What can journalists do to uncover scientific misconduct?

UK Conference of Science Journalists,
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Peter Aldhous,
San Francisco Bureau Chief
peter@peteraldhous.com

NewScientist

(With special thanks to Eugenie Samuel Reich)

Minnesota Mystery

Pluripotency of mesenchymal ste
derived from adult marrow

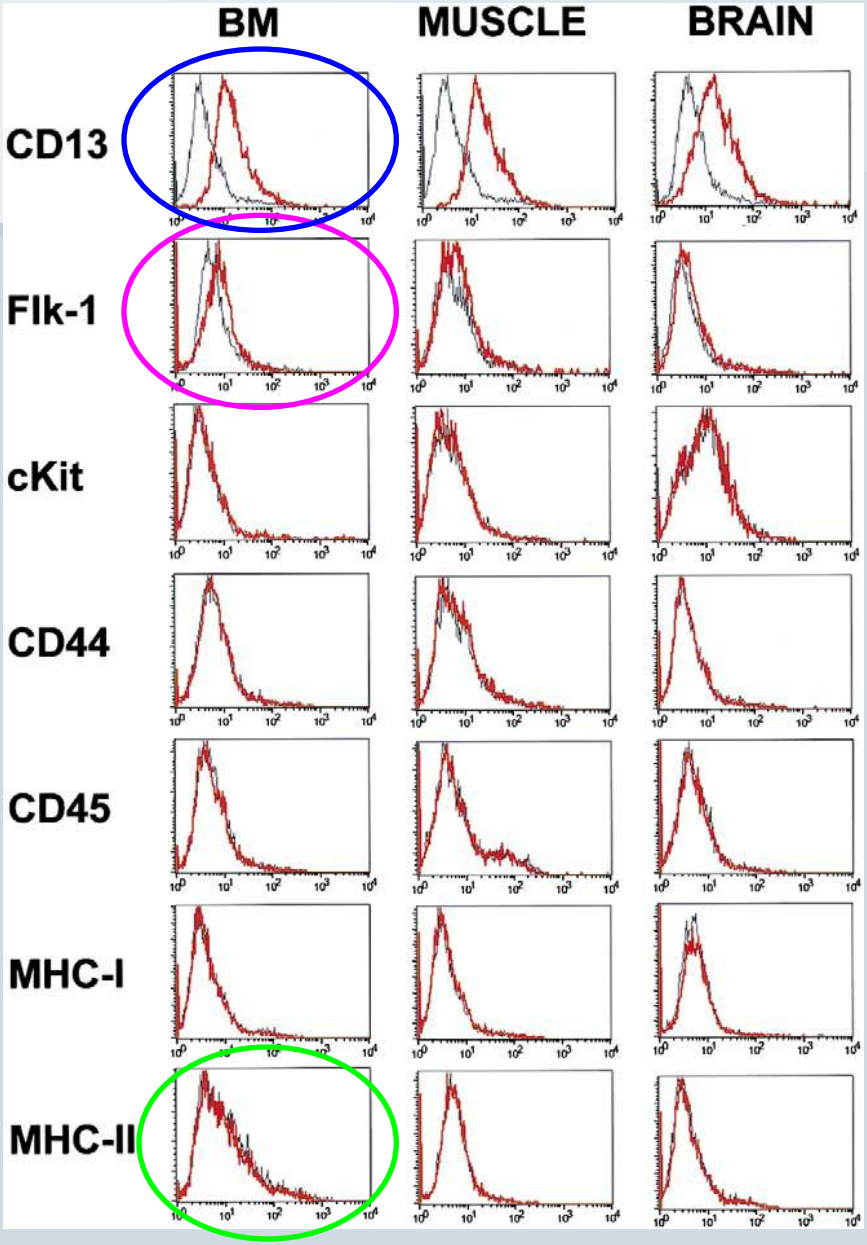
Yuehua Jiang*†, Balkrishna N. Jahagirdar*†‡, R. Lee Reinhardt§, Robert E. Schwartz*, C. Dirk Keene||, Xilma R. Ortiz-
Morayma Reyes*, Todd Lenvik*, Troy Lund*, Mark Blackstad*, Jingbo Du*, Sara Aldrich*, Aaron Lisberg*, Walter C. Lo
David A. Largaespada¶ & Catherine M. Verfaillie*‡

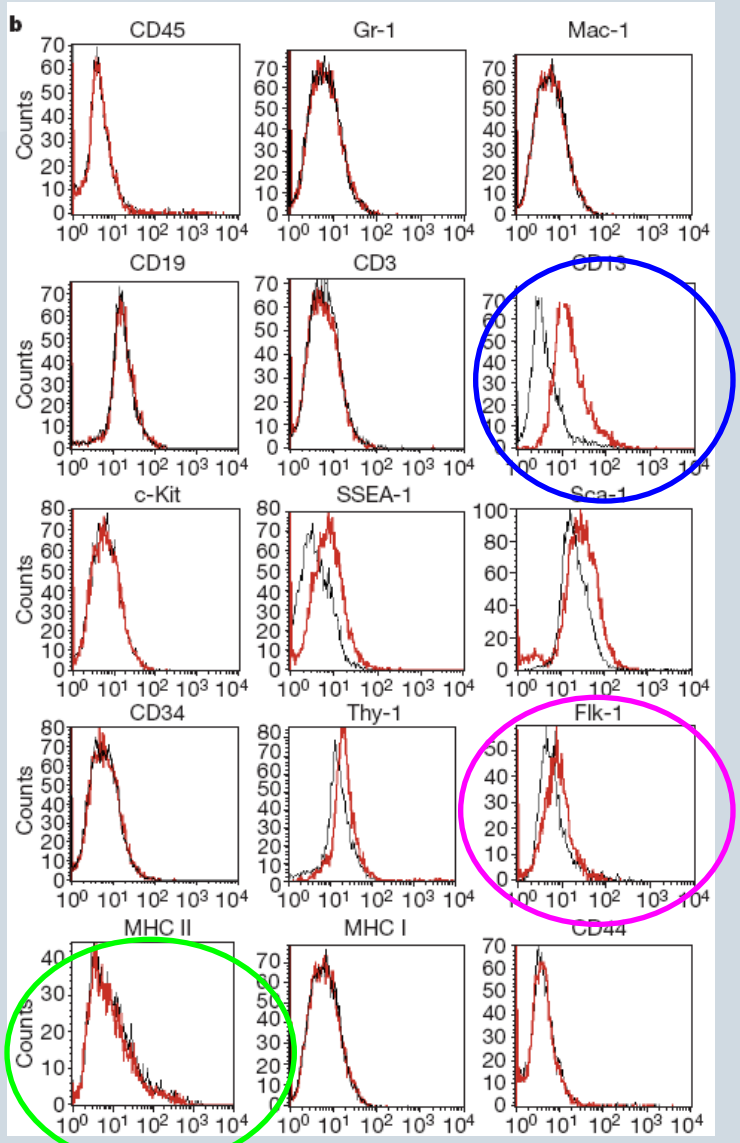
* Stem Cell Institute, ‡ Division of Hematology, Oncology and Transplantation, Department of Medicine, § Department of Microbiology, Cente
Immunology, || Department of Neurosurgery, and ¶ Department of Genetics, Cell Biology and Development, University of Minnesota Medical S
Minnesota 55455, USA
† These authors contributed equally to this work

We report here that cells co-purifying with mesenchymal stem cells—termed here multipotent adult progenitor cel
differentiate, at the single cell level, not only into mesenchymal cells, but also cells with visceral mesoderm, neuro
endoderm characteristics *in vitro*. When injected into an early blastocyst, single MAPCs contribute to most, if not all
types. On transplantation into a non-irradiated host, MAPCs engraft and differentiate to the haematopoietic lineage,
the epithelium of liver, lung and gut. Engraftment in the haematopoietic system as well as the gastrointestinal tract
when MAPCs are transplanted in a minimally irradiated host. As MAPCs proliferate extensively without obvious senesc
of differentiation potential, they may be an ideal cell source for therapy of inherited or degenerative diseases.

Catherine Verfaillie

What did we find?





This week

'Flawed' stem cell data withdrawn

PETER ALDHOUS
AND EUGENIE SAMUEL REICH

IT IS one of the best-known stem cell papers in the past five years, describing adult cells that seemed to hold the same promise as embryonic stem cells. Now, following inquiries by *New Scientist*, some of the data contained within the papers is being questioned.

In 2002, a team led by Catherine Verfaillie of the University of Minnesota, Minneapolis, described "multipotent adult progenitor cells" or MAPCs, isolated from the bone marrow of rodents (*Nature*, vol 418, p 41). These cells seemed able to develop into most of the body's tissues. Previously, only embryonic stem cells (ESCs) had proved so versatile, and the work was seized upon by opponents of ESC research, who claimed it showed similarly versatile cells could be harvested without destroying human embryos.

The results proved hard to repeat, and for more than six months from late 2003 even Verfaillie's own group was unable to isolate the cells. When *New Scientist* looked more closely, we found that six plots from the *Nature* paper and its supplementary information were duplicated in a second paper, published at about the same time in *Experimental Hematology* (vol 30, p 896), even though they were supposed to refer to different cells, taken from different mice. The plots described "marker" molecules on the surface of the cells, supposedly characteristic of MAPCs.

After *New Scientist* questioned the results, a panel of experts reviewed the data. Verfaillie, now at the Catholic University of Leuven (KUL) in Belgium, has since written to the two journals informing them of problems with data within the two papers, stating: "It was [the experts'] consensus opinion that the data were flawed and should not be relied upon as accurate representation of MAPC marker profiles."

The flaws she refers to do not relate to the duplications in the papers, and Verfaillie stands by the claim that MAPCs can develop into most of the body's tissues, arguing that later papers have described reliable methods for identifying them. In her most recent paper, Verfaillie and Irving Weissman, a stem cell biologist at Stanford University in California, showed that MAPCs can give rise to all the cell types found in blood (*New Scientist*, 27 January, p 17), but it is still unclear whether MAPCs are as versatile as she claimed in the original *Nature* paper.

Many researchers are unable even to isolate them. "They're very testy cells," observes Amy Wagers of Harvard University, who spent a week in Verfaillie's lab trying in vain to learn the technique.

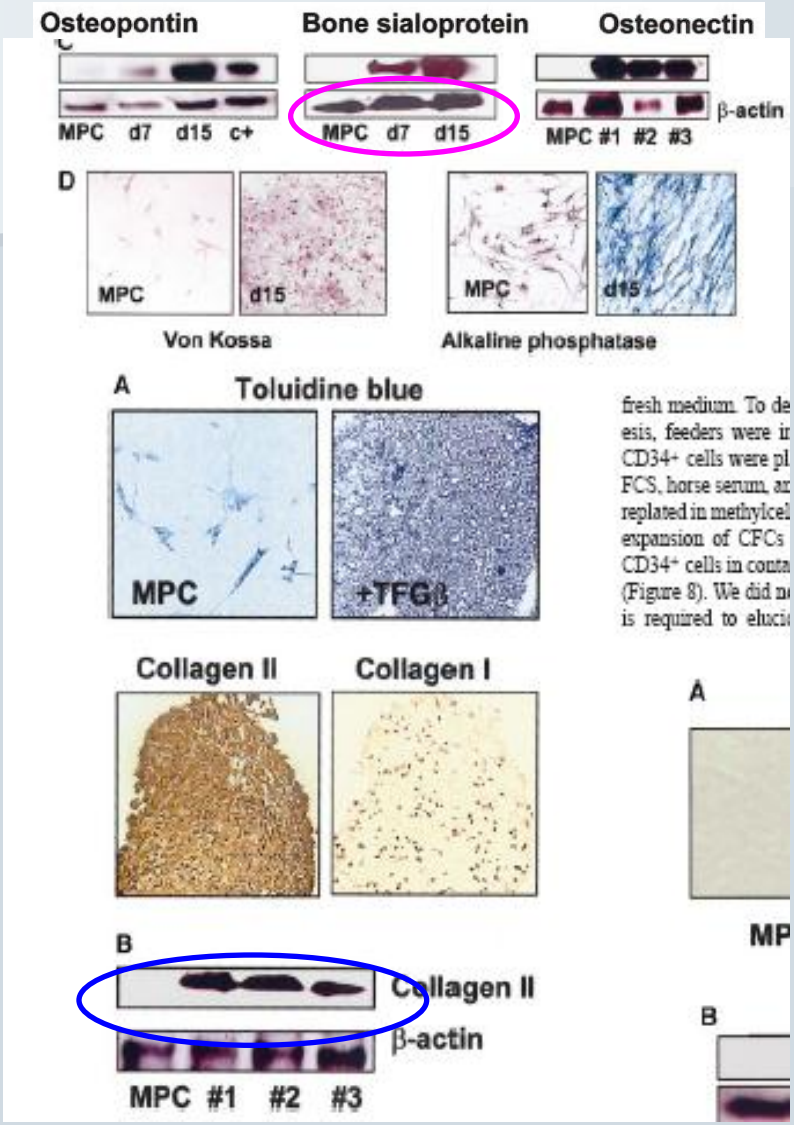
"The paper describes 'multipotent' cells that seemed able to develop into most of the body's tissues"

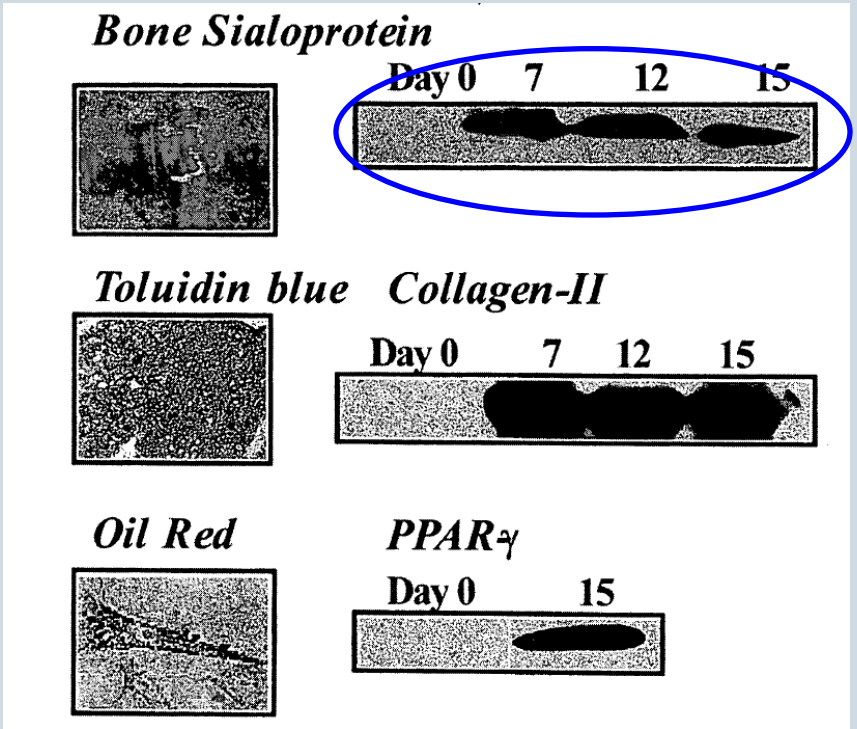
The problems with the marker profiles may help explain these difficulties. "If I had been following this recipe since 2002, I'd be extremely angry," says Jeanne Loring, a stem cell biologist at the Burnham Institute for Medical Research in La Jolla, California.

NewScientist

* Two papers corrected

Lightning strikes twice





We publish…and wait

This week

Fresh questions on stem cell findings

The discovery of more duplicated data is again casting a shadow over "versatile" adult stem cells

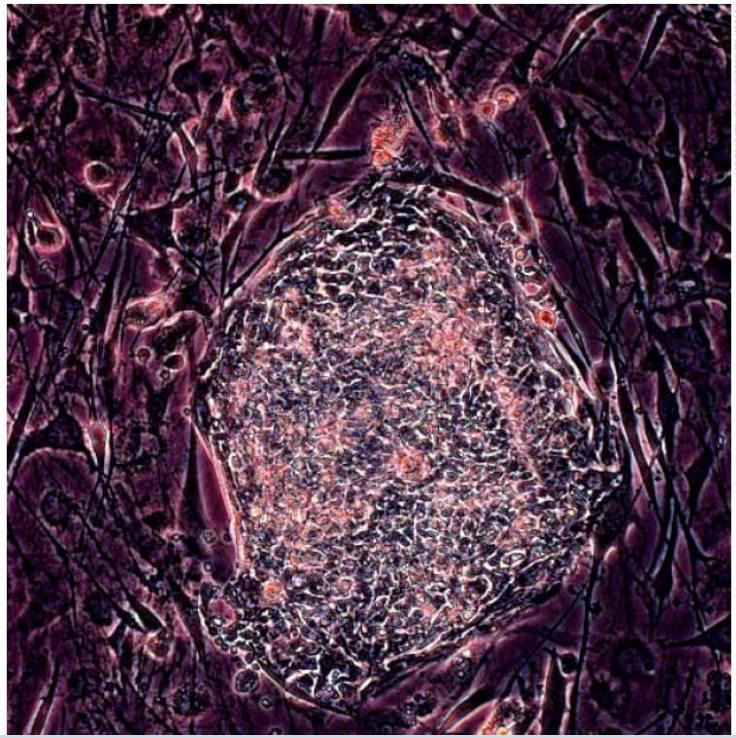
PETER ALDHOUS
AND EUGENIE SAMUEL REICH

FRESH questions surround some of the highest-profile research on adult stem cells. For the second time, *New Scientist* has discovered apparently duplicated data being used to describe results from different experiments in work published by a group of scientists at the University of Minnesota, Minneapolis.

The research relates to a particular type of adult stem cell

Given these difficulties, *New Scientist* decided more than a year ago to take a close look at the *Nature* paper. We found that some of the images within it also appeared in a second paper that was published at about the same time, where they were supposed to relate to a different experiment (see "Flaws and duplications").

Now *New Scientist* has examined a US patent (number 7015037) granted in 2006 that covers the isolation and use of MAPCs. The patent is exclusively



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NewScientist

Verdict: misconduct

Morayma Reyes

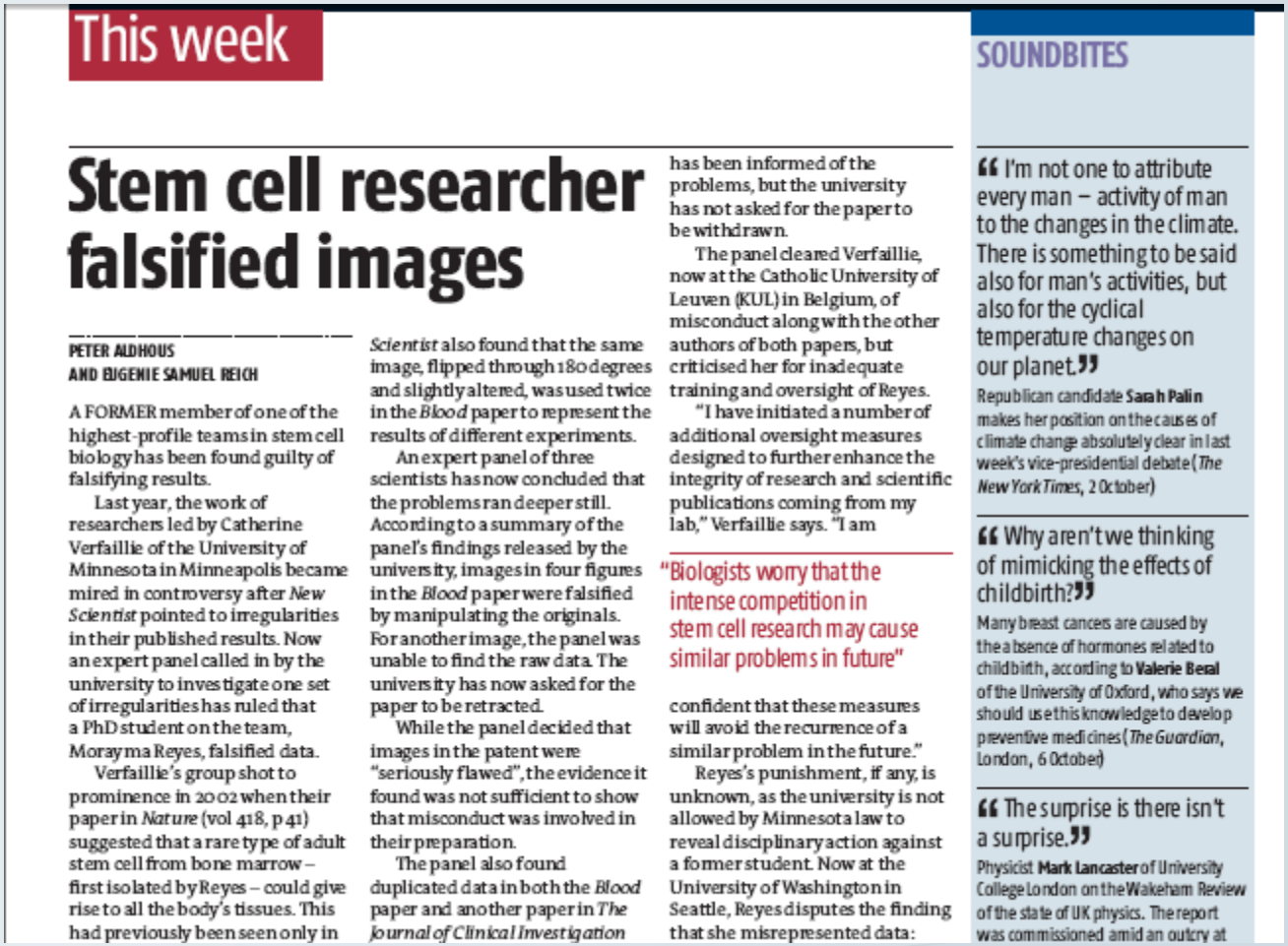
"In four figures in the *Blood* paper, the panel concluded that aspects of the figures were altered in such a way that the manipulation misrepresented experimental data and sufficiently altered the original research record to constitute falsification under federal regulations and University policy.

"Manipulations identified by the panel included: elimination of bands on blots, altered orientation of bands, introduction of lanes not included in the original figure, and covering objects or image density in certain lanes."

University of Minnesota statement,
October 2008

* One paper retracted; one more corrected

Which we report



This week

Stem cell researcher falsified images

PETER ALDHOUS
AND EUGENIE SAMUEL REICH

A FORMER member of one of the highest-profile teams in stem cell biology has been found guilty of falsifying results.

Last year, the work of researchers led by Catherine Verfaillie of the University of Minnesota in Minneapolis became mired in controversy after *New Scientist* pointed to irregularities in their published results. Now an expert panel called in by the university to investigate one set of irregularities has ruled that a PhD student on the team, Morayma Reyes, falsified data.

Verfaillie's group shot to prominence in 2002 when their paper in *Nature* (vol 418, p 41) suggested that a rare type of adult stem cell from bone marrow – first isolated by Reyes – could give rise to all the body's tissues. This had previously been seen only in

Scientist also found that the same image, flipped through 180 degrees and slightly altered, was used twice in the *Blood* paper to represent the results of different experiments.

An expert panel of three scientists has now concluded that the problems ran deeper still. According to a summary of the panel's findings released by the university, images in four figures in the *Blood* paper were falsified by manipulating the originals. For another image, the panel was unable to find the raw data. The university has now asked for the paper to be retracted.

While the panel decided that images in the patent were "seriously flawed", the evidence it found was not sufficient to show that misconduct was involved in their preparation.

The panel also found duplicated data in both the *Blood* paper and another paper in *The Journal of Clinical Investigation* has been informed of the problems, but the university has not asked for the paper to be withdrawn.

The panel cleared Verfaillie, now at the Catholic University of Leuven (KUL) in Belgium, of misconduct along with the other authors of both papers, but criticised her for inadequate training and oversight of Reyes.

"I have initiated a number of additional oversight measures designed to further enhance the integrity of research and scientific publications coming from my lab," Verfaillie says. "I am confident that these measures will avoid the recurrence of a similar problem in the future."

"Biologists worry that the intense competition in stem cell research may cause similar problems in future"

Reyes's punishment, if any, is unknown, as the university is not allowed by Minnesota law to reveal disciplinary action against a former student. Now at the University of Washington in Seattle, Reyes disputes the finding that she misrepresented data:

SOUNDBITES

"I'm not one to attribute every man – activity of man to the changes in the climate. There is something to be said also for man's activities, but also for the cyclical temperature changes on our planet."

Republican candidate **Sarah Palin** makes her position on the causes of climate change absolutely clear in last week's vice-presidential debate (*The New York Times*, 2 October)

"Why aren't we thinking of mimicking the effects of childbirth?"

Many breast cancers are caused by the absence of hormones related to childbirth, according to **Valerie Beral** of the University of Oxford, who says we should use this knowledge to develop preventive medicines (*The Guardian*, London, 6 October)

"The surprise is there isn't a surprise."

Physicist **Mark Lancaster** of University College London on the Wakeham Review of the state of UK physics. The report was commissioned amid an outcry at

NewScientist

The story continues

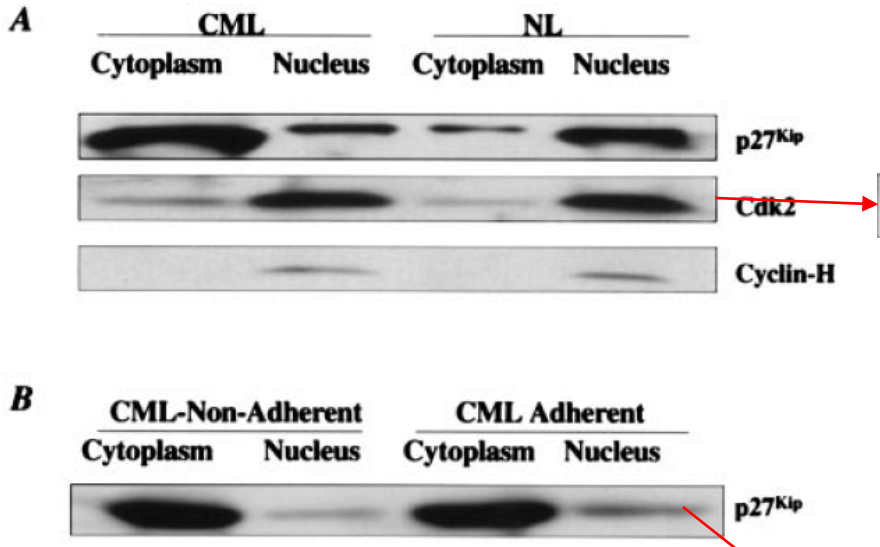
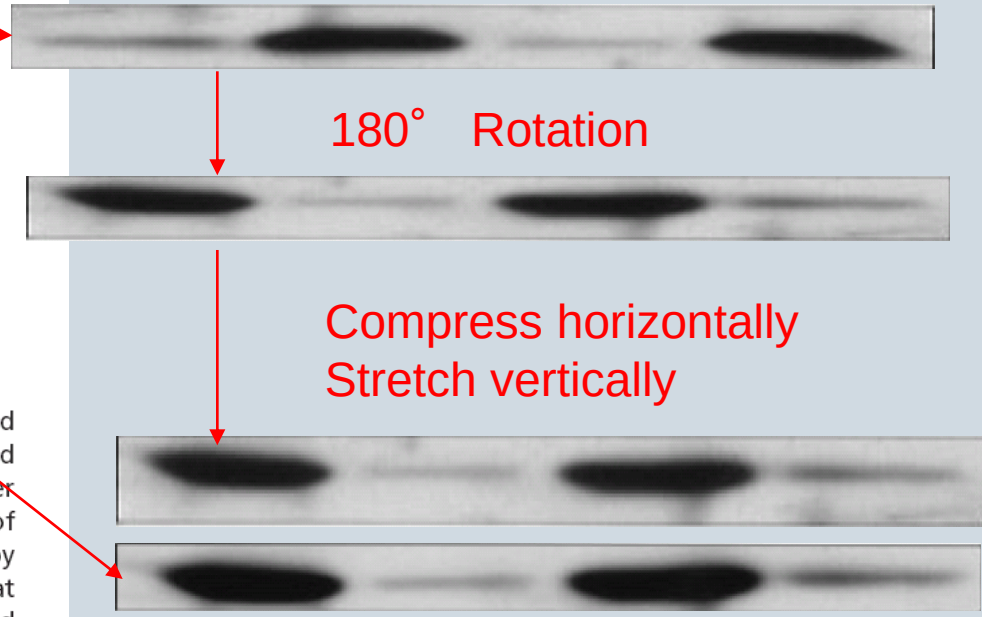
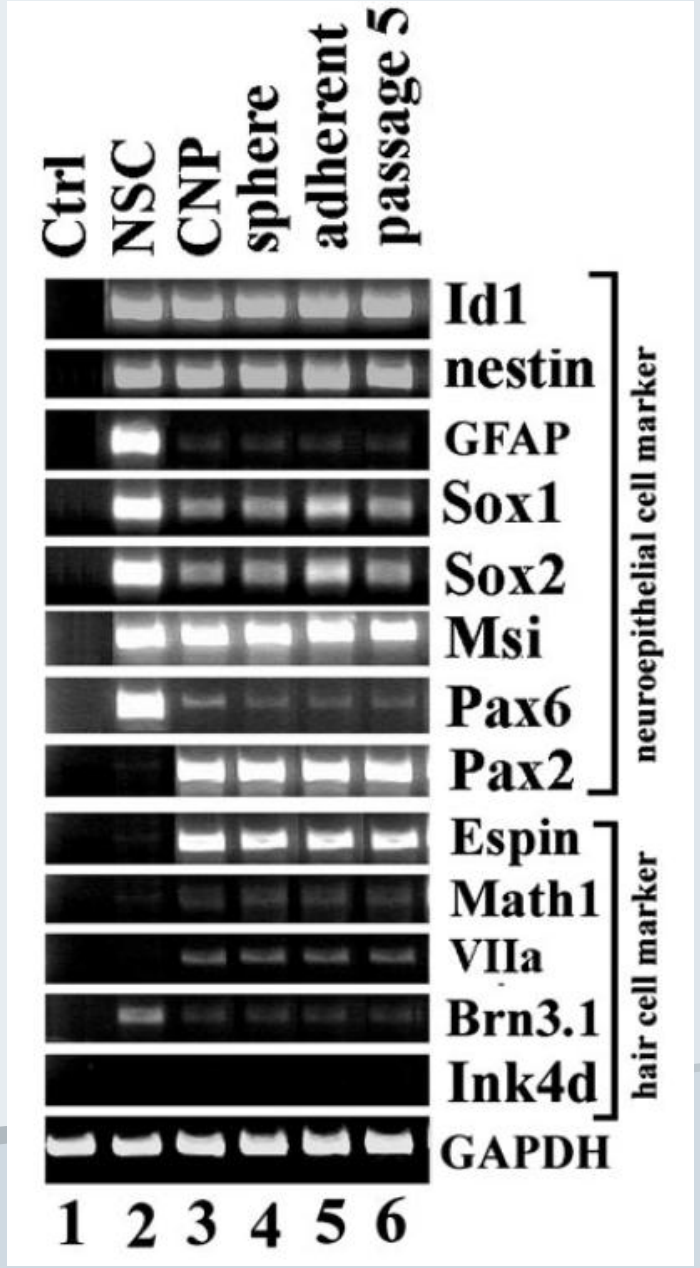


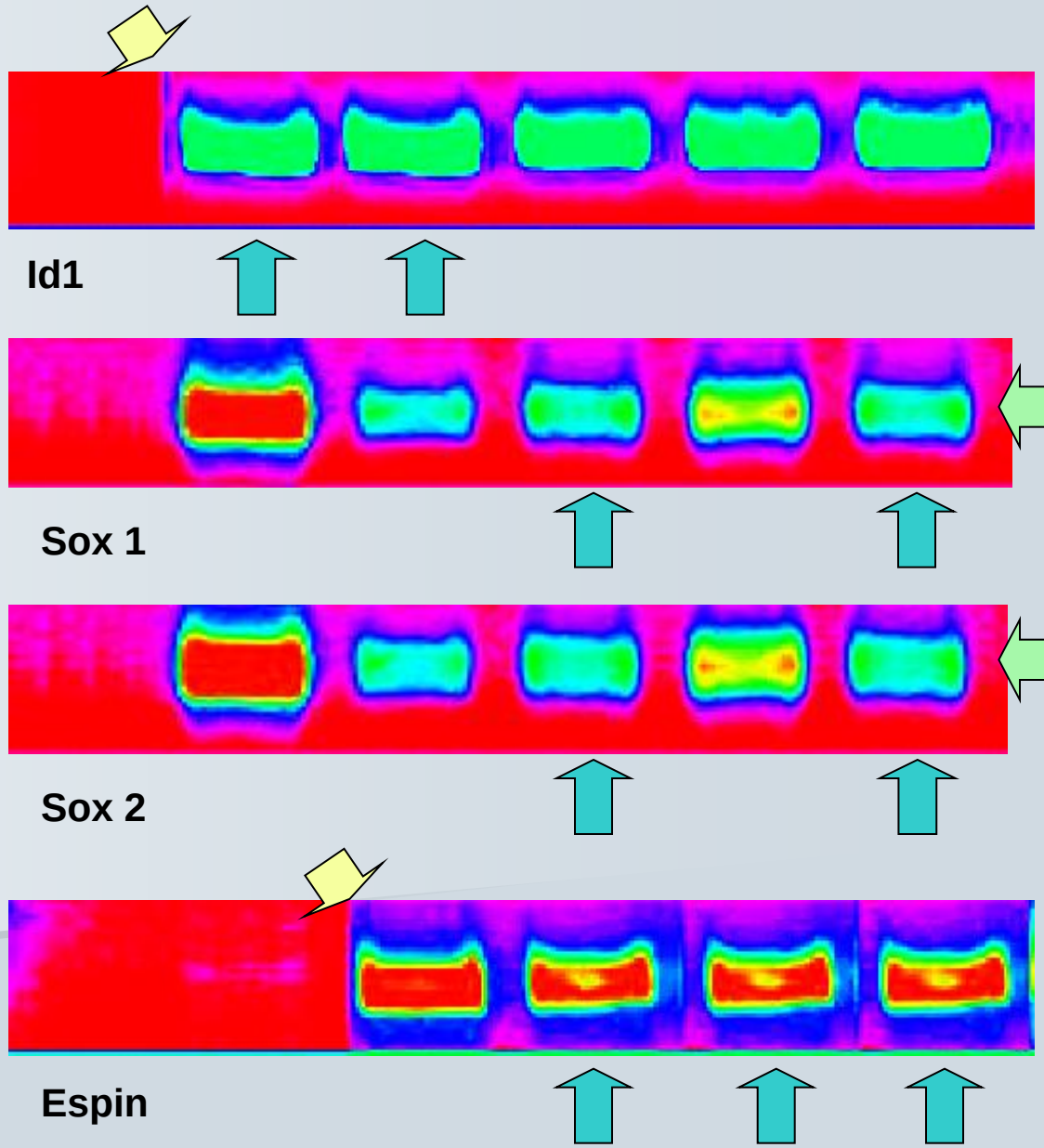
Fig. 5. In CML CD34$^+$ cells, >80% of p27^{Kip} is located in the cytoplasm and does not relocate to the nucleus after adhesion of cells to FN. Nuclear and cytoplasmic proteins were isolated separately from 10^7 CD34$^+$ cells either freshly selected (*A*), or recovered in the adherent and nonadherent fraction of adhesion assays (*B*). Proteins present in cytoplasm or nucleus were resolved by SDS/PAGE, and blots were probed with anti-p27^{Kip} antibodies and goat anti-mouse HRP-conjugated antibody. Blots were then stripped and reprobed with anti-cdk2 antibodies and goat anti-mouse HRP-conjugated antibody, and stripped again and probed with anti-cyclin-H antibodies and goat anti-mouse HRP-conjugated antibody. A representative example of three experiments is shown.

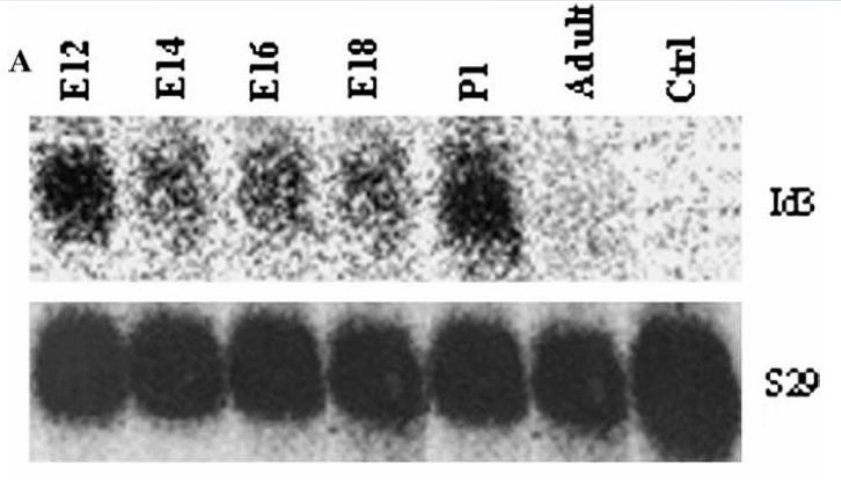


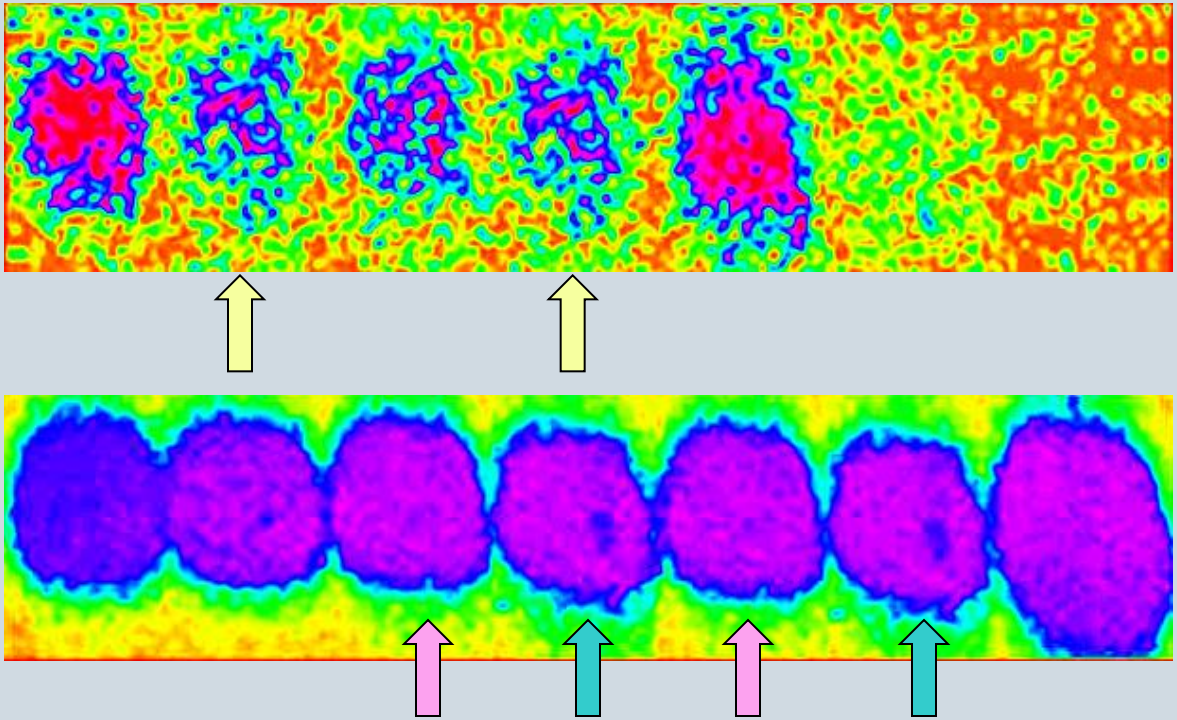
The data in figure 5B appears to be a rotated, distorted, cleaned-up version of data in the middle row of 5A

Yet another miscreant?









Id3

S29

Another investigation

Further doubts over stem-cell images

Peter Aldhous and
Eugenie Samuel Reich

LIGHTNING never strikes again in the same place? Tell that to the University of Minnesota in Minneapolis, which has launched yet another inquiry into research at its Stem Cell Institute after *New Scientist* raised further concerns about papers that seem to contain duplicated and manipulated images.

Two previous inquiries have led to three papers being corrected, one being retracted, and a finding of misconduct against Morayma Reyes, formerly a PhD student at Minnesota. In October 2008, an expert panel ruled that Reyes falsified images in a 2001 paper in *Blood* (vol 98, p 2615), describing a versatile type of stem cell from human bone marrow (*New Scientist*, 11 October 2008, p 8).

Reyes, who is now at the University of Washington in Seattle, protested her innocence, blaming "inexperience, poor training and lack of clear standards about digital image handling". She also argued that she followed standards for image processing that were common at Minnesota at the time. So *New Scientist* decided to look more closely at other papers co-authored by the Stem Cell Institute's former director, Catherine Verfaillie, in whose lab Reyes worked.

In doing so, we stumbled across problems in the lab of another researcher affiliated with the Stem Cell Institute, Jizhen Lin, who published a paper including Verfaillie among the authors in December 2008 (*American Journal of Physiology – Cell Physiology*, DOI: 10.1152/ajpcell.00324.2008).

This paper explores how stem cells from the inner ears of lab mice can give rise to neurons and specialised "hair cells" that detect sound waves. The question is whether images of gels documenting the activity of various genes have been spliced together, and whether some bands on the gels have been duplicated. In one case, an entire gel appears to have been used twice to describe results for different genes (see images, above).

After combing through more of Lin's research, we found possible duplications within images in six further papers, published between 2001 and 2007. None involved Verfaillie.

In April, *New Scientist* told the university of our concerns about Lin's work. The university took

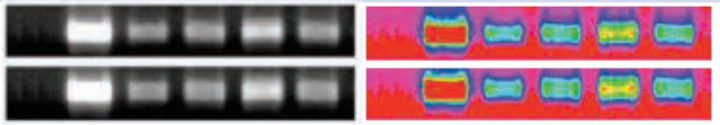
"What might emerge at other research centres if their publications were given similar scrutiny?"

Spot the similarities

Each of these images shows a gel recording the activity of an individual gene in cells from the inner ears of mice

Individual bands on a gel should have subtly different shapes, yet in this gel the first three bands from the right appear identical

These two gels are described as recording the activity of different genes, yet they appear identical. Within each gel, the first and third bands from the right also appear identical



On the right, images are coloured to accentuate variation in their grey-scale using a software tool supplied by the US Office of Research Integrity

SOURCE: AJP - CELL PHYSIOLOGY, DOI:10.1152/AJPCELL.00324.2008

AN UNEXPLAINED RESEMBLANCE

The University of Minnesota's decision to launch an inquiry into the research of Jizhen Lin (see main story) still leaves an earlier concern in limbo.

In November 2008, researchers led by Catherine Verfaillie, investigates the mechanisms involved in the proliferation.

The concern is that an image recording the presence of one of the responsible for duplicated and erroneous data in Verfaillie's best-known publication, which claimed that certain cells from bone marrow can mimic the

Verdict: not proven

"The investigation panel found that multiple images published in [six] papers were improperly manipulated and invalid.

"The panel determined the evidence was inconclusive as to who prepared the manipulated images, and there was insufficient evidence to find intent to misrepresent results or to find that the images had been submitted for publication with knowledge of the manipulations."

University of Minnesota statement,
February 2011

- Before verdict: one paper retracted; one corrected
- After verdict: nothing by June 2012

Perky cheerleaders?

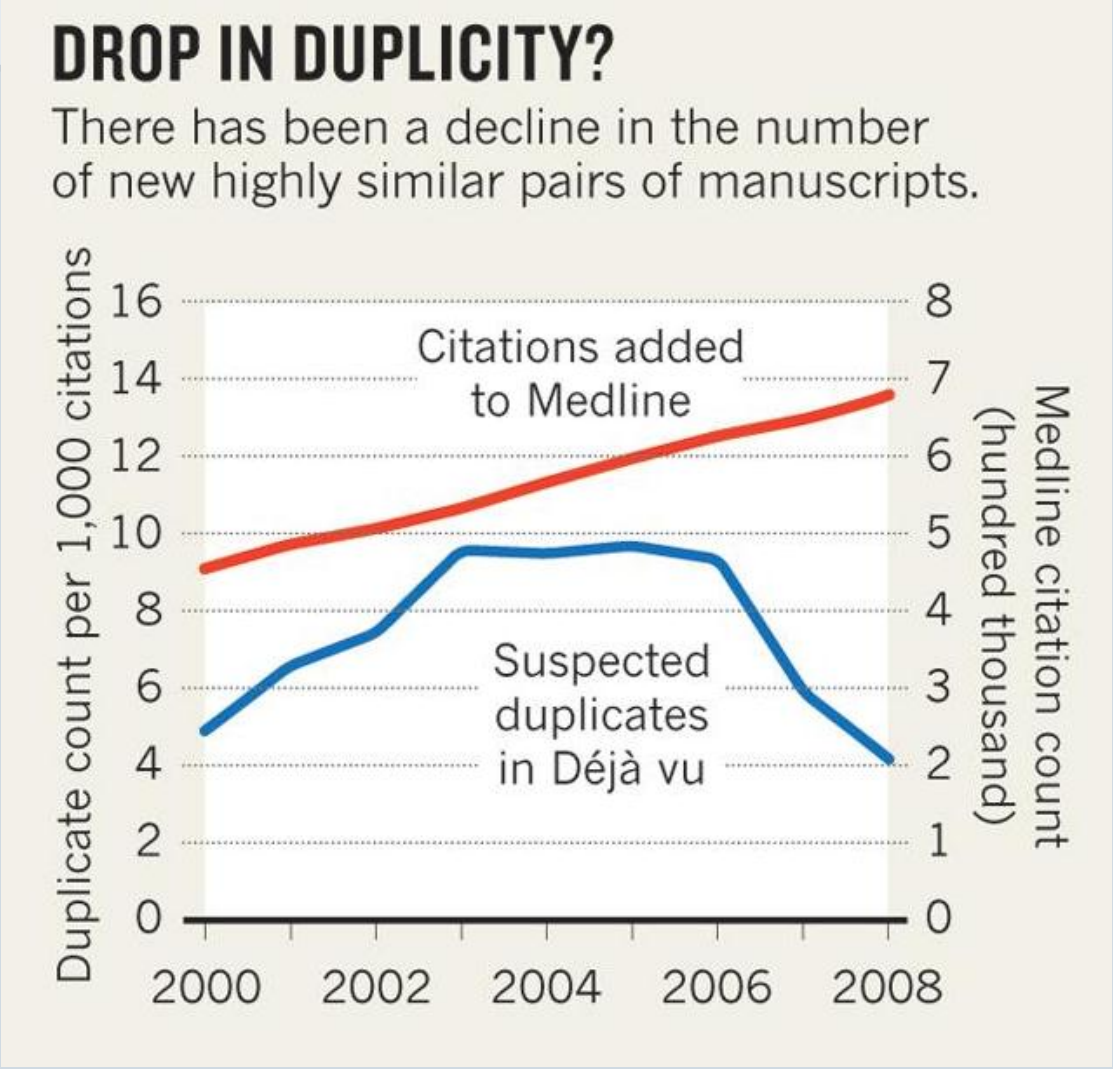
"When Professor Schmidtlapp says he's discovered something big, the science writers…don't draw their guns and make him put his cards on the table. They don't flyspeck his raw data, don't check his funding sources, don't scrutinize his previous articles for mistakes.

"They like science, they probably admire Schmidtlapp and they're excited by the prospect that he's right. So they just ask him how to spell whatever it is and write it down."

John Crewdson of the *Chicago Tribune*, in *Nieman Reports*, Winter 1993

Automated plagiarism tools are a deterrent

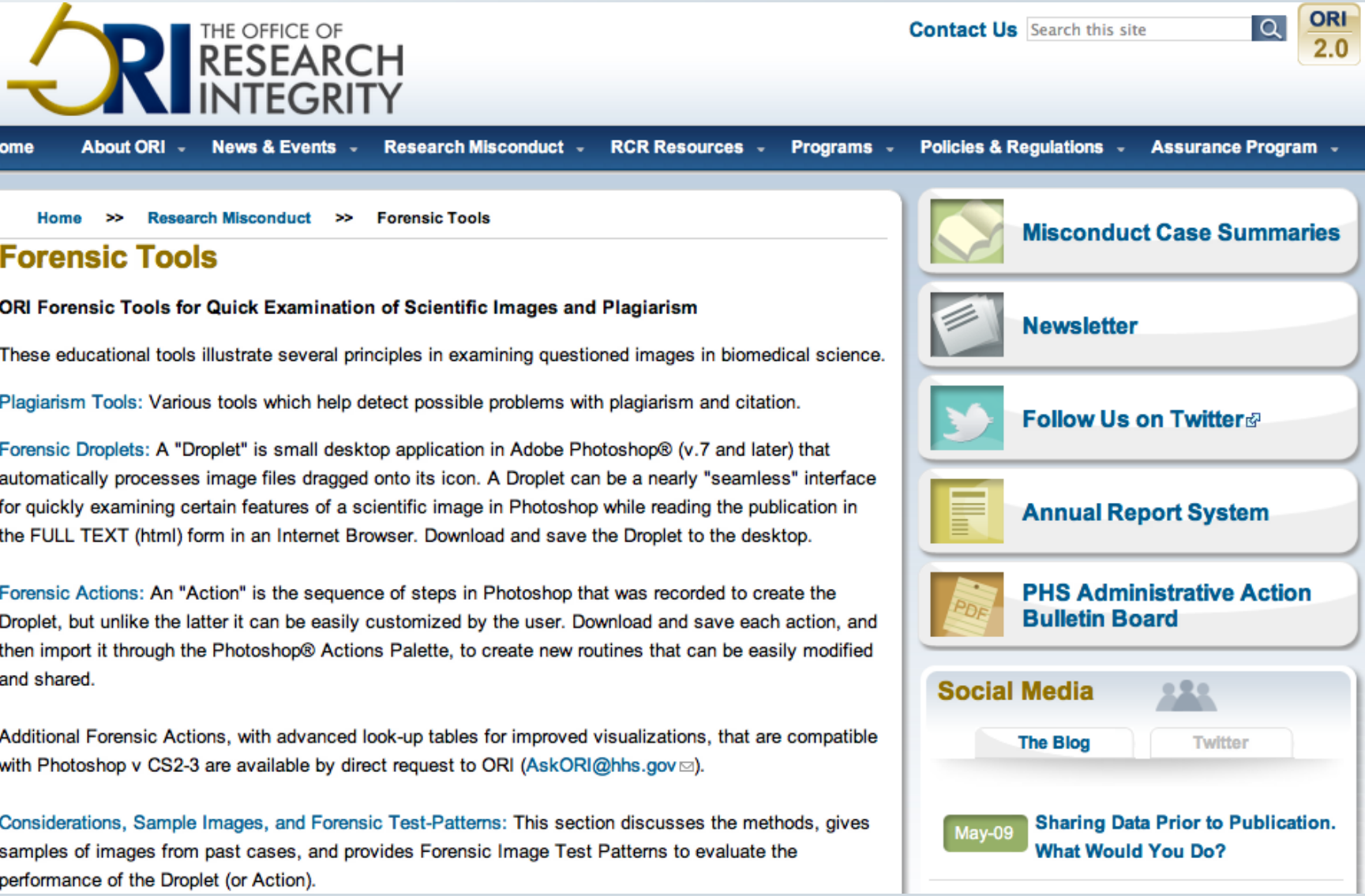
Is it possible to develop similar tools for image duplication/manipulation?



Nature, vol 468, p 745 (2010)

Digital image forensics

http://ori.hhs.gov/forensic-tools



Plagiarism detection tools

eTBLAST
Text-similarity search engine for PubMed, ClinicalTrials.gov etc
http://etest.vbi.vt.edu/etblast3/

Déjà vu
Database of highly similar papers
http://spore.vbi.vt.edu/dejavu/

Plagiarism Resource Site
http://plagiarism.bloomfieldmedia.com/
Includes download of free software, WCopyfind, and links to commercial plagiarism detection software

What can journalists do to uncover scientific misconduct?

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Peter Aldhous,
San Francisco Bureau Chief
peter@peteraldhous.com

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