



## LETTERS

edited by Etta Kavanagh

### Keeping the U.S. a World Leader in Science

JOHN MARBURGER'S RECENT, SOMEWHAT CRANKY STATEMENT THAT U.S. RESEARCHERS NEED TO rely more on private philanthropy and industry to expand the scientific enterprise ("U.S. science adviser tells researchers to look elsewhere," J. Mervis, *News of the Week*, 11 May, p. 817) provides a sobering revelation that the United States has begun to stumble as a world leader in science and technology. Failure to correct this situation will result in incalculable losses in terms of future U.S. economic well-being.

We at Research Corporation, America's first foundation for science advancement (begun in 1912), would like to say we stand ready to heed Marburger's marching orders. We'd like to boldly step forward to fund U.S. scientific research, so that the administration could continue to cut taxes for the rich and focus taxpayer dollars elsewhere, including the reported \$9 billion or so it spends every month in Iraq. Alas, we can't.

Our \$170 million endowment, even when combined with those of our sister science advancement foundations, isn't likely to meet all the needs of U.S. researchers left high and dry by flat federal funding. In 2004, the top 50 private U.S. foundations awarding science and technology grants distributed just under \$456 million (1). This sum pales in comparison to the impact and importance of federal dollars.

Today's flat federal funding means that many bright young researchers will be forced out of promising science careers in the coming decade unless something is done. Eventually, some may choose to go elsewhere to do science; China, Korea, and India are grand examples of countries ramping up their basic research efforts. Young Americans with advanced degrees in physics, chemistry, and other hard sciences doubtless would be resilient enough to adapt to these intriguing cultures as they enriched their foreign corporate and government sponsors.

**"[T]he technological fruits of scientific research have never been more important to economic development and national security."**

—Gentile

These developments couldn't have come at a worse time. In today's world, where humanity's knowledge base continues to expand at a frenetic pace, the technological fruits of scientific research have never been more important to economic development and national security.

Last year, the Task Force on the Future of American Innovation reported survey results that indicated 70% of the public supports increasing federal funding by 10% a year for the next seven years for university research in science and engineering. The same survey showed that 49% of the electorate believes the United States' ability to compete economically in the world has grown worse over the past few years.

Unless we quickly come to an understanding that a simple-minded scheme to privatize scientific research, incrementally or otherwise, will not work, I fear that the nightmare of the United States as a scientifically developing-world nation could become a reality.

JAMES M. GENTILE

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#### Reference

1. The Foundation Center, Statistical Information Service (see [http://foundationcenter.org/findfunders/statistics/pdf/04\\_fund\\_sub/2004/50\\_found\\_sub/f\\_sub\\_u\\_04.pdf](http://foundationcenter.org/findfunders/statistics/pdf/04_fund_sub/2004/50_found_sub/f_sub_u_04.pdf)).

### Experimental Data for Structure Papers

We are writing to address the retraction of five papers on structural studies of ATP-binding cassette (ABC) transporters—three in *Science* (G. Chang *et al.*, "Retraction," Letters, 22 Dec. 2006, p. 1875), one in the *Proceedings of the National Academy of Sciences* (1), and one in the *Journal of Molecular Biology* (2). We have much sympathy for your readers but very little for the magazine. This is not the first time incorrect structures have been published in *Science* (3), and it will not be the last time. We and all of your readers make mistakes; crystallography is fortunate that by careful treatment of the experimental and derived data, most serious mistakes are caught and corrected before publication. The necessary tools and techniques are well described [for example, (4), and references therein] and widely used by our community. Inherent in structural analysis is a degree of subjectivity (3), which is particularly relevant in low-resolution studies such as those made by Chang and co-workers. Essentially correct structures have been built at 4.5 Å resolution, but it is not surprising that some of them turn out to be wrong upon further scrutiny.

For this scrutiny to take place, however, readers must be provided with the original experimental data, not only the derived atomic coordinates. Only armed with these data can an investigator conduct an independent evaluation that may result in a reinterpretation of the published structure.

The last time this happened, the structural community, with some prodding (most successfully from the major funding agencies) improved the frequency with which original experimental data (the so-called structure factors) are deposited at the Protein Data Bank. The response from and guidelines required by the publishing community, however, were very variable. Unfortunately, the higher the impact factor of the journal, the less likely it was that the experimental data were deposited. In *Science*, during the period from 1995 to 2002, only 38% of the deposited atomic models included the experimental data. *Nature* and *Cell* were only slightly better.

Depositing the experimental data does not



Computer viruses  
turn 25

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Water in the early  
solar system

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guarantee that incorrect structures will not get published, but it does mean that an independent evaluation can be made of the experimental basis for the derived model. In the case of the ABC transporter structures, the serious errors in the atomic models could only have been corrected if the complete set of diffraction data (including the diffraction data from the single heavy atom derivative) had been deposited. No journal, as far as we know, demands this.

We call on *Science* and other journals to implement strict requirements for depositing original experimental data, both to forestall the publication of erroneous models in the future and to give readers the power to conduct independent evaluations of published models.

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#### References

1. C. Ma, G. Chang, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 3668 (2007).
2. G. Chang, *J. Mol. Biol.* **369**, 596 (2007).
3. C.-I. Brändén, T. A. Jones, *Nature* **343**, 687 (1990).
4. G. J. Kleywegt, *Acta Crystallogr. Sect. D Biol. Crystallogr.* **D56**, 249 (2000).

## PDB Improvement Starts with Data Deposition

A SMALL SOFTWARE FLAW RECENTLY TRIGGERED the retraction of a series of high-profile x-ray structures ["Retraction," *Letters*, 22 Dec. 2006, p. 1875; (1, 2)]. Although in this case, the inaccurate protein structures were wrong and were promptly retracted, the Protein Data Bank (PDB) (3) still holds other structures that either are entirely wrong or are not correct enough to

be used for the design or explanation of biological experiments.

In 1996, Hooft *et al.* (4) reported one million anomalies in the PDB, and we recently detected 10 times as many anomalies in a PDB that is 10 times as large. Most of these anomalies are of minor importance, and a small fraction are genuine discoveries that warrant further studies. However, a substantial number are serious errors. Using today's tools, we can correct many of the erroneous structures, provided that the original experimental x-ray data are available. We re-refined all 1195 PDB files that had a reported resolution of 2.0 Å and that were deposited after 1992 with the use of an experimental data file that included an  $R_{\text{free}}$  set. The details of the re-refinement procedure, the original and re-refined coordinate sets, structure validation reports for the original and TLS-refined coordinates, and all  $R$  and  $R_{\text{free}}$  values are available online (5).

The crystallographic community has long been advocating the deposition of experimental data. This has resulted in a clear policy by the International Union of Crystallography (IUCr) (6) and many scientific journals that the deposition of these data is required before publication. Unfortunately, 11% of the macromolecu-

lar x-ray structures released in 2006 lacked the experimental data, and another 4% did not have a properly defined  $R_{\text{free}}$  set.

The re-refinement results (5) show that today's software can clearly improve the quality of most structures solved in the past. The vast majority of our test set clearly improved in terms of  $R_{\text{free}}$  and in terms of protein geometry. These results show the benefits of storing experimental x-ray data; these data allowed us to keep old protein structures relevant by means of re-refinement with the use of the latest insights and technologies. In anticipation of future improvements in refinement tools, we strongly urge journals and scientists to ever more rigorously strive for the deposition of all the original experimental x-ray data.

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1. C. Ma, G. Chang, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 3668 (2007).
2. G. Chang, *J. Mol. Biol.* **369**, 596 (2007).
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4. R. W. W. Hoofst, G. Vriend, C. Sander, E. E. Abola, *Nature* **381**, 272 (1996).
5. PDB Redo ([http://swift.cmbi.ru.nl/pdb\\_redo/](http://swift.cmbi.ru.nl/pdb_redo/)).
6. International Union of Crystallography, Commission on

Biological Macromolecules, *Acta Crystallogr. Sect. D Biol. Crystallogr.* **D55**, 2 (2000).

*Editor's Note:* *Science* seeks to enforce accepted community standards. With this motivation, we have required deposition of structure factors since 2002.

## Permanent Reversal of Diabetes in NOD Mice

WE DISAGREE WITH HOW J. NISHIO *ET AL.* (1) represent our published data on the permanent reversal of type 1 diabetes in NOD mice (2). Nishio *et al.* state (1) that "a FCA alone control was not included in the report by Kodama *et al.*" (3). Further, in their response to our Technical Comment (4), they claim in numerous locations, including the abstract, that "[t]he experiments of Faustman *et al.* lack adequate controls," and "we continue to wonder why Faustman *et al.* have not performed the essential Freund's complete adjuvant alone control" (4). These statements in their papers are misrepresentations. These specific FCA (CFA)-alone controls were published in 2001 in our *Journal of Clinical Investigation* (JCI) paper (5). Nishio *et al.* cite our JCI paper that con-

tains the numerous CFA control studies. The CFA-alone controls are present in eight locations in our manuscript: Fig. 1a; Fig. 1b; Fig. 2, Group D; Fig. 5, Group B; Fig. 6, Group D; Fig. 7c, Group B; Table 1, Group D; and Table 2, Group B.

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1. J. Nishio *et al.*, *Science* **311**, 1775 (2006).
2. D. Faustman *et al.*, *Science* **314**, 1243 (2006); [www.sciencemag.org/cgi/content/full/314/5803/1243a](http://www.sciencemag.org/cgi/content/full/314/5803/1243a).
3. S. Kodama, W. Kührtreiber, S. Fujimura, E. A. Dale, D. Faustman, *Science* **302**, 1223 (2003).
4. J. Nishio *et al.*, *Science* **314**, 1243 (2006); [www.sciencemag.org/cgi/content/full/314/5803/1243c](http://www.sciencemag.org/cgi/content/full/314/5803/1243c).
5. S. Ryu *et al.*, *J. Clin. Invest.* **108**, 63 (2001).

## A Diver's Perspective on Coral Damage

I MUST TAKE EXCEPTION TO A COMMENT AND its implications in Richard Stone's otherwise excellent article "A world without corals?" (News Focus, 4 May, p. 678). Stone introduces the human toll on reefs by citing damage

inflicted by “divers clumsily breaking off chunks of coral.” It is undeniable that recreational divers will, on occasion, inadvertently injure corals. However, I have been a certified SCUBA diver since 1992 and have logged over 150 ocean dives all over the world, and in that time I have seen only sporadic instances of divers impacting corals. Formal dive training by all major certification agencies includes instruction on reef protection, and the vast majority of dive tour operators repeatedly lecture divers about avoiding contact with coral and other marine life. It is undeniable that our coral reefs are threatened by human activities, but it is unfair to imply that sport divers at all popular reefs contribute significantly to this

plight. Rather than a threat, I would argue that the growth of recreational diving is a major benefit to the future of our reefs: Divers are among the most environmentally conscious individuals I have met (note the “army of snorkeling and diving volunteers” described in the article), and this pastime depends on having beautiful, healthy corals to explore. As proof of this view, one need only visit Bonaire, a popular dive destination and the site of some of the world’s healthiest coral reefs. Bonaire instituted strong legislation, including laws enacted in 1975 that made it illegal to break or sell coral. Subsequent efforts in cooperation with the World Wildlife Fund established a vast marine park that completely encompasses the island.

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Tyzio *et al.* (Reports, 15 December 2006, p. 1788) reported that maternal oxytocin triggers a transient excitatory-to-inhibitory switch of  $\gamma$ -aminobutyric acid (GABA) signaling during labor, thus protecting the fetal rat brain from anoxic injury. However, a body of evidence supports the possibility that oxytocin is released from the fetal pituitary during delivery, not only from the mother, particularly under conditions of hypoxic stress.

Full text at

[www.sciencemag.org/cgi/content/full/317/5835/197a](http://www.sciencemag.org/cgi/content/full/317/5835/197a)

### RESPONSE TO COMMENT ON “Maternal Oxytocin Triggers a Transient Inhibitory Switch in GABA Signaling in the Fetal Brain During Delivery”

Roman Tyzio, Rosa Cossart, Ilgam Khalilov, Alfonso Represa, Yehezkel Ben-Ari, Rustem Khazipov

We tested the hypothesis that cortisol-induced release of fetal oxytocin triggers a perinatal inhibitory switch in  $\gamma$ -aminobutyric acid (GABA) signaling. The cortisol analog methylprednisolone did not modify GABA driving force and intracellular chloride concentration in 1-day-old rat hippocampal neurons. Together with the immaturity of the fetal rat hypothalamo-neurohypophysial system, these results suggest that oxytocin in the rat fetal brain is mainly provided by the mother.

Full text at

[www.sciencemag.org/cgi/content/full/317/5835/197b](http://www.sciencemag.org/cgi/content/full/317/5835/197b)

## Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web ([www.submit2science.org](http://www.submit2science.org)) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

### TECHNICAL COMMENT ABSTRACTS

#### COMMENT ON “Maternal Oxytocin Triggers a Transient Inhibitory Switch in GABA Signaling in the Fetal Brain During Delivery”

Lionel Carbillon