LETTERS

Retraction

IN OUR REPORT "REELIN PROMOTES PERIPHERAL synapse elimination and maturation" (*1*), we presented data indicating that Reelin, a protein previously implicated in brain development (*2*), promotes synapse elimination and maturation at the neuromuscular junction. These conclusions were based mainly on our observations that Reelin was expressed and secreted by spinal motor neurons at the peripheral synapse; that mutant mice lacking Reelin (*reeler*) exhibited connectivity defects that included multiple fiber and multiple synapse innervation; and that intramuscular injection of Reelin stimulated axonal withdrawal. Several groups recently failed to reproduce our findings regarding the connectivity defects in *reeler* mice [see the Technical Comment in this issue (*3*)], prompting us to reexamine all the main points of the study. Two laboratories (G.D. and F.K.) attempted to replicate the data using reagents and mice similar to those used for our original Report, including two *reeler* strains obtained from the Jackson Laboratory and expanded by inbreeding for several generations.

The expression data for Reelin (Fig. 1 in our Report) and Reelin signaling proteins (Fig. 2) at the neuromuscular junction could not be reproduced. Recent immunofluorescence experiments in our laboratories also indicate that spinal motor neurons do not, in fact, express Reelin, consistent with the findings of others (*4*).

Upon reexamination, the number of end plates in *reeler* mice was not increased in whole mount preparations of the diaphragm as compared with wild-type mice, unlike the results shown in Fig. 3 and Table 1. Single fiber analysis confirmed that *reeler* muscles bear only one end plate per fiber, not multiple end plates as indicated in Fig. 4, disproving one important aspect of the reported connectivity phenotype. We were able to confirm the abnormal morphology and reduced size of *reeler* end plates. However, because the *reeler* mice that we examined in the Report were severely impaired due to genetic background and inbreeding, we now recognize that these abnormalities may have resulted from profound ataxia or central defects, rather than from absence of Reelin in the muscle. The same caveat applies to the electron microscopy data (Fig. 3 and Table 2).

The second aspect of the *reeler* connectivity phenotype, the presence of multiple axons innervating the same end plate (Fig. 4 and Table 1), has been clearly disproved by others and could not be replicated in our laboratories [see the Technical Comment and Response in this issue (*3*, *5*)]. Our physiological recordings (Fig. 4I) may have been contaminated by an artifact resulting from incomplete block of action potentials in atrophic preparations of *reeler* muscles. Because no polyneuronal innervation exists in adult *reeler* synapses, the reported effect of injected Reelin in promoting axonal withdrawal (Fig. 4K) clearly must be wrong. Recent experiments in G.D.'s laboratory involving Reelin injection in the muscle of young wild-type mice, similar to those described in Fig. 4L, produced unreliable results. Because the activity of Reelin itself is in question, we also seriously doubt that the serine protease inhibitor Pefabloc SC prevents Reelin from promoting multiple axonal withdrawal as reported in Fig. 4L. Thus, the conclusion that Reelin promotes synapse elimination through its protease activity is not warranted. We did not attempt to replicate the data concerning the effect of Pefabloc SC alone (Fig. 4M), which may be correct, consistent with other studies implicating endogenous serine proteases in synapse elimination (*6*, *7*).

With the exception of the in situ hybridization (produced by C.H. in M.S.'s laboratory), electron microscopy (J.C. Jr.'s laboratory), and electrophysiology data (D.R.M.'s laboratory), all data published in the Report were produced by C.C.Q. when he was in G.D.'s laboratory. We cannot presently explain the lack of reproducibility of the data. All authors agree that the study is critically flawed to an extent that we must retract it.

CARLO C. QUATTROCCHI,[1] CHENG HUANG,[2] SANYONG NIU,[3,6] MICHAEL SHELDON,[3] DAVID BENHAYON,[7] JOINER CARTWRIGHT JR.,[4] DENNIS R. MOSIER,[5] FLAVIO KELLER,[8] GABRIELLA D'ARCANGELO[3,6]

[1]Houston, TX, USA. [2]Department of Human Genetics, [3]Department of Pediatrics, [4]Department of Pathology, [5]Department of Neurology, Baylor College of Medicine, Houston, TX 77030, USA. [6]The Cain Foundation Laboratories, Houston, TX 77030, USA. [7]Department of Anatomy and Neurobiology, University of Tennessee, Memphis, TN 38163, USA. [8]Laboratory of Developmental Neuroscience, Universita' Campus Bio-Medico, Rome 00155, Italy.

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8. We thank A. Renfro, M. Roceri, and R. Panteri for conducting recent experiments attempting to replicate published data.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.letter2science.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.

Biomedical Research Publication System

WE WOULD LIKE TO EXPRESS OUR CONCERNS about the current publication system for basic biomedical research and to propose an improved system that takes better advantage of Web technology. In the present system, journal Web sites serve primarily as "mirrors" of paper journals and therefore can publish only a limited number of accepted manuscripts. However, as the output of research increases, existing journals no longer provide sufficient space for the volume of information. The problem is compounded by the culture of "publish in high-profile journals or perish," which makes it difficult for authors who publish in specialized journals to be credited favorably for grant competition, job applications, or promotion (*1*).

There are a number of serious consequences to this problem. The direction of research is dictated more and more by publishability in high-profile journals, instead of by strict scientific considerations, while fields not deemed fashionable are facing an increasing shortage of young researchers. Furthermore, because of the unpredictability of the publication process, scientists become increasingly apprehensive about sharing their preliminary findings and interacting with one another openly. The fierce competition for publication in high-profile journals may encourage aggressive behavior and discourage others from staying in academic research.

We believe that modifying the current system may alleviate the above problems. Because of the striking differences in volume and cost, paper journals should be used to complement, rather than duplicate, what is published on the Web. Thus, the new system we propose would consist of a high-capacity Web site for posting peer-reviewed papers. A paper version of the journal would be reserved for the fraction

of the Web-published papers that have made the strongest impact.

> **"The fierce competition for publication in high-profile journals may encourage aggressive behavior and discourage others from staying in academic research."**
>
> –*WANG* ET AL.

Editors would continue to solicit reviews and enforce an objective scientific standard. However, in this system, a paper would not be rejected on the basis of judgments of "novelty," "priority," or "descriptiveness." Reports that confirm or challenge previous studies or describe significant negative findings would all be considered for publication. This approach should provide cross-examination of results and help fight against misconduct. The scientific editors would also select from the Web-published papers the outstanding papers for republication in the paper version (*2*). With more time and objective parameters (*3*), the decision will be influenced less by haggling and more by quality.

In addition, the reviewers' comments and the authors' responses to those comments would be published on the Web, thereby encouraging constructive reviews and providing additional insights for readers. Authors of thoughtful, named reviews may be credited accordingly, as part of their productivity and evidence of stature. The new system may also correct the bias against specialized journals: With a high acceptance rate for Web journals but no guarantee for selection in the paper version, scientists will likely choose journals more rationally during submission and develop a balanced view of the value of different journals.

The problems of publishing in basic biomedical research have already exerted serious negative impacts on scientific interactions and education. It would be highly irresponsible for scientific publishers to fail to correct these problems, and equally irresponsible for the scientific community to allow the situation to deteriorate.

YU-LI WANG,[1]* KEITH BURRIDGE,[2] MICAH DEMBO,[3] GIULIO GABBIANI,[4] STEVEN K. HANKS,[5] HIROSHI HOSOYA,[6] PAUL JANMEY,[7] ROGER KARLSSON,[8] UNO LINDBERG,[8] ISSEI MABUCHI,[9] CAROL OTEY,[10] KLEMENS ROTTNER,[11] J. VICTOR SMALL,[12] C.-L. ALBERT WANG,[13] SALLY ZIGMOND[14]

[1]University of Massachusetts Medical School, 377 Plantation Street, Suite 327, Worcester, MA 01605, USA. [2]Department of Cell and Developmental Biology, University of North Carolina, Campus Box 7090, Chapel Hill, NC 27599–7090, USA. [3]Department of Biomedical Engineering, Boston University, 44 Cummington Street, Boston, MA 02215–2407, USA. [4]Department of Pathology, University of Geneva, 1 rue Michel-Servet, 1211 Geneva 4, CH-1211 Switzerland. [5]Department of Cell and Developmental Biology, Vanderbilt University, 21st and Garland, Nashville, TN 37232–2175, USA. [6]Department of Biological Science, Graduate School of Science, Hiroshima University, 3-1, Kagamiyama 1 chome, Higashi-Hiroshima, Hiroshima, Japan 739-8526. [7]Department of Physiology, Institute of Medicine and Engineering, University of Pennsylvania, 3340 Smith Walk, 101 Vagelos Labs, Philadelphia, PA 19104–6306, USA. [8]Department of Cell Biology, Wenner-Gren Institute, Stockholm University, SE-106 91, Stockholm, Sweden. [9]Department of Biology, University of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo 153-8902, Japan. [10]Department of Cell and Molecular Physiology, University of North Carolina, Campus Box 7545, Chapel Hill, NC 27599–7545, USA, [11]German Research Center for Biotechnology, Mascheroder Weg 1, D-38124 Braunschweig, Germany. [12]Institute of Molecular Biotechnology, Austrian Academy of Sciences, Dr. Bohrgasse 7, A-1030 Vienna, Austria. [13]Boston Biomedical Research Institute, 64 Grove Street, Watertown, MA 02472–2829, USA. [14]Department of Biology, University of Pennsylvania, 415 South

University Avenue, Philadelphia, PA 19104–6018, USA.
*To whom correspondence should be addressed. E-mail: yuli.wang@umassmed.edu

Notes
1. The phenomenon appears to be an unfortunate consequence of the emphasis on the aggregate "impact factor" of journals. Although such indices may be useful for judging a paper's impact, journals are now under strong pressure to protect or improve their standing, often by publishing articles in fashionable fields and with a predictable readership.
2. The online service Faculty of 1000 may serve as a reference for a similar task. With a dedicated panel and focusing on defined scope, the process should be manageable by a panel a fraction that of Faculty of 1000 (about 1400 evaluating members).
3. For example, it should not be difficult to determine if a paper has stimulated discussions or new studies. One may also use the number of online hits as a reference, although such measures may be prone to hacking and manipulations.
4. This article was initially drafted by the corresponding author. The final form has incorporated many insightful comments from the co-signatories, as listed alphabetically, and from some colleagues who wish to remain anonymous.

Bacterial Resistance of *daf-2* Mutants

IN THEIR BREVIA "LONG-LIVED *C. elegans daf-2* mutants are resistant to bacterial pathogens," D. A. Garsin *et al.* show that long-lived *C. elegans daf-2* mutants are resistant to killing by bacterial pathogens (20 June, p. 1921). Partial loss-of-function mutations in *daf-2*, which encodes an insulin-like receptor, result in de-repression of the transcription factor *daf-16*, leading to life extension and increased resistance to bacterial pathogens *Enterococcus faecalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Garsin *et al.* conclude that the insulin signaling pathway modulates both inherent longevity and pathogen resistance to affect overall survival in a manner dependent on the pathogenicity of the bacteria *C. elegans* is fed.

Although recent papers support the link between aging and innate immunity via the insulin pathway (*1*), there should be some caution in interpreting the data of Garsin *et al*. The insulin pathway is involved in inherent longevity by the up-regulation of several cellular stress-response genes such as *ctl-1*, *ctl-2*, and *sod-3*. These genes exert antioxidant activity through the production of catalase and superoxide dismutase. Expression of all of these genes is increased in animals with reduced *daf-2* activity and decreased in animals with reduced *daf-16* activity (*1*). It is known that *E. faecalis* (*2*) and *P. aeruginosa* (*3*) produce superoxide and hydrogen peroxide under aerobic conditions, and that *C. elegans* is extremely sensitive to hydrogen peroxide –mediated killing by bacteria (*4*). For these bacteria, the "pathogen specific life extension" may thus be due to the increased ability of *C. elegans daf-2* mutants to neutralize superoxide and hydrogen peroxide. This would reflect the inherent longevity of *daf-2* mutants, rather than improved immune function and/or a pathogen-dependent response. Although oxygen reactive species and neutralizing enzymes may participate in both aging and innate immunity, it is a matter of semantics whether antioxidants should be considered as an antibacterial defense mechanism.

MAIKE BOLM,[1] GURSHARAN S. CHHATWAL,[1] WOUTER T. M. JANSEN[2]
[1]Department of Microbial Pathogenesis, GBF-German Research Centre for Biotechnology, Braunschweig 38124, Germany. [2]Medical Microbiology, University Medical Centre Utrecht, G04-614, Heidelberglaan 100, Utrecht 3584 CX, Netherlands.

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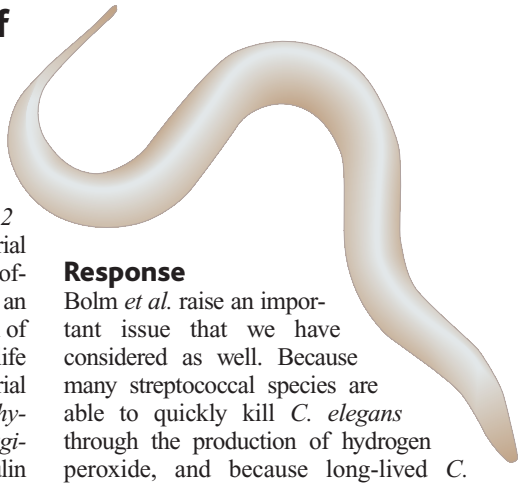

Response

Bolm *et al.* raise an important issue that we have considered as well. Because many streptococcal species are able to quickly kill *C. elegans* through the production of hydrogen peroxide, and because long-lived *C. elegans daf-2* and *age-1* mutants are more resistant to oxidative stress, Bolm *et al.* suggest that the apparent resistance of these mutants to bacterial pathogens is a consequence of their tolerance to reactive oxygen species. We had previously published that long-lived *age-1* mutants in the *daf-2* signaling pathway are more resistant to killing by *P. aeruginosa* when the bacteria are grown under conditions that produce large quantities of phenazines, tricylic secondary metabolites that react with oxygen to generate cytotoxic oxidants (*1*). However, unlike this phenazine-based "fast-killing" model, the *C. elegans* "slow-killing" models described in our Brevia are quite distinct and require a variety of bacterial virulence–related factors not known to be directly involved in the production of reactive oxygen species (*2*–*5*). Thus, we attribute the pathogen resistance of *daf-2* and *age-1* mutants observed under slow-killing conditions to multifactorial protection against an array of bacterial virulence factors, although some component of enhanced resistance to oxidative stress cannot be ruled out. Bolm *et al.* state that the resistance to bacterial killing may reflect the "inherent longevity of *daf-2* mutants, rather than improved immune function," but this conclusion depends on how one defines "inherent longevity." In a recent publication, Murphy *et al.* demonstrate by full-genome microarray analysis that the *daf-2* signaling pathway regulates the expression of a variety of genes, ones that are involved in conferring resistance to oxidative stress as well as some that confer resistance to pathogen attack (*6*). In short, although a detailed mechanistic understanding of longevity or immunity has not yet been reached, it appears that both are multifactorial and that the factors that regulate each may very well overlap. Experiments under way in our laboratories are addressing this point.

FREDERICK M. AUSUBEL,[1] JAKOB BEGUN,[1] DENNIS H. KIM,[1] TERENCE MOY,[1] GARY RUVKUN,[1] STEPHEN B. CALDERWOOD,[2] COSTI D. SIFRI,[2] DANIELLE A. GARSIN[3]
[1]Department of Molecular Biology, Massachusetts General Hospital, Boston, MA 02114, USA. [2]Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA 02114, USA. [3]University of Texas Health Sciences Center at Houston, Houston, TX 77030, USA.

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The Full Story on Neutrino Detection

CHARLES SEIFE'S NEWS FOCUS ARTICLE "Wanted: one good cosmic blast to shake the neighborhood" (9 Jan., p. 164) opens with a vivid account of neutrinos from Supernova 1987A zipping through Earth to be detected in underground water tanks on 23 February 1987. He writes, "Even before astronomers could see the stellar pyre blaze forth, particle physicists knew that a star had died when they spotted the flashes of 20 subatomic particles, neutrinos, in detectors in Japan and the United States." It's a great story, but not quite true: 23 February was a Monday, and by the 24th, astronomers (including me) were in full swing doing ultraviolet and optical observations. The neutrino detector in Japan recorded its data on tape, the tapes were gathered up and shipped by bus from Kamioka to Tokyo on their regular schedule, and the analysis was carried out overnight on Friday so that the joyful members of Masatoshi Koshiba's group could see the result on Saturday morning (*1*). For the Irvine-Michigan-

CREDIT: PRESTON HUEY/*SCIENCE*

Brookhaven detector in Ohio, I called my colleagues at the University of Michigan Physics department on Tuesday the 24th to get them to search their data, but they were all away skiing at Moriond, and the results were reported on 11 March, 16 days after the event (*2*).

Seife also understates the opportunity. He writes that "dozens of supernovae pop off somewhere in the universe each year." For a typical galaxy, the rate is about 1 per century, so for an observable universe with 10^{11} galaxies, that's about 10^9 popping off each year. You could call that "dozens," but it's a hundred million dozens.

But Seife is surely right that we are better prepared now for the next nearby supernova. I'm standing by, ready to hear from my subterranean colleagues when they get the flash from deep inside a collapsing star. We've been maintaining a program for the Hubble Space Telescope that is ready to go when the Supernova Early Warning System (SNEWS) team finds an event. And here's a comforting thought—since the Milky Way is ~50,000 light years across, the expanding spheres of neutrinos from hundreds of events are already on their way to us, propagating just a smidgen below the speed of light. It's just a matter of being in the right place at the right time.

ROBERT P. KIRSHNER

Harvard-Smithsonian Center for Astrophysics, 60 Garden Street, Cambridge, MA 02138, USA.

References and Notes

1. International Astronomical Union Circular 4338, 10 March 1987. This story is vividly told by the NOVA program *Death of a Star*, available from http://main.wgbh.org/wgbh/shop.
2. International Astronomical Union Circular 4340, 11 March 1987. A first-hand account is in my book, *The Extravagant Universe: Exploding Stars, Dark Energy, and the Accelerating Cosmos* (Princeton Univ. Press, Princeton, NJ, 2002).

CORRECTIONS AND CLARIFICATIONS

News of the Week: "Hybrid mosquitoes suspected in West Nile virus spread" by J. Couzin (5 Mar., p. 1451). The photo accompanying the story should be credited to Stephen Higgs, University of Texas Medical Branch, Galveston.

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Reelin Promotes Peripheral Synapse Elimination and Maturation"

C. Bidoia, T. Misgeld, E. Weinzierl, M. Buffelli, G. Feng, A. Cangiano, J. W. Lichtman, J. R. Sanes

Quattrocchi *et al*. (Reports, 1 Aug. 2003, p. 649) reported that the extracellular matrix protein Reelin is required for naturally occurring synapse elimination and synaptic maturation in skeletal muscle. Their conclusion was primarily based on analysis of neuromuscular synapses in *reeler* mice, which lack Reelin. We present data from three laboratories that have been unable to replicate these results.

Full text at www.sciencemag.org/cgi/content/full/303/5666/1977b

RESPONSE TO COMMENT ON "Reelin Promotes Peripheral Synapse Elimination and Maturation"

G. D'Arcangelo

The crucial experiments described in Quattrocchi *et al*. were reexamined in my laboratory, but the results could not be replicated. Therefore, I agree with the conclusions of the comment by Bidoia *et al*.

Full text at www.sciencemag.org/cgi/content/full/303/5666/1977c

See related Retraction on page 1974