# Research News

# "Dangerous" Liaisons in Cell Biology

*When* Cell *readers perused an enthusiastic commentary supporting the work of an obscure Italian team, they couldn't know that the authors had a vested interest in the outcome of the research*

ON 2 JUNE, the journal *Cell* published some astonishing research results, together with an accompanying editorial, that have touched off a spirited debate among molecular biologists. If the paper is correct, a relatively obscure team of Italian scientists has pulled off a major technical achievement. If, however, the Italian team's results eventually collapse under the intense scrutiny they now face, molecular biology may have been treated to its own version of the cold fusion affair.

But in probing the affair since it was splashed over the world's press, *Science* has learned that the research has other, unexpected elements of concern. Namely, two prominent scientists who penned the laudatory *Cell* editorial as apparently disinterested observers, thus effectively promoting the importance of the science, both of whom work for a commercially-sponsored laboratory, were closely involved in the preparation of the paper prior to its submission to *Cell*, as well as in subsequent follow-up research. Moreover, their involvement appears to include potentially valuable patent rights.

***"Transgenic animals are not my field, and I feel a little bit uncomfortable about it."***

Corrado Spadafora

The *Cell* paper that sparked all this interest carried a report from a group of scientists in Rome, headed by molecular biologist Corrado Spadafora, that foreign genetic material had been inserted into mice by an extraordinarily simple method. The technique involves little more than dipping sperm into a solution containing foreign DNA (see box).

Just as cold fusion was reported by electrochemists intruding in the world of plasma physics, Spadafora's team claims no particular expertise in the field of animal breeding. And, as with cold fusion, a provocative element in this case is the potential commercial payoff if the research proves to be correct.

*Science* has learned that patent applications relating to extensions of Spadafora's work have already been filed by the Vienna-based Research Institute of Molecular Pathology, a joint research facility established last year by the West German company Boehringer Ingelheim and the U.S. company Genentech. Spadafora's paper is accompanied by a "mini-editorial" penned by two of the institute's scientists, director Max Birnstiel and Meinrad Busslinger, in which they describe Spadafora's research as "astounding" and potentially "a cornerstone in biology." However, in their *Cell* commentary, Birnstiel and Busslinger fail to acknowledge their own stake in the technique.

The editorial notes that the experiments could turn out to be a breakthrough both because of their technical simplicity and because of their "potential usefulness for introducing commercially important features" into a wide range of animals, including those of agricultural importance.

Such comments from two respected—and, as far as any observer could tell, disinterested—scientists were widely quoted in the media coverage of the *Cell* paper. There is no question that this added legitimacy to the paper's scientific content and it drew attention to the possible importance for society of the breakthrough. Both of these elements seem to have helped make the story more newsworthy.

*Washington Post* correspondent William Booth, for example, who quoted their remarks in the third paragraph of his story on the results, says that "the research seemed interesting regardless [of the editorial]." But he added that "the editorial was useful because it gave reporters something quotable."

But how would he have felt about quoting the Austrians if he knew their institute had a significant investment in the technique? Booth says: "I would have been more skeptical about what they had said."

What Booth—and *Cell*'s scientist-readers—couldn't know was that some of the key aspects of the experiments have been successfully repeated at the Austrian institute itself. Busslinger told *Science* in a telephone interview earlier this week that none of the research described in the *Cell* paper had been carried out in Vienna at the time the paper was written. But he admitted that Spadafora had come to the Vienna institute with his original research findings, and that the two IMP scientists had advised him "what kind of additional experiments he should do," what type of additional controls were necessary, and so on, "so that the scientific community would buy the results."

Busslinger also said that, after Spadafora's manuscript was submitted to *Cell*, the institute began its own experiments in an attempt to provide an explanation for the Italian team's findings, experiments whose results have since led to a potentially lucrative patent application. Busslinger acknowledges that this was somewhat unorthodox: "You could say that [our awareness of Spadafora's results] was privileged knowledge—that's true."

*Cell* editor Benjamin Lewin defends his decision to commission the editorial from Birnstiel and Busslinger, saying that it is "not unprecedented" to ask a scientist to expand on the broader implications of a paper by a scientific colleague. But he says that he was not aware that the institute for whom the two work had any direct commercial interest in the research itself.

Lewin then told *Science*: "There is always a concern if someone published a paper which may be advancing their own interests." But he went on to say that he cannot see this being caused "by a mini-review pointing out the importance of a bit of science."

Others, however, say they would have been happier if it had been made clear that the two scientists were working for a privately funded laboratory that, together with its two sponsors, Genentech and Boehringer Ingelheim, stands to gain from the research that the scientists were commenting upon.

Eric Davidson, professor of biology at the California Institute of Technology, says, for

example, "I am not sure if it is exactly fair to the scientific community to hear these words from a former basic scientist who is now the director of a commercially sponsored laboratory, and is therefore involved in this type of research to make money."

As for comparisons with cold fusion, ironically, it was Birnstiel and Busslinger themselves who first raised the parallel in their *Cell* editorial. Biologists reading the paper, they wrote, "may experience the same surprise and bafflement that overcame physicists informed recently about the possibility of nuclear fusion occurring at room temperature." Readers of the journal, they added, would be expected to treat the report "with the same hefty dose of skepticism."

One good reason for such skepticism is that other researchers well versed in embryology have often tried introducing the DNA through the obvious route of the sperm—and failed. But some researchers suggest that Spadafora's inexperience in the field may, in fact, have been a bonus. "It may well be that, not being constricted by the conventional way of doing things, they had a little bit of space to do the extra experiments," says John Clark, a leading British researcher on transgenic animals who works at the Edinburgh-based Institute of Animal Physiology and Genetics Research of the U.K.'s Agricultural and Food Research Council.

Spadafora is in fact very modest about his achievements, which stands in sharp contrast to the statements made by some of the leading actors in the cold fusion affair. "Cold fusion it is not," says *Cell* editor Lewin. "The analogy is inappropriate; we went through the scientific aspects [of his paper] in great detail, and it was refereed, returned to the authors, and re-refereed in the normal way before publication," he says, adding that although this process took place "reasonably expeditiously," it was not given particularly special treatment.

Lewin emphasizes, like many in the scientific community, that the real test will come when others report on the success—or lack of it—in attempting to achieve the same results. This is likely to take several months, since it will require the gestation and birth of at least two generations of mice.

"We hope to have something to report, one way or the other, by the beginning of September, and we plan to report it first to the scientific community. That's the way these things should be done," says Ralph Brinskter of the University of Pennsylvania in Philadelphia, who is trying to repeat Spadafora's experiments.

Even if other scientists manage to replicate the results reported in *Cell*, several other obstacles remain to be overcome before it is known whether the technique is really useful.

One is whether enough foreign DNA can be introduced into animals in the way discovered by Spadafora and his colleagues—and survive intact—to obtain adequate gene expression. The plasmids used in the Rome experiments, for example, contained relatively short sequences, and there is some evidence in the paper that the DNA may get a bit mangled in the process.

A second step to take will be the question of deciding what types of genes it would be most appropriate to introduce into animals by this technique. "If other scientists show that this technique works, then it could well remove a potential bottleneck [in producing transgenic animals] if not in mice, then certainly in terms of improving farm animals," says Clark.

A third question relates to the ethical implications of the research. The Italian scientists point out that, if the technique replaces other methods of producing transgenic animals, it will have "established a simple and straightforward technology of introducing DNA into mammals, offering many advantages over other methods."

Given the fierce public debate that is currently building up in Italy on this topic—a public petition demanding a ban on all patenting of living organisms has already collected more than 100,000 signatures—the debate about how the research itself should move forward is unlikely to be left in the hands of the scientific community.

■ DAVID DICKSON

## Old Technique, New Luck

Corrado Spadafora is a molecular biologist whose principal scientific interest was originally the structure of chromatin. He is currently working at the National Research Council's Institute of Biomedical Technology, in Rome. It was his study of the activity of the enzyme micrococcal nuclease, and his discovery that the head of the sea urchin sperm could be made to absorb both the enzyme and DNA itself, that led him into the field of genetic transfer. After showing that the sperm of *Xenopus* could also be encouraged to absorb DNA, he spent several fruitless years trying to bring eggs fertilized with the augmented sperm to term, but never succeeded in obtaining sexually mature offspring. But after a visit to the Institute of Molecular Pathology, Vienna, to discuss his results with Max Birnstiel, Spadafora decided to turn from frogs to mice, and success quickly followed—the *Cell* paper describes how 30% of the offspring of mice fertilized with the technique have been shown to have absorbed the foreign DNA.

Spadafora is described by a former colleague at the French National Institute of Health and Medical Research's molecular biology and genetic engineering unit in Strasbourg, where he worked for several years in the late 1970s, as "a very gentle person" and a dedicated scientist "who could be found working in the laboratory, like many of us, at all hours of the day and night." Spadafora himself says that he was "very lucky" to stumble across findings that may turn out to have applications in a wide number of fields. "I have spent most of my scientific work studying chromatin and DNA formation," says Spadafora. "Transgenic animals are not my field, and I feel a little bit uncomfortable about it."

Why had his technique worked, where efforts by others had failed? Without revealing his current ideas on the mechanisms at work, Spadafora says that "there appears to be something protecting the sperm" which does not normally allow DNA to penetrate. "It is something we are working on at the moment," he says. ■ D.D.