# Is it somebody else's problem to correct errors (or worse) in the scientific literature?

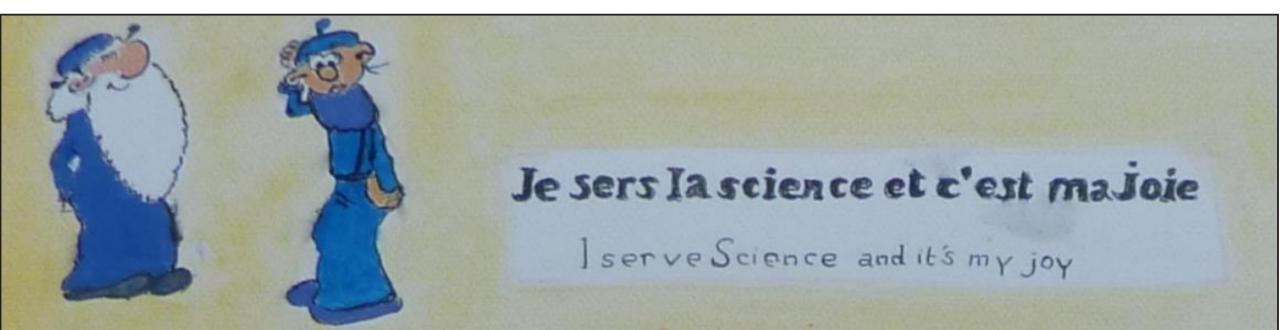
25/01/2023

raphael.levy@univ-paris13.fr

Mastodon: @raphavisses

Blog: <a href="https://raphazlab.wordpress.com/">https://raphazlab.wordpress.com/</a>

Université Sorbonne Paris Nord <u>Laboratory for Vascular Translational Science</u> UFR SMBH, 1 rue de Chablis - 93017 Bobigny







### Is it somebody else's problem to correct errors (or worse) in the scientific literature? Elisabeth Bik, Guillaume Cabanac & Cyril Labbé











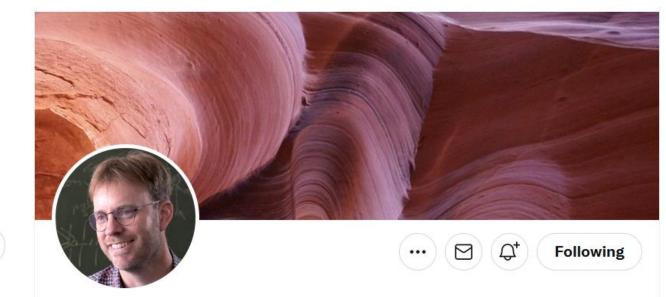
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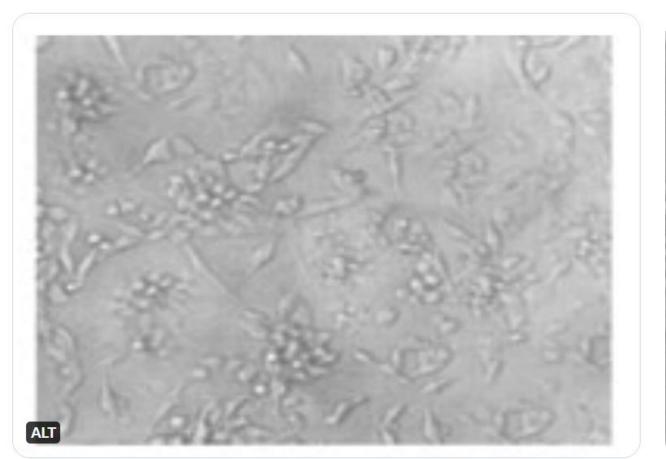
Science & Technology (i) Toulouse, France Sirit.fr/~Guillaume.Cab... O Born March 8, 1982 Joined January 2011

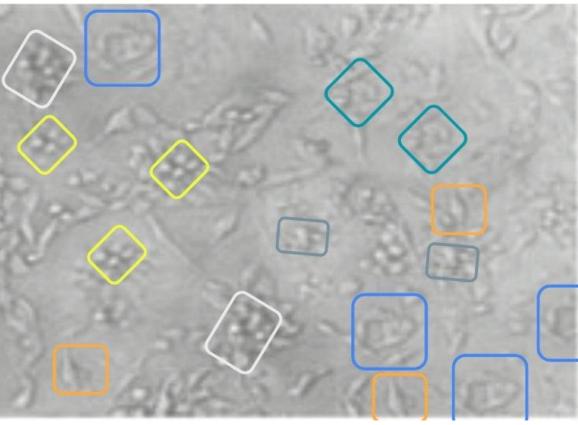
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Is it somebody else's problem to correct errors (or worse) in the scientific literature? Elisabeth Bik



Another beautiful #ImageForensics challenge for you. Just one photo, but can you spot the problem(s) here? Cited 15 times.





### Is it somebody else's problem to correct errors (or worse) in the scientific literature? Elisabeth Bik

### T Elisabeth Bik Retweeted



Elisabeth Bik @ @MicrobiomDigest · 16h

Replying to @raoult\_didier

This paper was retracted from IJID.

Can you please explain why it was retracted?

ncbi.nlm.nih.gov/pmc/articles/P...

Int J Infect Dis. 2021 Sep 29

doi: 10.1016/j.jijd.2021.05.065 [Epub ahead of print]

WITHDRAWN: Early combination therapy with hydroxychloroquine and azithromycin reduces mortality in 10,429 COVID-19 outpatients

Matthieu Million, a,b Jean-Christophe Lagier, a,b Herve Tissot-Dupont, a,b Isabelle Ravaux, a Catherine Dhiver, a Christelle Tomei, a Nadim Cassir, a,b Léa Delorme, a Sébastien Cortaredona, a,c Stéphanie Gentile, d,e Elisabeth Jouve, d Audrey Giraud-Gatineau, a,c.† Herve Chaudet, a,c.† Laurence Camoin-Jau, a,g Philippe Colson, a,b Philippe Gautret, a,c Pierre-Edouard Fournier, a,c Baptiste Maille, b,j Jean-Claude Deharo, b,j Paul Habert, j,k,j Jean-Yves Gaubert, j,k,j Alexis Jacquier, m Stéphane Honore, a,c Katell Guillon-Lorvellec, a Yolande Obadia, Philippe Parola, a,c Philippe Brouqui, a,b Didier Raoult, a,b, and IHU COVID-19 Task Force

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Abstract

Abstract

### Is it somebody else's problem to correct errors (or worse) in the scientific literature? Guillaume Cabanac & Cyril Labbé









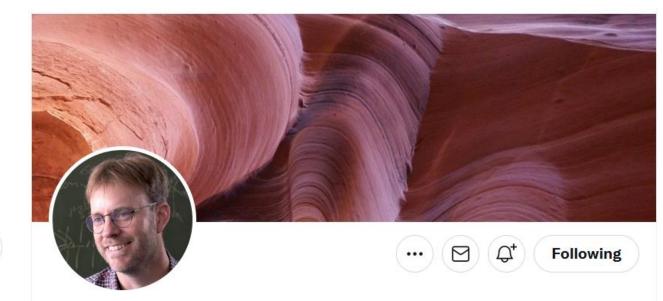
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○ The Netherlands Scienceintegritydigest.com/about/
 □ Joined October 2013

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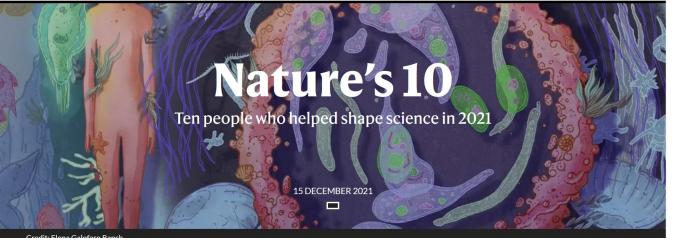
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☐ Science & Technology (i) (init.fr/~Guillaume.Cab... Q Born March 8, 1982 III Joined January 2011

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### **Guillaume Cabanac: Deception sleuth**

This computer scientist helped to uncover a new kind of fabricated paper.

By Diana Kwon

nderground creepy crawly state. Bosom malignancy.
Sun oriented force. These might sound like expressions from a work of fiction, but they are actually strange translations, pulled from the scholarly literature, of scientific terms – ant colony, breast cancer and solar energy, respectively.
Guillaume Cabanac, a computer scientist at the University of Toulouse, France, spots such bizarre phrases in academic papers

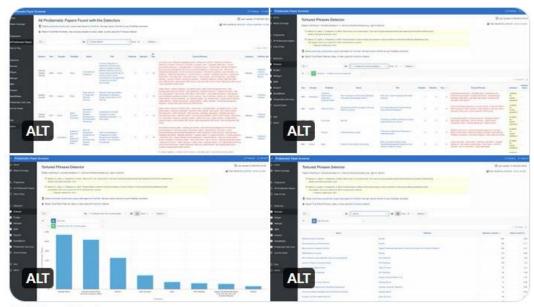
### **Today... 18,500 problematic articles flagged!**



#### Guillaume Cabanac @gcabanac · 8h

The 'Problematic Paper Screener' flags 11,478 problematic articles with 7 detectors. Cited 84k times . Your human re-assessment welcome @PubPeer for 6,779 papers with tortured phrases. Let's depollute the scientific literature pirit.fr/~Guillaume.Cab... twitter.com/gcabanac/statu

...



COPE and 7 others



### Biogenic Sustainable Nanotechnology

Trends and Progress

Micro and Nano Technologies

2022, Pages 149-184



### 7 - Fabrications and applications of

polymer-graj sustainability

Established Phrases (expected)
negatively charged
positively charged
electrostatic attraction
lactic acid
drug delivery
protein expression
surface roughness
double-stranded
functional groups
heat conductivity

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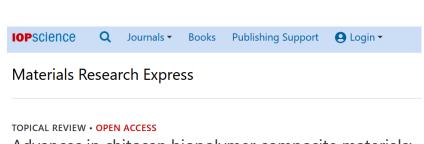
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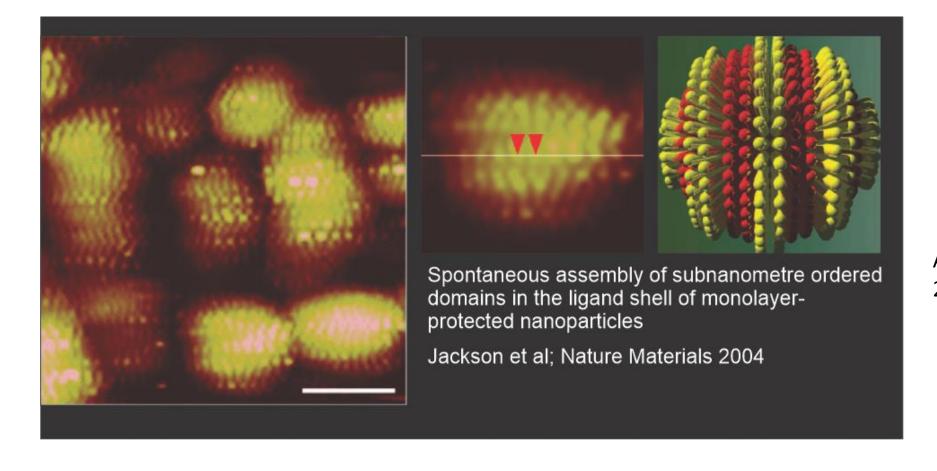
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Advances in chitosan biopolymer composite materials: from bioengineering, wastewater treatment to agricultural applications

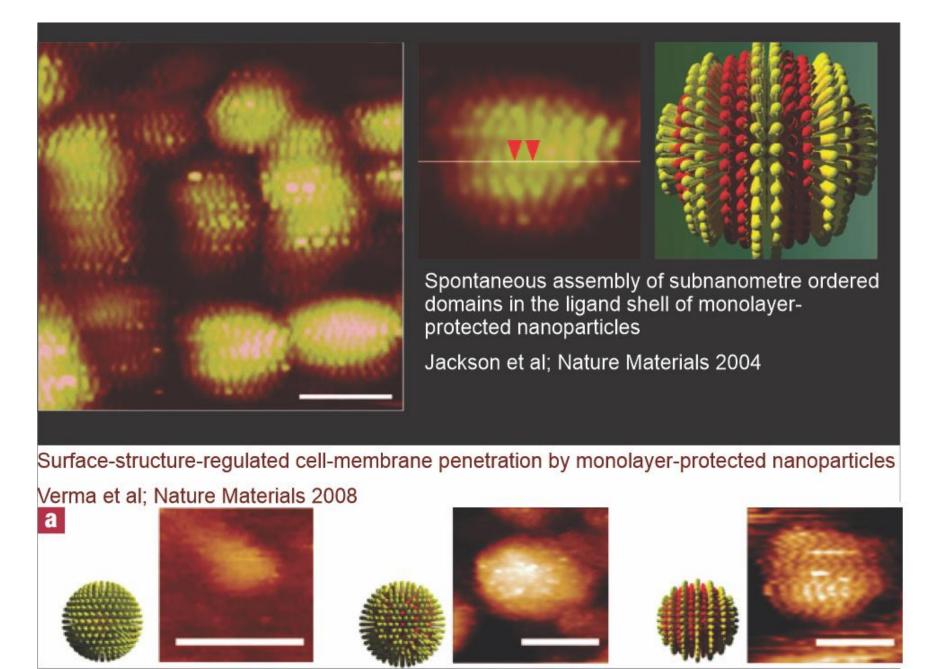
"In any case, there are still difficulties in chitosan in the acidic arrangement in the generous wastewater stream because of the end of the acidic arrangement and the poisonousness and gear misfortune caused by standard acids like HCl or H2SO4 [143]."

Is it somebody else's problem to correct errors (or worse) in the scientific literature?

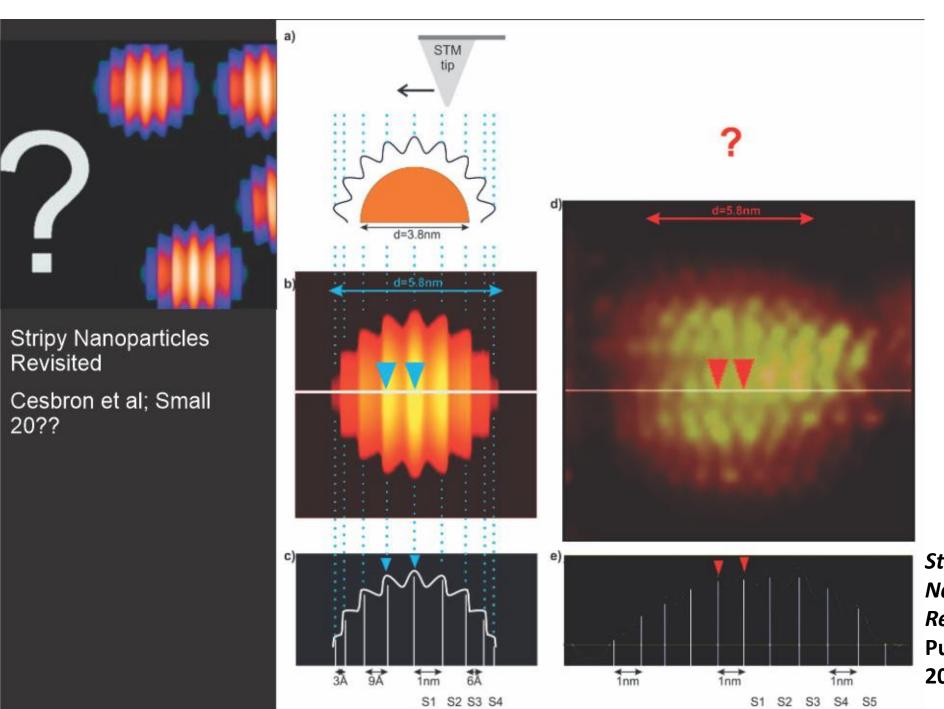


As a post-doc in 2004? Yes

Is it somebody else's problem to correct errors (or worse) in the scientific literature?



As a young PI in 2008... Stripy Nanoparticles Revisited Submitted 2009



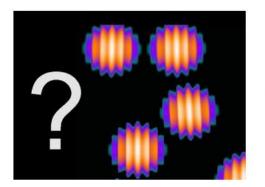
Stripy
Nanoparticles
Revisited
Published
2012



A blog: a good place to discuss scientific articles without having to wait three years for referees comments & editors'

decisions...

### 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

Is it somebody else's problem to correct errors (or worse) in the scientific literature? As a PhD student, Predrag thought it was his job (but he wasn't allowed to).



BLOG RAPHAËL

**#SCICOMM TIPS** 

STRIPY REVISITED

SPHERICAL NUCLEIC ACIDS

NANOBUBBLES

## SEVEN YEARS OF IMAGING ARTIFACTS: WHAT GIVES?



This is a guest post by Predrag Djuranovic, currently a graduate student at the MIT Department of Materials Science and Engineering.

In 2005, I was a graduate student in Francesco Stellacci's lab at MIT. My project was investigating a potential phase separation in the ligand shells on semiconductor nanoparticles. I explain below how, after months of strenuous STM imaging, I came to the conclusion that the "ripples" and "hexagonal packing", were nothing but common scanning artifacts, called feedback oscillations or "ringing".

When I started to have doubts, I performed simple control experiments, i.e. STM imaging on *bare* conducting substrates (clean substrates without any ligands). I selected two conductive substrates: gold foil (surface roughness comparable to the size of gold nanoparticles) and ITO

Search ...

My Tweets

### COMMENTS

Down the rabbit hole... on

What's a limit of detection an...

Down the rabbit hole... on

Guest Post: Sensing by Surface...

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#### MATERIALS SCIE





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HOME NEWS

23 JANUARY 2014 I BY PAUL JUMP



« Psychiatrists From Another Dimension (Part 2) Medical Journal Apologizes "For The Distress Caused" By A Paper »

### Postpublication "Cyberbullying" and the Professional Self

By Neuroskeptic | January 27, 2014 4:47 pm



REWIRING NATUR

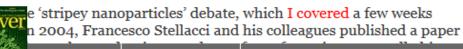








An article in *Science* has been getting a lot of attention this week: Nano-Imaging Feud Sets Online Sites Sizzling



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### Stellacci 'stripy nanoparticle' dispute heats up

Analysis critical of professor's discovery claim is published on arXiv







ABOUT

WEBINARS

/E NANOPARTICLES LOST THEIR STRIPES?

s lost their stripes?

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GET IN TOUCH

### ARE FLAWS IN PEER REVIEW SOMEONE ELSE'S PROBLEM?

By Philip Moriarty On April 8, 2013

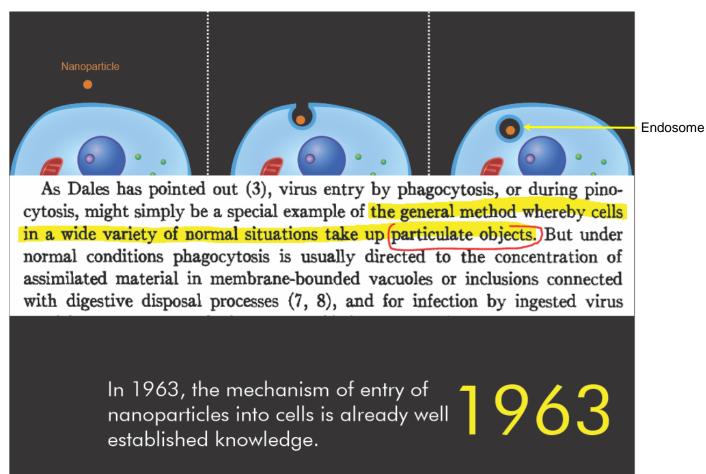
L ARTICLES

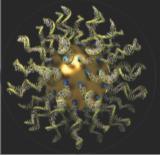


## In the stripy controversy, did science "self-correct"?

### 2011-... Another scientific controversy

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





### SPHERICAL NUCLEIC ACIDS

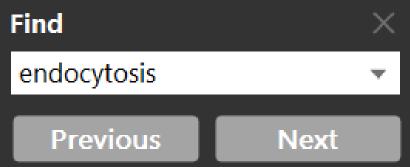
### Oligonucleotide-Modified Gold Nanoparticles for Intracellular Gene Regulation

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

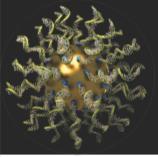
We describe the use of gold nanoparticle-oligonucleotide complexes as intracellul regulation agents for the control of protein expression in cells. These oligonucleotide-modified nanoparticles have affinity constants for complementary nucleic acids that are higher than their unmodified oligonucleotide 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.

Tucleic 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



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.



### SPHERICAL NUCLEIC ACIDS

### Olinonucleotide-Modified Gold

the design of two sets of antisense Au NPs, with

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nanoparticles, we demonstrated a tunable gene knockdown.

stants and oligonucleotide loading on the performance of such particles in the context of EGFP expression.

Tucleic acid-based methods for controlling esized that this particular type of Au NP

### What happens after the 2006 paper?

- 1. Promises. Lots of promises. Big ones.
- 2. Many more publications that still fail to answer basic questions about the technology.
- 3. IP, Aurasense LCC, Aurasense Therapeutics, Exicure, raising millions of dollars of public and private funds.
- 4. Commercialisation (SmartFlares) and clinical trials.
- 5. Prizes. Lots of prizes.

### 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. ... broadspectrum antibiotics ... traumatic brain injury. ... could positively impact tens of millions of people" "Live cell RNA detection is now possible using inert nanoparticle technology to

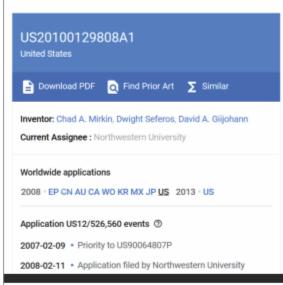
2006-2009

2013-2015

specifically detect native mRNA"

# IP, Aurasense LCC, Aurasense Therapeutics, Exicure, raising millions of dollars of public and private funds.

Particles for detecting intracellular targets



www.prnewswire.com > news-releases > aurasense-thera... \*

#### AuraSense Therapeutics Completes \$13.6 Million Series C ...

17 Jun 2014 - PRNewswire/ -- AuraSense Therapeutics, a Chicago-based biopharmaceutical company commercializing spherical nucleic acid (SNA™) ...

www.americaninno.com > ChicagoInno \*

#### AuraSense Raises \$18 Million Series C - AmericanInno

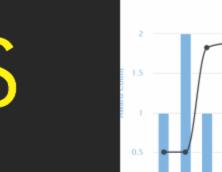
6 Feb 2015 - Biotech Startup AuraSense, Backed by Bill Gates and Google's Eric ... The company has raised more than \$27 million since it launched in 2009 ...

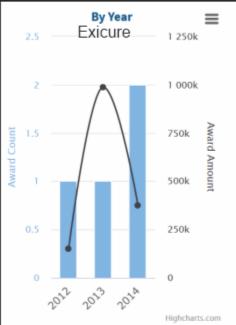
www.fiercebiotech.com > biotech > exicure-bags-cash-a... \*

#### Exicure raises \$11.2M in cash as psoriasis, I-O assets near ...

6 Nov 2017 - China's Luye Pharma led the \$11.2 million financing with support from ... That work led to the creation of AuraSense Therapeutics, which in ...

Department of Defense Department of Health and Human Services





www.genengnews.com > ... > Gene Therapy \*

### Purdue Pharma, Exicure Launch Up-to-\$790M+ SNA

Aurasense

12 Dec 2016 - Agreement gives **Purdue** Pharma options to develop **Exicure** AST-005, three additional targets for psoriasis and other ...

Biotech

Backed by Bill Gates, low-profile Exicure steps into spotlight with a \$42M R&D gamble

### Prizes. Lots of prizes.





Professor Chad Mirkin Northwestern University

Awarded for his development of spherical nucleic acids and new nanotechnology-based tools in biomedicine and materials science







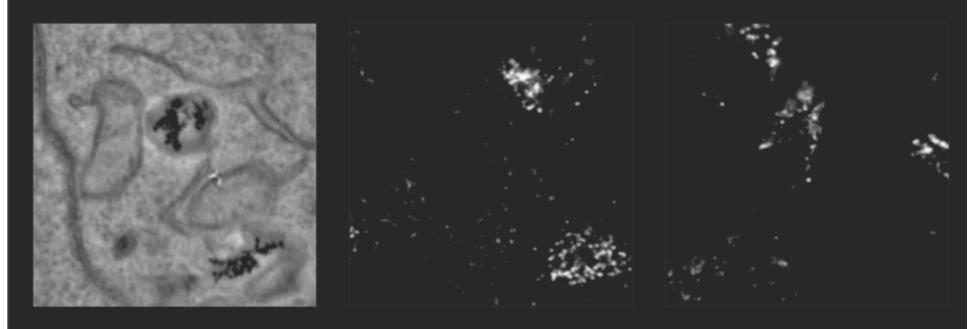
Chad Mirkin is the Director of the International Institute for Nanotechnology and the George B Rathmann Professor of Chemistry, Chemical and Biological Engineering, Biomedical Engineering, Materials Science and Engineering, and Medicine at Northwestern University. He is a chemist and a world-renowned nanoscience expert, who is known for his discovery and development of spherical nucleic acids (SNAs) and SNA-based biodetection and therapeutic schemes, the invention of Dip-Pen Nanolithography and related cantilever-free nanopatterning techniques, On-Wire and Co-Axial Lithography, and contributions to supramolecular chemistry and nanoparticle synthesis. He has authored over 600 manuscripts and over 900 patent applications worldwide (252 issued), and he is the founder of multiple companies, including Nanosphere, AuraSense, and AuraSense Therapeutics.

Mirkin has been recognized with over 100 national and international awards including, the ACS Nano Lectureship Award for the Americas (2014), the Linus Pauling Medal (2013), the Walston Chubb Award for Innovation (2013), the ACS Award for Creative Invention (2012) and the \$500,000 Lemelson-MIT Prize (2009). He is a Member of the President's Council of Advisors on Science & Technology (Obama Administration), and he is the only chemist to be elected to





## Spherical nucleic acids do not detect mRNA; case study #1 (Liverpool, UK)



"Our results indicate that SNAs [...] cannot be used to report on mRNA levels in live cells. [...] Once taken up we consistently observe a punctate distribution indicating retention within vesicular compartments. This was confirmed by electron microscopy and photothermal imaging. Furthermore, the controls (the scrambled and constitutively-fluorescent uptake control) showed similar levels of fluorescence."

## Spherical nucleic acids do not detect mRNA; case study #2

(former manager of cell-based assays at EMD Millipore)

Is it somebody else's problem to correct errors (or worse) in the scientific literature?

I spent 8 months doing applications development on Smartflare and found zero evidence that it recognizes the targeted mRNAs. [...] I was hoping that they would take it off the market but they keep going due to the few publications showing positive results.



Luke Armstrong

It wasn't Luke's job.

## Spherical nucleic acids do not detect mRNA; case study #4 (Kraków, Poland)

Is it somebody else's problem to correct errors (or worse) in the scientific literature?

We report a total lack of correlation between fluorescence intensities of SmartFlare probes and the levels of corresponding RNAs assessed by RTqPCR. To ensure strong differences in the levels of analysed RNAs, their expression was modified via: (i) HMOX1-knockdown generated by CRISPR-



For Maria & Joanna, it was important to do it.

Cas9 genome editing, (ii) hemin-mediated stimulation of HMOX1- and IL1β-mediated stimulation of IL6- and PTGS2 transcription, (iii) lentiviral vector-mediated Nrg1 overexpression.

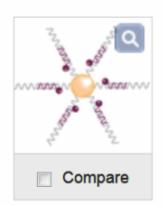
Article Open Access | Published: 15 September 2017

SmartFlares fail to reflect their target transcripts levels

Maria Czarnek & Joanna Bereta ⊠

2017

## Spherical nucleic acids do not detect mRNA; case study #6



### SF-913 | SOX2; Human, Cyanine5 RNA Detection Probe | SmartFlare

With SmartFlare™ RNA Detection probes, you can detect RNA in live cells. With an overnight incubation of SOX2; Human, Cyanine5 RNA Detection Probe you can detect the presence of SOX2 within your cells More >>

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Catalogue Number	Availability	Packaging	Qty/Pack	Price	Quantity	
SF-913	Discontinued		250 reactions	_	_	Add To Favorites



"In science, we need to share the bad news as well as the good news. In your introduction you mentioned four clinical trials. One of them has reported. It showed no efficacy and Purdue Pharma which was supposed to develop the drug decided not to pursue further. You also said that 1600 forms of NanoFlares were commercially available. This is not true anymore as the distributor has pulled the product because it does not work. Finally, I have a question: what is the percentage of nanoparticles that escape the endosome.."



Home / News & Opinion

### RNA Detection Tool Debate Flares Up at ACS Meeting

Researchers have flagged several issues with so-called SmartFlares over the years, and it's still unclear why they don't appear to work under certain circumstances.

Sep 5, 2018 KATARINA ZIMMER



97







35

A recent American Chemical Society Meeting in Boston last month, an ongoing disagreement over a particular tool for detecting and visualizing RNA in living cells, called SmartFlares, reached a fever pitch. At one point, Chad Mirkin, a chemist at Northwestern University who helped develop the technique, called outspoken critic Raphael Levy, a biochemist at the University of Liverpool, a "scientific terrorist."

"SNAs will dramatically expand the field of nucleic acid medicines and allow Exicure to develop drugs that impact diseases localized in tissues conventional nucleic acids won't enter, including the skin, eye, lung, ear"





"on November 9, 2021, the Audit Committee of our Board of Directors was notified of a claim made by a former Company senior researcher regarding alleged improprieties that researcher claims to have committed with respect to our XCUR-FXN preclinical program for the treatment of Friedreich's ataxia."

## In the spherical nucleic acid controversy, did science "self-correct"?

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

2006

2013

Commercialization of SNAs (SmartFlares) to detect mRNAs

2014

TheScientist TOP 10 Innovations 2013

2015

Publication (by us) of *The spherical nucleic acids mRNA* detection paradox; Confirmation from an ex-application development specialist that the SmartFlares do not work

2016

2017

2018

Publication (by Czarnek and Bereta) of *SmartFlares fail to reflect* their target transcripts levels = Catalogue nation from Availability another group that the SmartF SF-913

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





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**SCIENCES** 

# Une affaire d'inconduite scientifique agite un laboratoire de recherche en chimie

Publications trafiquées ou simples erreurs ? Une directrice de recherche d'une unité mixte CNRS-Sorbonne Paris Nord attend le verdict de la procédure disciplinaire. « Le Monde » a enquêté sur cette affaire, qui met aussi à l'épreuve les instances scientifiques.

Par David Larousserie

Publiá hiar à 15h33 . A Lactura 6 min

## Context: the discovery

The advert for a lecturer position mentioned in the previous slide was eventually advertised. As I was the contact person for the teaching, a potential candidate asked for a meeting. This person was a research and teaching associate (ATER) in CSPBAT. I accepted to meet her. Before the meeting, I had a quick look at her publications and I found this in the first article I opened:

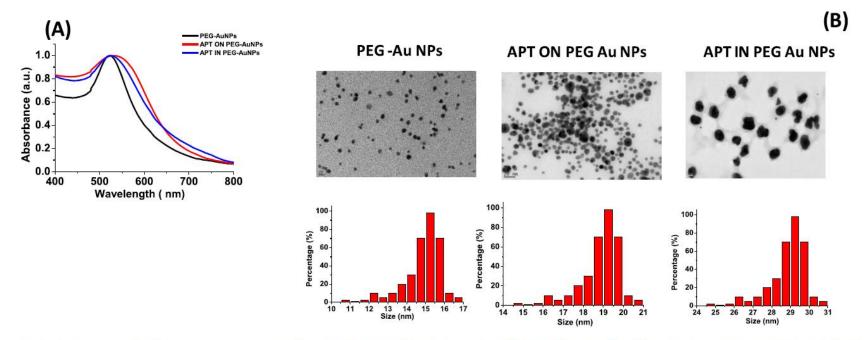
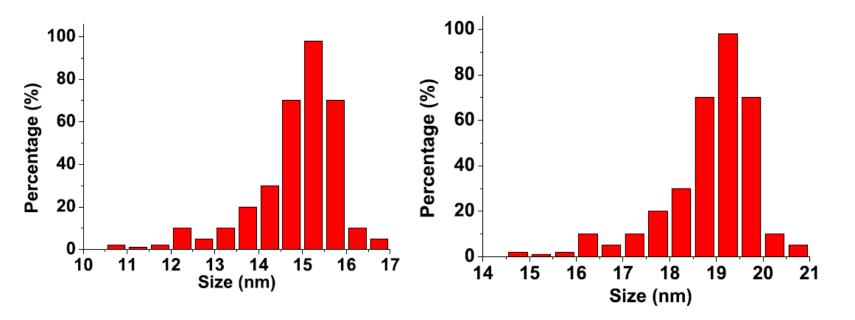
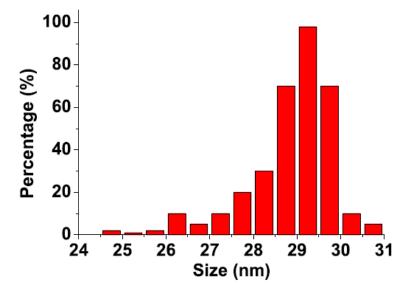
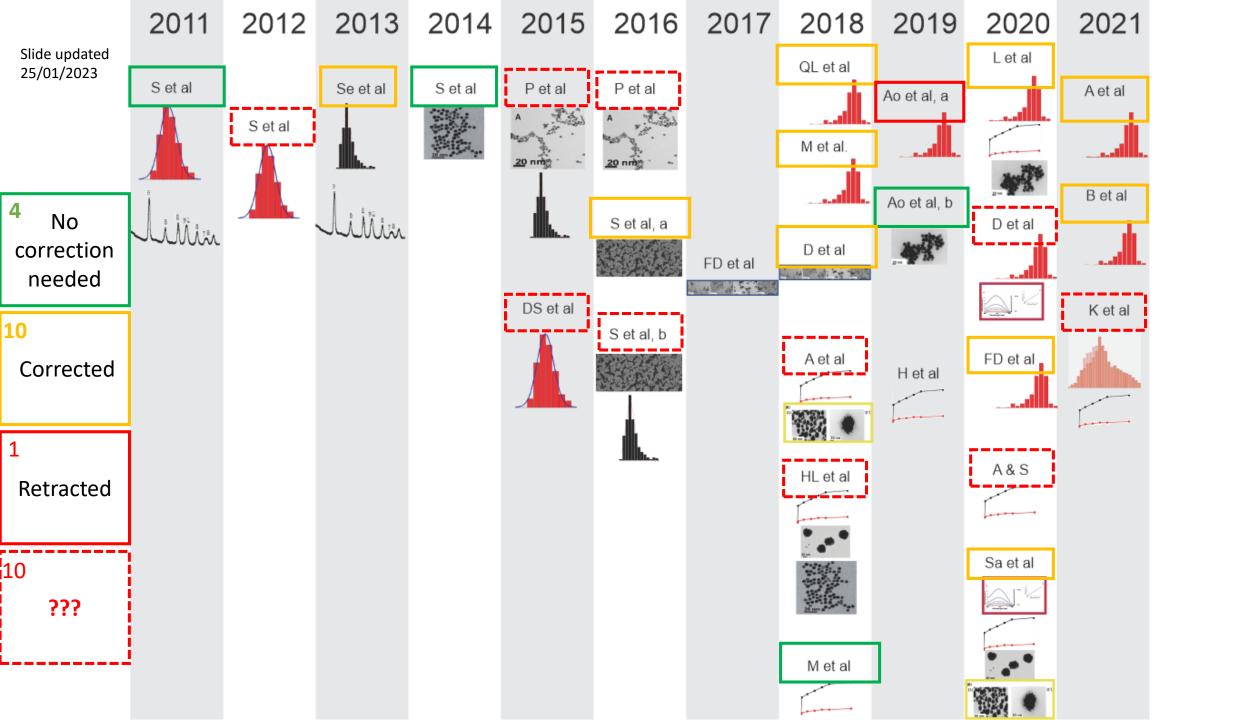


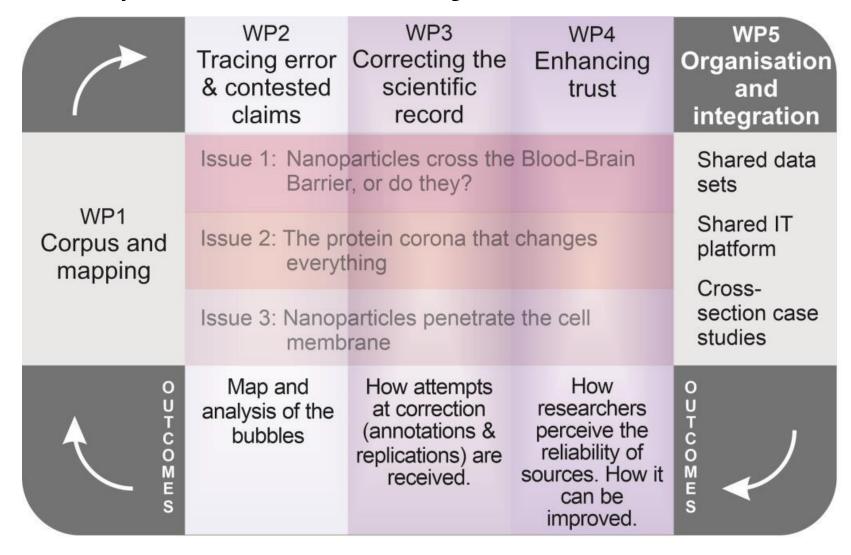
Figure 1. (A) Normalized UV—vis absorption of APT ON PEG-AuNPs (red line), APT IN PEG-AuNPs (blue line), and PEG-AuNPs (black line); (B) TEM images and size distribution of PEG-AuNPs (on the left) before and after functionalization of APT by carbodiimide chemistry (APT ON PEG-AuNPs in the middle) and chelation reaction (APT IN PEG-AuNPs on the right). Scale bars: 20 nm.





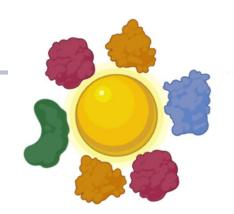


# ERC Synergy project NanoBubbles: How, when and why does science fail to correct itself?



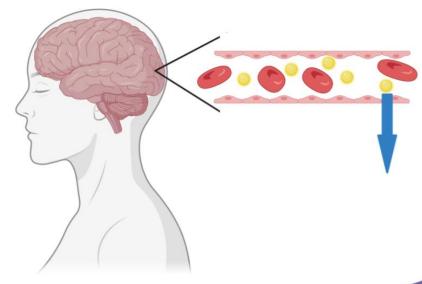
### 3 bubbles

The protein corona that changes everything



Nanoparticles penetrate the cell membrane





### Multidisciplinary perspectives on errors and correction of science

#### Science and Technology Studies

- Tacit knowledge
  - laboratories & conferences
  - ethnographic studies
- Explicit knowledge
  - journals & textbooks
  - historical, literary & quantitative/digital methods

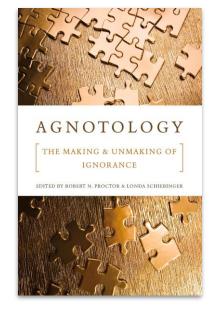
#### Sociology of error

science as a social and human activity

redirecting the focus from individual misconduct or sloppiness to collective processity Press,

#### Sociology of promises or expectations

- when expectations become performative
- how promises and hypes end, or are adjusted and corrected?



Proctor & Schiebinger. Agnotology: The Making and Unmaking of Ignorance.

Peak of Inflated Expectations

Plateau of Productivity

Slope of Enlightenment

Trough of Disillusionment

Technology Trigger

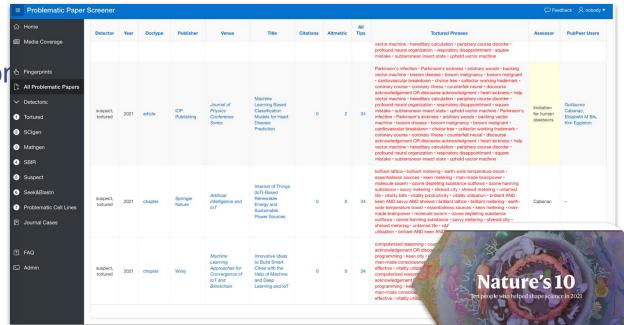
TIME

### Digital methods: scientometrics and text analysis

- large corpora
- automatic screening of scientific publication
  - 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/



Image: Qwedgeonline 'Tight Rope' URL

No over-stretched claims!

THIS IS US

Node color = PI official attachment

Edge = shared research topic

Post-publication peer review Correction practices Claims and hype Conferences Replication ...









European Research Council
Established by the European Commission



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



