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Antitumor effects of hCG in KS

To the editor:

The letter of Drs. Sairam and Antakly (*Nature Biotechnology* 15:1228, November 1997) is misleading. They claim that our *Nature* paper[1] on Kaposi's sarcoma (KS) in pregnant women was wrong in its interpretation that "hCG" was active against tumor cells. In response to a report in *Nature Biotechnology*[2] describing our recent presentations at international meetings that we now know that the activity is not hCG but an associated polypeptide accompanying some preparations of hCG, they claim that they "had reached the same conclusion some time ago," and attempt to trivialize our discoveries, noting "massive amounts of impure hCG" were needed. They go on to describe their recent note in *Endocrinology*, that they could separate "the activity" from hCG[3].

Our *Nature* paper described a novel neoplastic cell line from AIDS-associated KS, which produced a transplantable metastatic sarcoma in immune deficient mice, noted that the tumor regressed in early pregnancy, and that sera from women in early pregnancy had anti-KS activity. Because hCG is the most obvious hormone of early pregnancy of humans, we first tested it. We noted that some crude clinical grade hCG preparations had anti-KS activity. The "massive amounts" Sairam and Antakly stated that we used were in the nanomolar range in the in vitro clonogenic assays.

Several clinicians then used the same clinical grade preparations in treating KS. At least five reports[4–8] describe beneficial effects of these hCG preparations against KS tumors even in late stage when patients were resistant to chemotherapy or could not receive chemotherapy due to drug toxicity.[7–8] Treatment with "hCG" was without toxicity. We already noted in these publications that the active moiety was not hCG but an accompanying factor[4,6,7]. Within days of the publication of our May 1995 *Nature* paper[1] we suspected the activity was not hCG itself since the anti-KS activity varied among different preparations while the standard hCG units remained the same. By mid-1995, we repeatedly stressed this at several meetings.

In May 1995 we demonstrated that purified hCG was inactive (unpublished). With our collaborator Steve Birken, the activity was separated from hCG and shown to be a polypeptide by mid-1996. These results were widely presented, including at least one meeting that Dr. Antakly attended. We also reported that the activity was mimicked by a βhCG synthetic peptide. As *Nature* editors know, all these results were submitted for publication 1.5 years ago. We ultimately agreed with reviewers who felt we should wait until we identified the polypeptide. Consequently, we elected to present progress reports and hold publication. We will alter this plan.

Astonishingly, in Sairam and Antakly's note, they not only do not identify the activity, they actually hypothesize it may very well be an hCG β-chain internal fragment, (our hypothesis and based on our data), yet the tone of their letter and the title given by *Nature Biotechnology* ("Debunking hCG"), implies the opposite.

The fact is simple: Some important biological effects of an unknown polypeptide have been discovered by us. The activity reported by Sairam and Antakly falls in the low molecular weight region, appearing to be in the range of salt. No data was presented to show its chemical nature. Since their hCG preparation contains phenol (which elutes near their peak), and phenol is toxic to KS tumor cells, it may very well be that the contributions of Sairam and Antakly are in the partial purification of phenol.

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1. Lundardi-Iskandar, Y. et al. 1995. *Nature* **377**:21–22.
2. Hopp, T. 1997. *Nature Biotechnology* **15**:834–835.
3. Kachra Z. et al. 1997. *Endocrinology* **138**:4038–4041
4. Gill, P.S. et al. 1996. *N. Engl. J. Med.* **335**:1261–1269.
5. Lundardi-Iskandar, Y. et al. Submitted.
6. Gill, P.S. et al. 1997. *J. Natl. Cancer Inst.* **335**:1797–1802
7. Hermans, P. et al. *J. Hum. Virol.* In press.
8. Harris, P. et al. 1995. *Lancet* **346**:118–119.

Baby-making and cookie cutters

To the editor:

Ruth Schwartz Cowan's review of my book *Unzipped Genes: Taking Charge of Baby-Making in the New Millennium* (*Nature Biotechnology* 15:1013–1014, October 1997) seriously distorts both the spirit and the text of the book. The book sets forth four principles to guide genomic decision-making in the coming generations.

The first principle is that the human genome is *res communes*, and therefore not pollutable. Cowan criticized the book for not defining pollution as "transgenic hybridization." She should recall that our DNA has plenty of transgenic hybridization—it is called retroviral nucleotides. Genomic pollution was defined, in the book, as birthing genomes for purposes other than family-building, i.e., spare organs.

The second principle is that of absolute procreative freedom. Cowan said her "mind boggles" at the book's disregard for the "evolutionary consequences" of unrestricted parent-directed germline therapy. To the contrary, the book made clear that "evolutionary consequences" would most likely come from state-directed germline therapy, the antithesis of which would be a constitutional bioethic in favor of parental procreative freedom.

The third principle is the state's right to prohibit forced pregnancies. The book forecasts that over the course of the next millennium it is inevitable that unintended pregnancy will be prevented via "inocuseeding"—the banking of sperm (and possibly eggs) accompanied by biochemical vaccination against impregnation. Cowan converts this straightforward extrapolation of current reproductive technology trends into a fanciful notion indeed. She says that if we allow this to occur, "all the sperm in the state of, say, Tennessee could be rendered unusable by a governor who happened to have a fit of pique one day." By this logic, we all need to keep guns at home in case the government goes berserk (or the United Nations invades). That is, indeed, the logic of the pro-gun lobby.

The purpose of the third principle is to prevent by private action that which the state cannot be allowed to do: force people to produce genomes against their will. Cowan missed the point entirely due to her difficulty in seeing unwanted pregnancy as a disease, a major point of the book.

Finally, Cowan misread the fourth principle, which prohibits genomic discrimination. She notes that this principle would prevent a woman from aborting a Down's syndrome fetus. Not at all. The book clearly said that procreative liberty trumps all but the first principle, the proscription of genomic pollution. The point of the fourth principle is that a woman should *not be forced* to abort a Down's syndrome fetus, a society should be *taught* by government to respect persons with Down's syndrome.

Cowan was clearly disturbed by my book, and repeatedly criticized the title's *double entendre*. But I stand by the appropriateness of the title as illustrative of the conflict between the casual nature of sex and the serious nature of the genomes produced thereby. I also stand by the appropriateness—and even the urgency for—the four hierarchical bioethical principles in light of the rapid advances in reproductive technology and genomic engineering. Lastly, I stand by the aptness of my metaphor which Cowan derided—RNA are like cookie cutters. Just ask an amino acid.

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