle B) has 110 to 120 strands. Whereas particle A exhibits a binding constant to its complementary sequence that is approximately equal to that of an unmodified ASODN, particle B has an affinity ~35 times as high as that of the unmodified ASODN (fig. S1) (*23*). This result is consistent with a cooperative binding theory, which predicts that higher oligonucleotide packing densities result in a corresponding increase in association constant (*15*). Taken together, particles A and B offer the opportunity to study the potential of ASNPs in regulating gene expression and, more specifically, the effect of particle binding constants and oligonucleotide loading on the performance of such particles in the context of EGFP expression.

www.sciencemag.org SCIENCE VOL 312 19 MAY 2006

Nanoparticles (SNAs) to interfere with gene regulations inside cells.

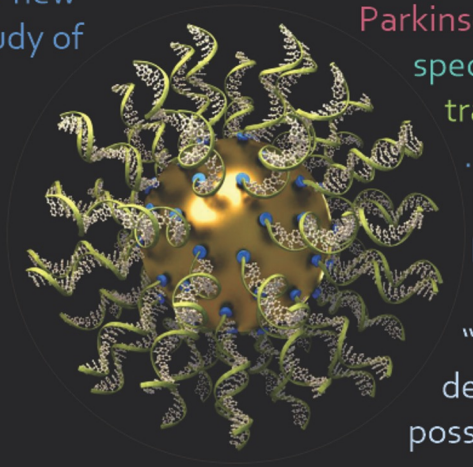
But how do they escape endosomes?

Second attempt at "correcting science": the spherical nucleic acid controversy

Promises. Lots of promises. Big ones.

"...opens the door for new possibilities in the study of gene function and nanotherapies."

"...can be used as both transfection agents and cellular "nano-flares" for detecting mRNA in living cells."



"...new avenues for tackling glioblastoma, Alzheimer's, and Parkinson's. ... broad-spectrum antibiotics ... traumatic brain injury. ... could positively impact **tens of millions** of people"

"Live cell RNA detection is now possible using inert nanoparticle technology to specifically detect native mRNA"

2006-2009

2013-2015

Nanoparticles (SNAs) to interfere with gene regulations inside cells.

Nanoparticles (SNAs) to detect mRNAs inside cells.

But how do they escape endosomes?

Second attempt at "correcting science": the spherical nucleic acid controversy

2013

Commercialization of SNAs (SmartFlares) to detect mRNAs inside cells.

2014

Publication (by us) of *The spherical nucleic acids mRNA detection paradox* ;

2015

Confirmation from an ex-application development specialist that the SmartFlares do not work

2016

Publication (by Czarnek and Bereta) of *SmartFlares fail to reflect their target transcripts levels* = independent confirmation from another group

2017

that the SmartFlares do not work

Catalogue Number	Availability
SF-913	Discontinued

2018

Commercialization stops.

Chad Mirkin calls me *a scientific terrorist* and *a scientific zealot* for asking a question about this at the ACS National meeting in Boston

The questions raised by those controversies are (mostly) not about science

2013

2014

2015

2016

2017

2018

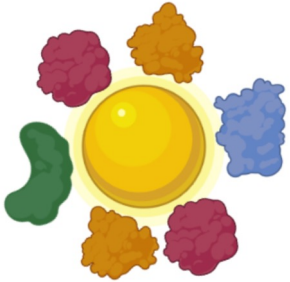
Encounter with Sociologist Marianne Noël at the 2015 ACS National meeting in Boston

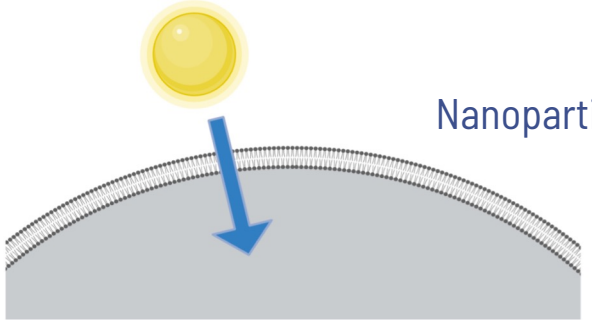
April 2019: Seed Meeting of the French Embassy in London - *NanoBubble: scientific controversies in nanoscience in the age of fake news, social media and post-publication peer review*

November 2019: NanoBubbles submitted as an

3 bubbles

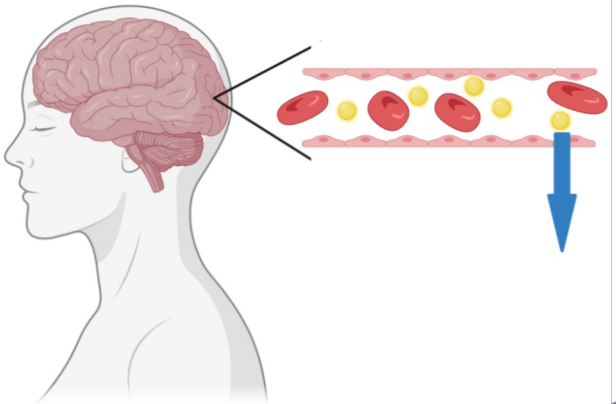
The protein corona that changes everything





Nanoparticles penetrate the cell membrane

Nanoparticles cross the Blood-Brain Barrier, or do they?



The STS framework

Science and Technology Studies

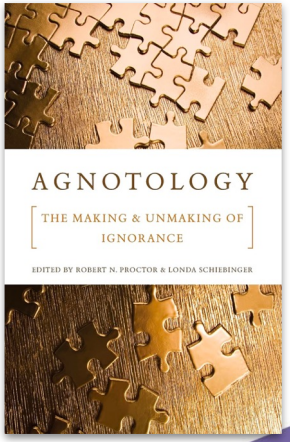
STS framework

- A new field (1970s) of **Science and Technology Studies**
  - interdisciplinary field
  - combining history, sociology, philosophy, anthropology, policy studies...

- **Controversy studies**
  - historical and sociological studies of disagreements
  - where the actors deconstruct each other's claims

- **Agnotology**

  why and how some scientists and firms promote ignorance

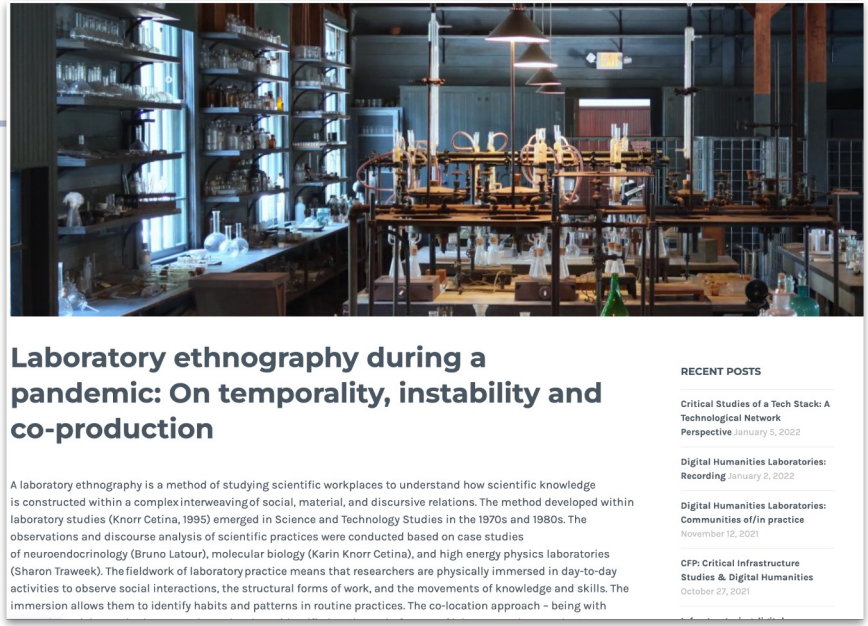


Proctor & Schiebinger.
Agnotology: The Making and Unmaking of Ignorance. Stanford University Press, 2008

STS framework

- **Tacit knowledge**
  - laboratories & conferences
  - ethnographic studies

- **Explicit knowledge**
  - journals & textbooks
  - historical, literary & quantitative/digital methods



Laboratory ethnography during a pandemic: On temporality, instability and co-production

A laboratory ethnography is a method of studying scientific workplaces to understand how scientific knowledge is constructed within a complex interweaving of social, material, and discursive relations. The method developed within laboratory studies (Knorr Cetina, 1995) emerged in Science and Technology Studies in the 1970s and 1980s. The observations and discourse analysis of scientific practices were conducted based on case studies of neuroendocrinology (Bruno Latour), molecular biology (Karin Knorr Cetina), and high energy physics laboratories (Sharon Traweek). The fieldwork of laboratory practice means that researchers are physically immersed in day-to-day activities to observe social interactions, the structural forms of work, and the movements of knowledge and skills. The immersion allows them to identify habits and patterns in routine practices. The co-location approach – being with

RECENT POSTS

Critical Studies of a Tech Stack: A Technological Network Perspective January 5, 2022

Digital Humanities Laboratories: Recording January 2, 2022

Digital Humanities Laboratories: Communities of/in practice November 12, 2021

CFP: Critical Infrastructure Studies & Digital Humanities October 27, 2021

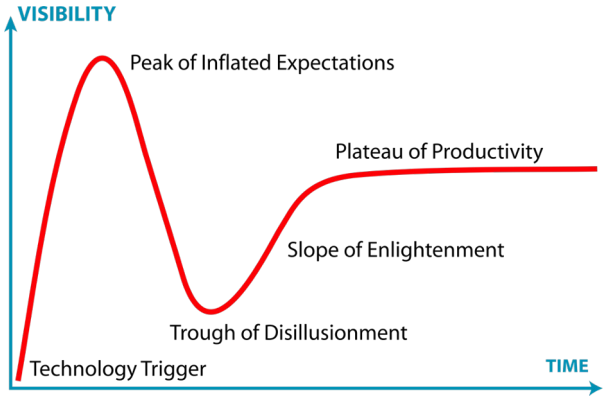
Source: ***DH Infra project*** *blog. February 8th, 2021*
https://dhinfra.org/163/laboratory-ethnography-during-a-pandemic-on-temporality-instability-and-co-production

Csiszar, A. The Scientific Journal: Authorship and the Politics of Knowledge in the Nineteenth Century. University of Chicago Press, 2018

STS framework

- **Sociology of error**
  - to explain the persistence of error and failures of self-correction
  - science as a social and human activity
  - redirecting the focus from individual misconduct or sloppiness to collective processes

- **Sociology of promises or expectations**
  - when expectations become performative
  - claims about nano's potential are increasingly challenged from within nanobiology itself
  - how promises and hypes end, or are adjusted and corrected?



Gartner Hype Cycle - Wikipedia

Digital methods

Scientometrics and text analysis

- large corpora

- automatic screening of scientific publications
  - to detect unreliable or odd results

tortured phrases (colossal information/big data, counterfeit consciousness/artificial intelligence)

automatically generated papers

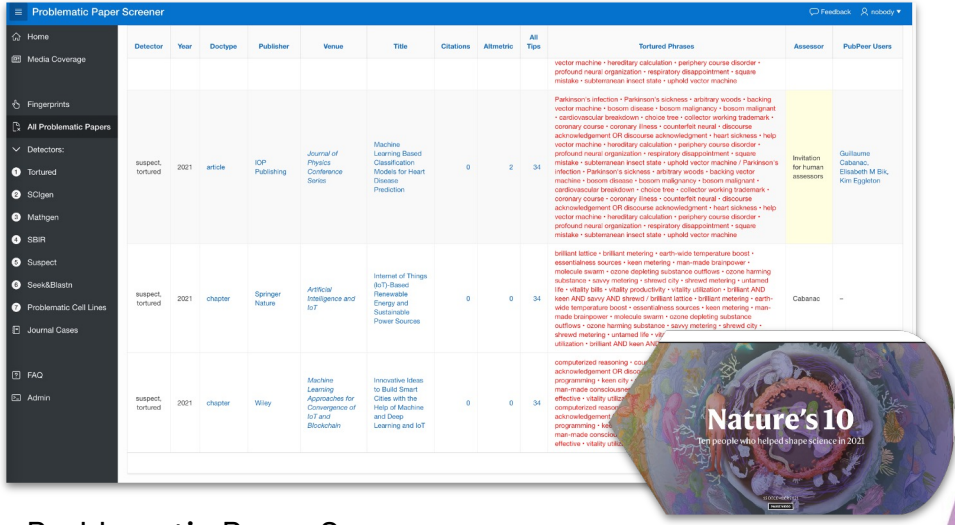
incorrect use of nucleotide sequence reagents

  - to track claims and counter-claims

  - to study citations

critical citations to detect disagreement

how claims circulate



Problematic Paper Screener
https://www.irit.fr/~Guillaume.Cabanac/problematic-paper-screener/

Ethical reflections

Ethical aims require ethical reflection

Aim: ensure good, rigorous science through effective methods of correction

Requires: rigorous and transparent ethical approaches and procedures

Image: Qwedgeonline 'Tight Rope' URL

Some of our ethical concerns

Avoiding 'tickbox' ethics (rules, regulations); interrogating different values (and how to balance them)

How to treat fairly and ethically anyone under scrutiny

How to avoid being 'integrity police', including in our own institutions

Tension between being neutral observers vs. activism (whistleblowing; reporting fraud)

Balancing conference observation with consent (public vs. private spaces)

Embedded practice; integrated oversight

Aim: promotion of ethical discussion, including on legal instruments / hoops

Practice: embedded ethics rapporteur to foster regular, sustained discussion / reflection

Benefits: oversight of project (decision making and struggles), easy access to key information, fostering good will towards ethics through open discussion, avoiding conflation with compliance / minimal oversight (lip service to ethics)

Struggles: continuous reflection needed, e.g. to sustain critical distance, to deliver unwelcome advice / guidance, to agree what is sufficient for monitoring and managing ethics, to sustain collective support and oversight in the light of other project aims

First ethics periodic report (D2.6)

- Special dispensation to embed internal Ethics Rapporteur (rather than external Ethics Advisor) **(March 2021, Appendix 2)**
- Consortium Agreement (CA) includes outline of aim to embed ethics by design approach within the structure of the project **(June 2021, Appendix 1)**.
- Discussion and listing of ethical concerns, preliminary resolutions, agreements, plans for next steps **(February 2021, Chapter 1)**
- First agreement on social media data, adoption of guidance framework **(September 2021, Chapter 2)**
- Joint Consortium and Ethics Advisory Board (EAB) meetings **(June 2021, November 2021, March 2022, Chapter 3)**
- NanoBubbles Memorandum of Understanding (MoU), agreed and approved by members and EAB (**November 2021, Chapter 4**)

Recent and upcoming activities (D2.7)

Ethics meeting with new NanoBubbles members (February 2022):

- On witch-hunting and protecting participants
- On what is public or private
- On the difference between fraud and hype (and related)
- On how we distinguish data from different conference spaces, including public presentations and panel discussions

Workshop on diversity and inclusivity, Dr Chris Campbell, Psychology (June 2022)

- On implicit bias
- On inequality
- Impacts on science and participants
- What has been done (what works, what doesn't)
- What we can do (measurable goals; cultivate cultural curiosity)

2-day meeting / workshop (January – February 2023)

- Ethics training (theories and approaches), plus discussion
- Critical thinking (training)
- Shared vocabulary (discussion)
- Creating ethics guidelines/frameworks for ourselves, e.g. how to deal with reporting errors in specific cases (workshop)

Synergy in action!

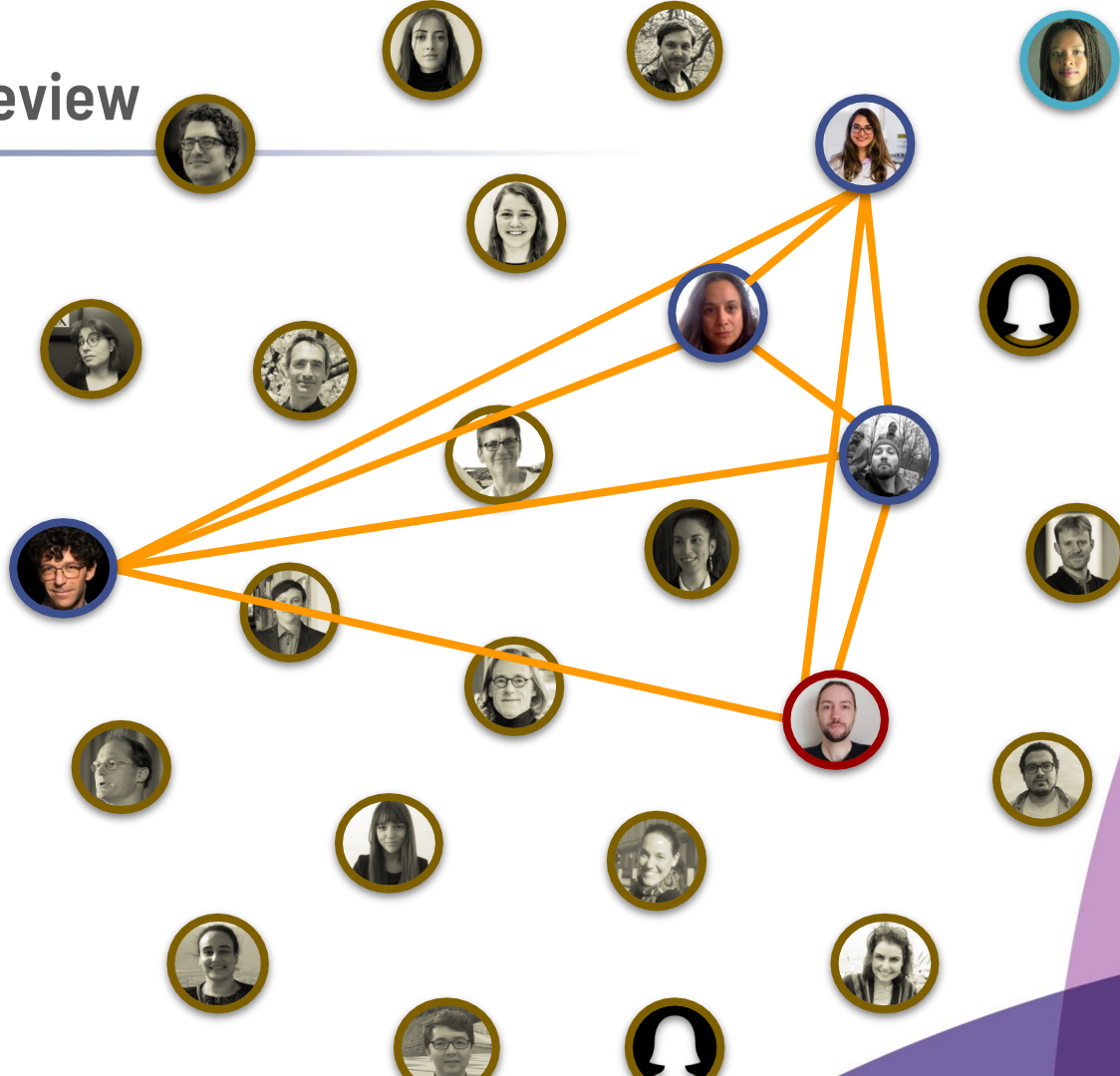
No over-stretched claims!

THIS IS **US**

Node color =
PI official attachment

Edge =
shared research topic

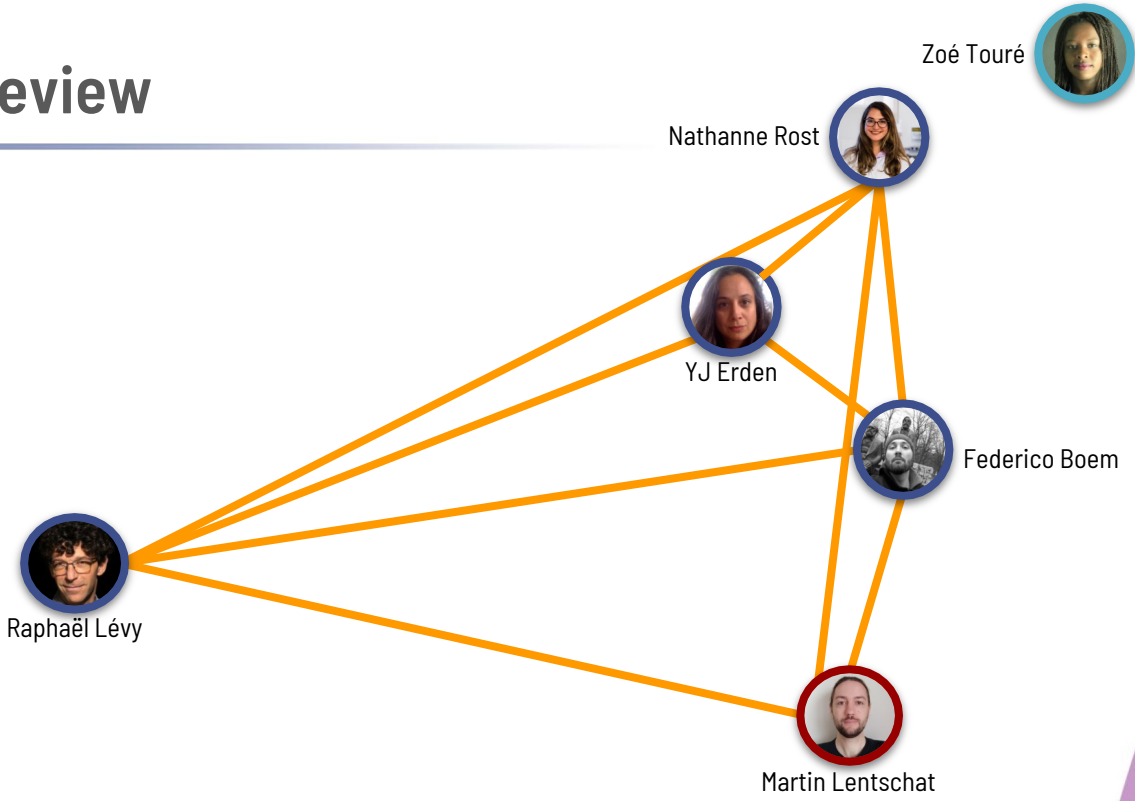
Post-publication peer review



Post-publication peer review

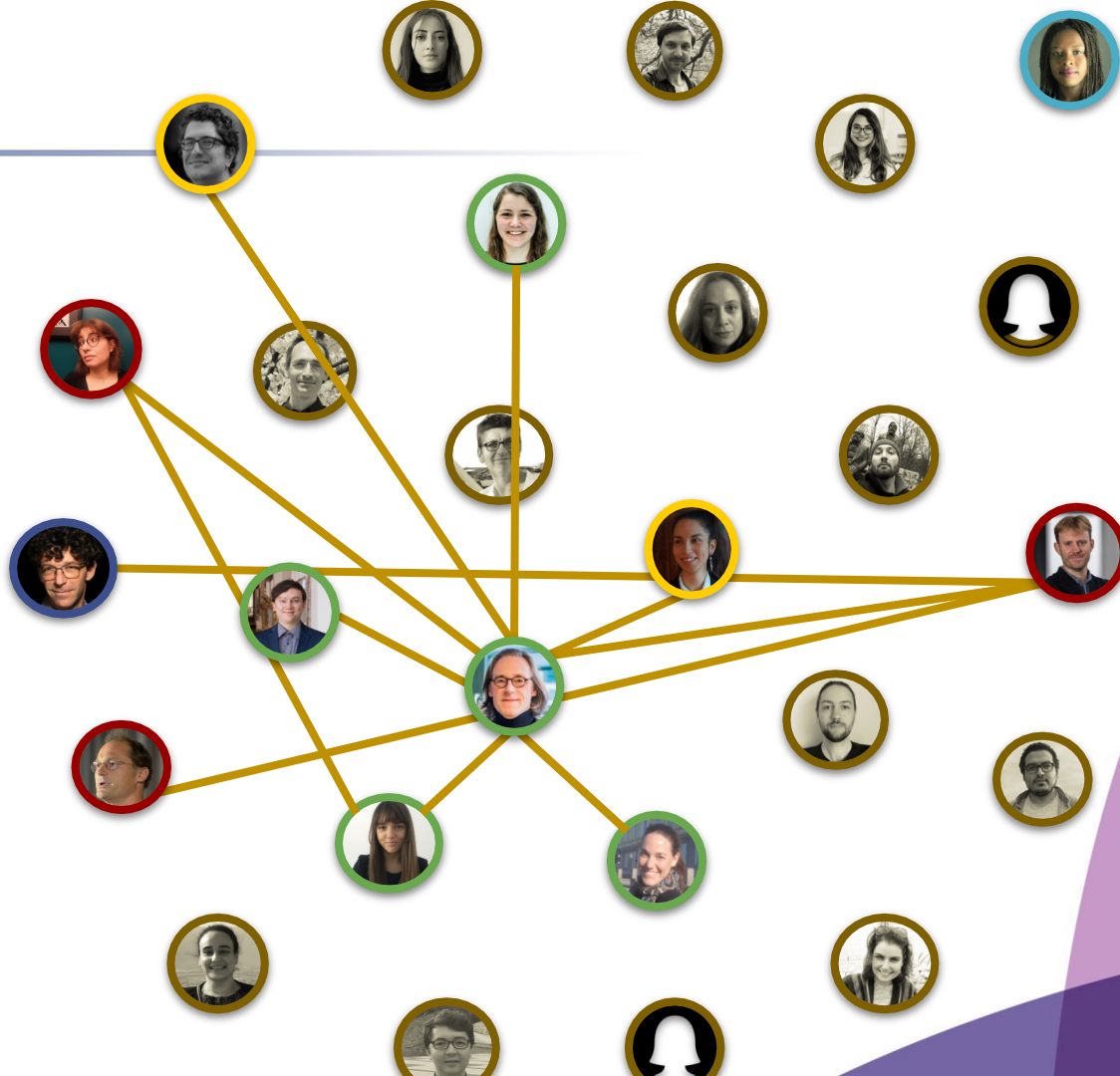
hypothes.is

PUBPEER
The online journal club



Correction practices

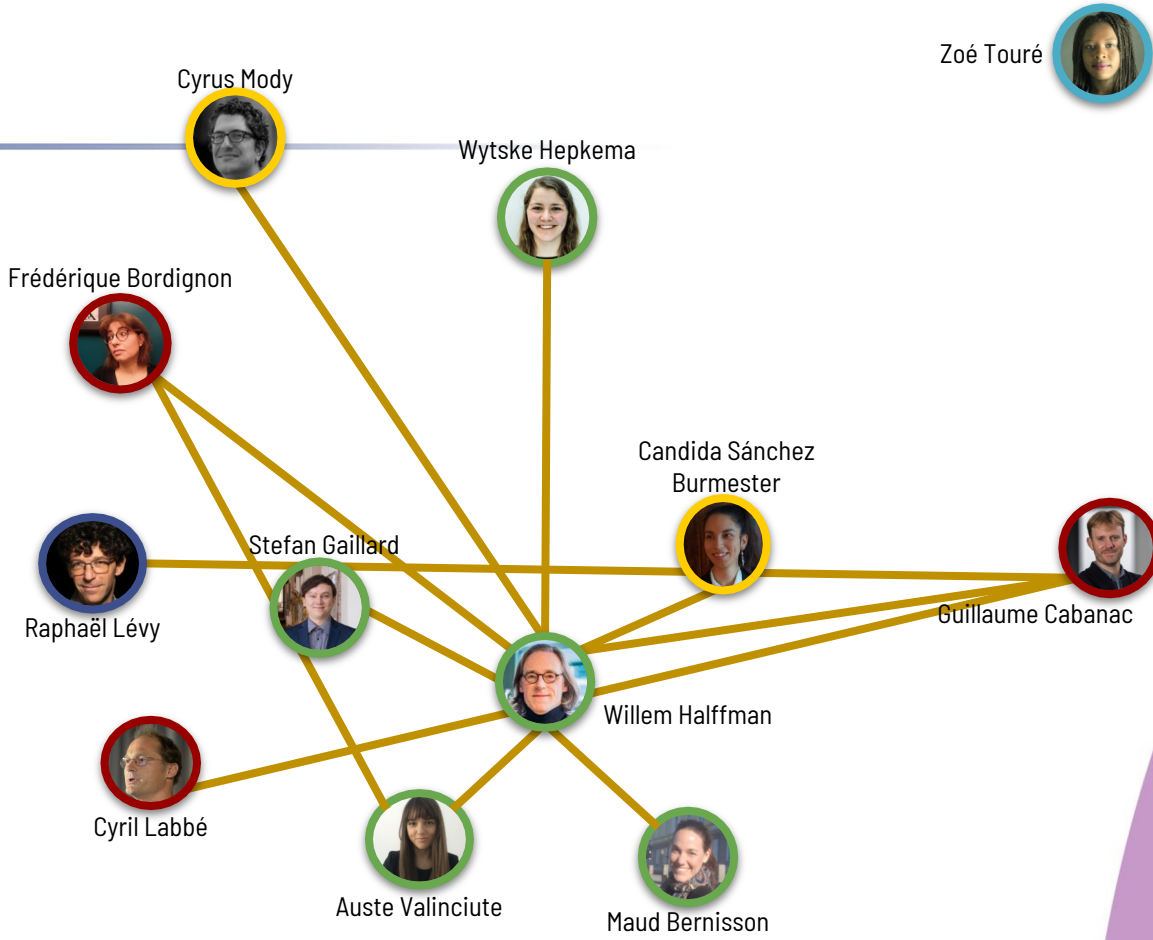
Correction practices



Correction practices

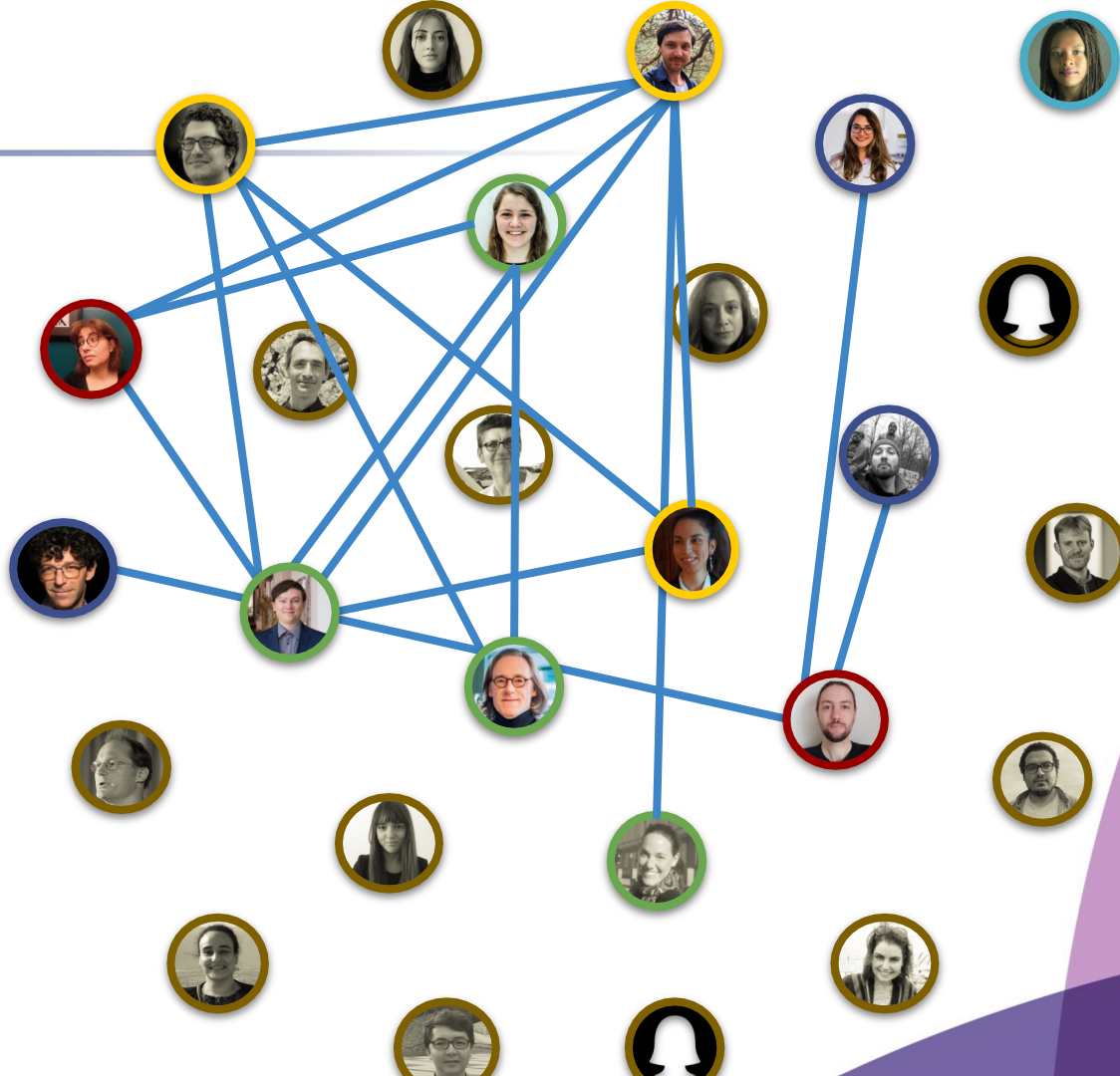
PUBPEER
The online journal club

WIKIPEDIA
The Free Encyclopedia



Claims & promises

Claims & promises



Claims & promises

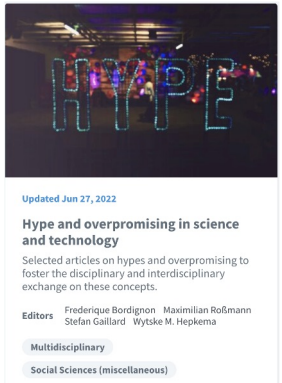
- **Future-related claims**

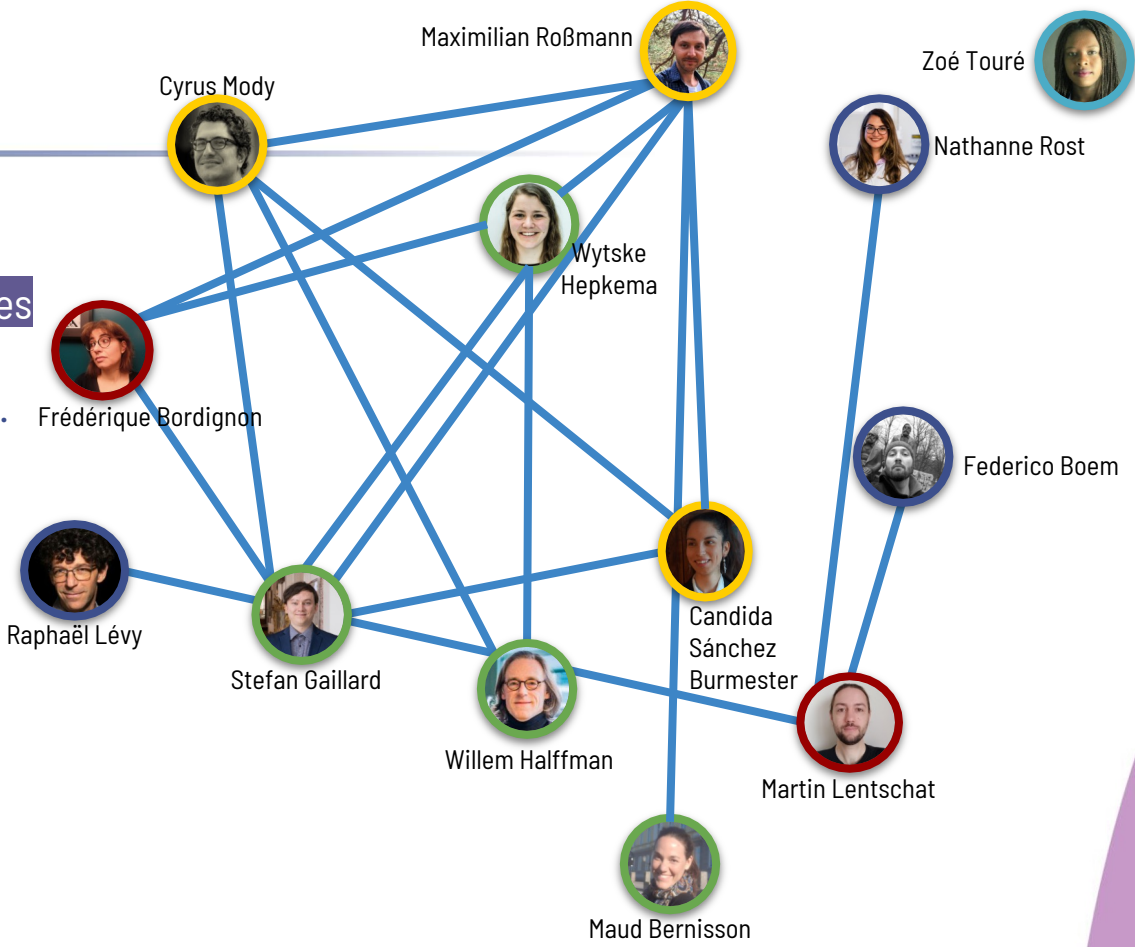
"By 2010 a third generation of nanostructures will emerge, which feature nanosystems with thousands of interacting components".

- **Generation and impact of a promise**

- **Peeriodical**

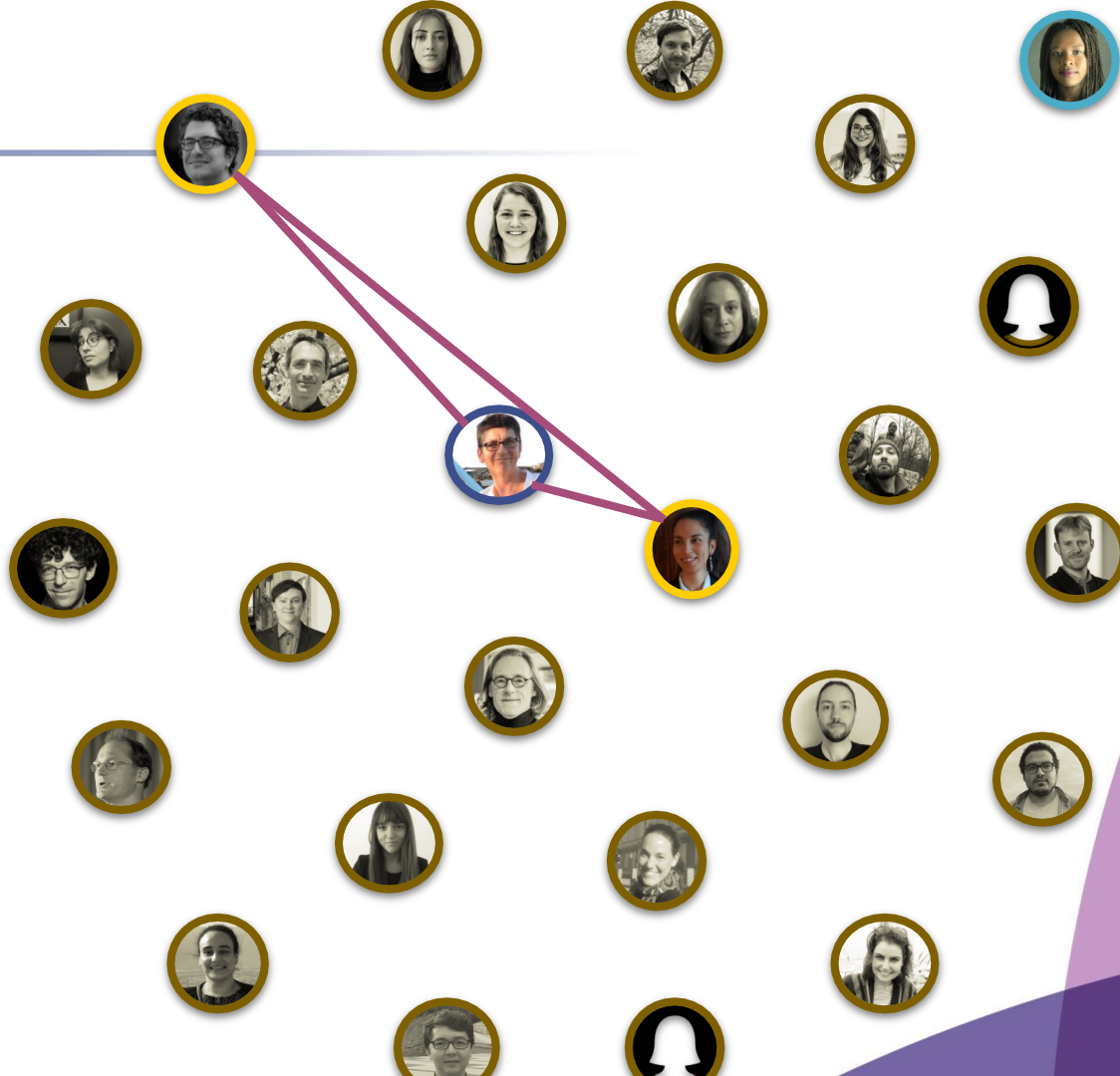
PEERIODICALS
Select the best science beta



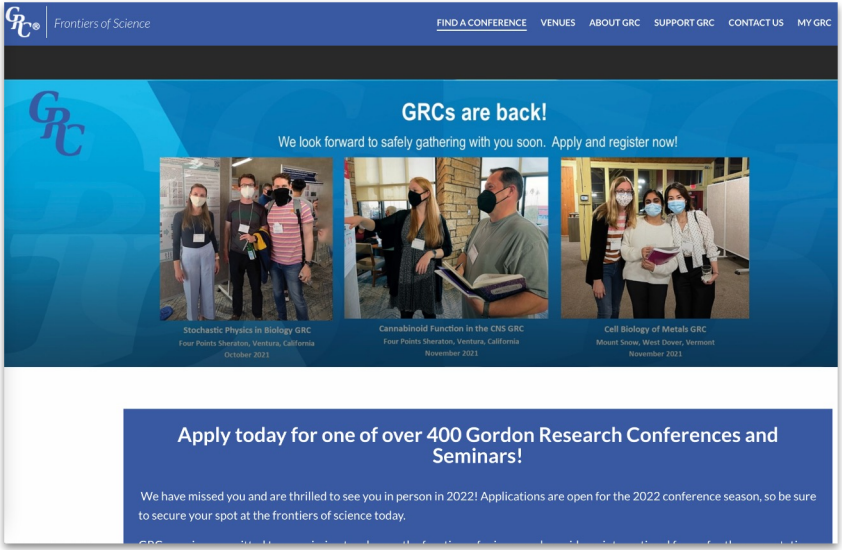


Conferences

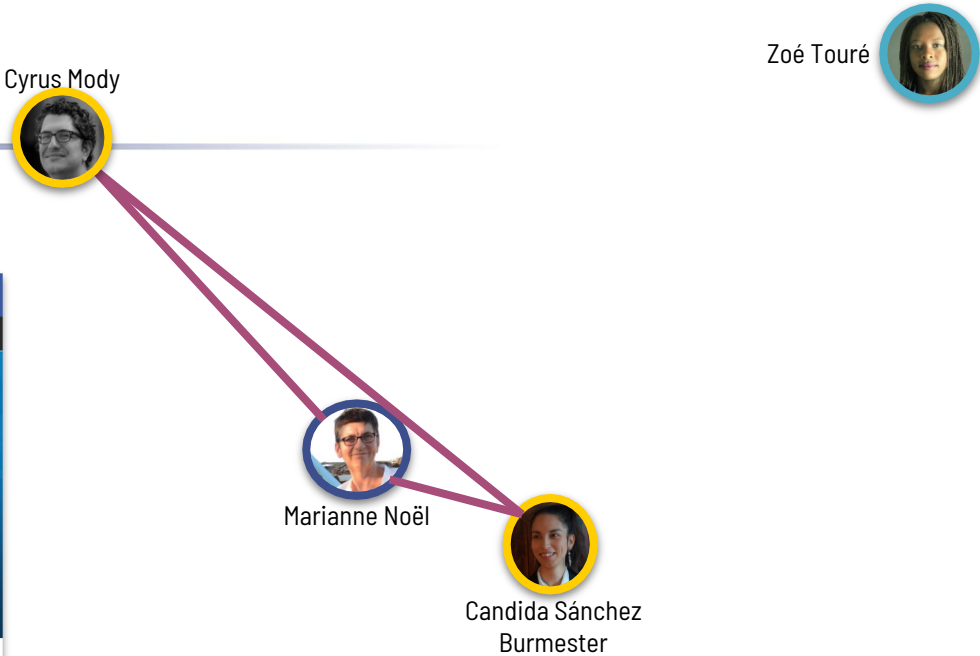
Conferences



Conferences

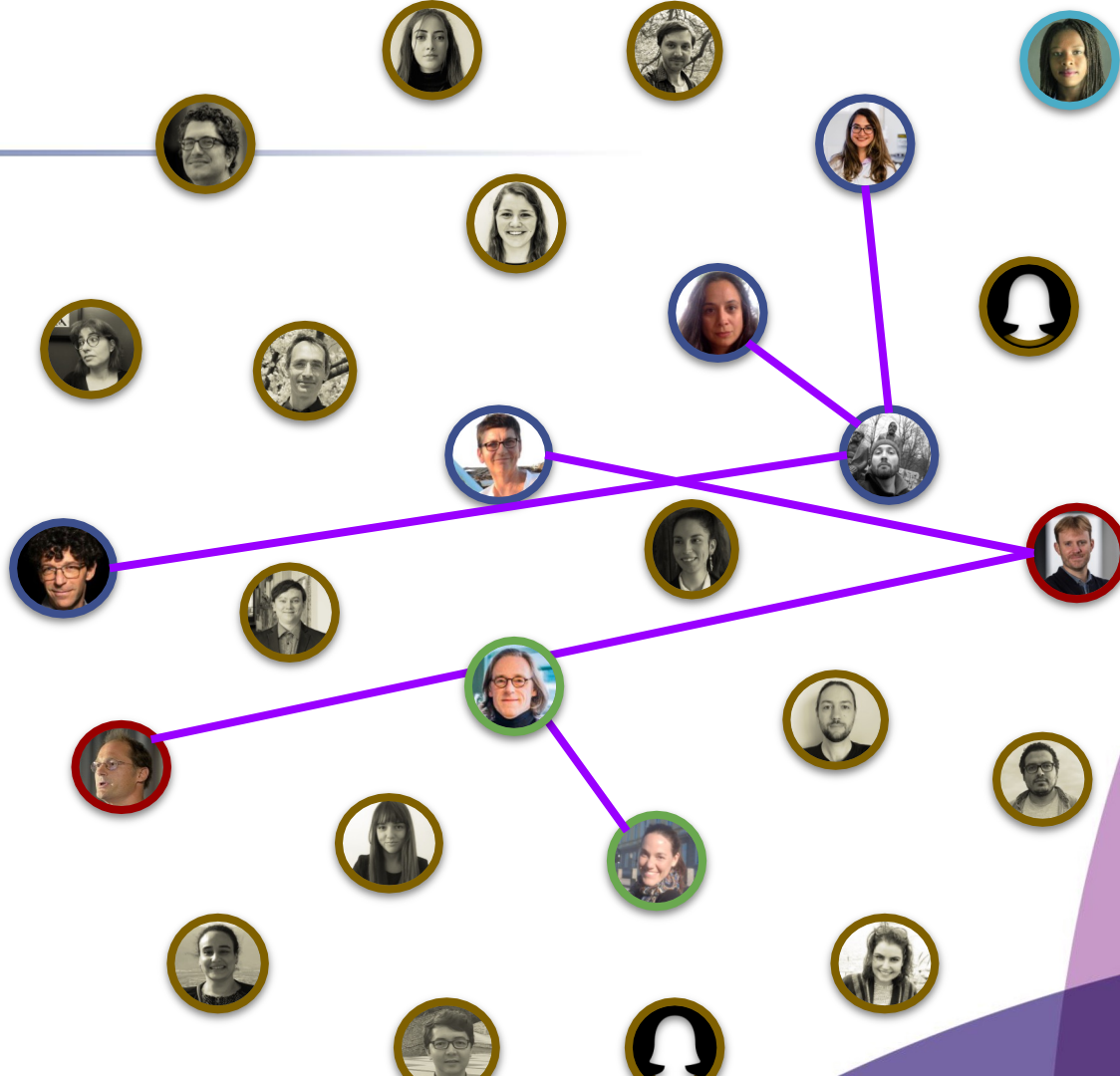


Example: Gordon Research Conferences



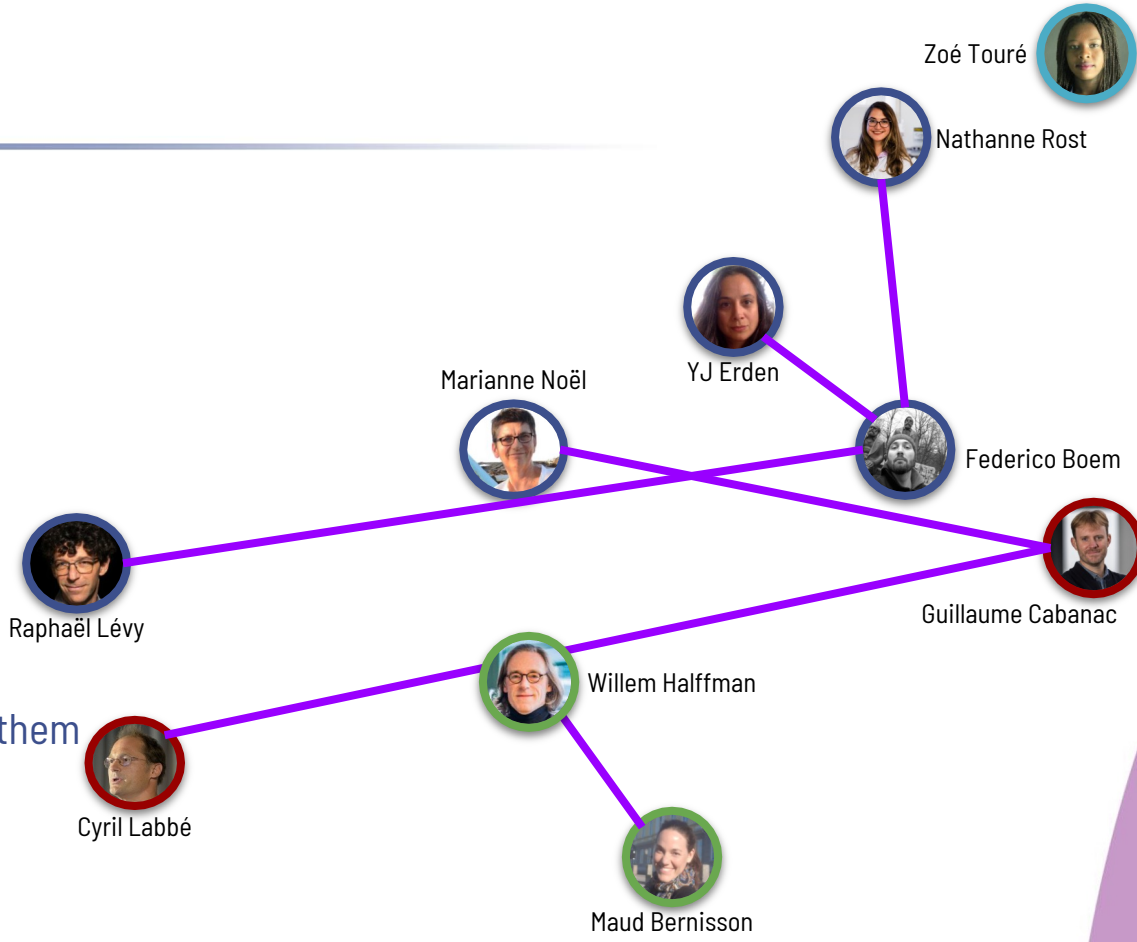
Scientific publishing

Scientific publishing



Scientific publishing

- Journals are a crucial arena for **debate**
- Journals are challenged by alternative publication formats
- How they handle the correction of errors
- **Business considerations** may prevent them from correcting errors



No over-stretched claims!

THIS IS **US**

Many other projects:

- negative results
- replications
- critical citations
- retraction notices
- shared vocabulary
- ...

This presentation is part of the project **NanoBubbles: how, when and why does science fail to correct itself?** that has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme. Grant agreement number ID: 951393

Thanks!

https://nanobubbles.hypotheses.org

@_Nano_Bubbles