Problems with Co-Funding in Canada

The Canadian Federal Government has prudently invested substantial new resources in research operations and infrastructure, thereby bringing the level of research support in Canada on par with that of most other G8 countries and enabling a world-class research enterprise. Much of this renewed commitment to research, however, is in the form of “co-funded” programs. In Canada, co-funding schemes typically require an equal or greater match of funds from an independent partner, either local, provincial, or foreign governments; private foundations; or industry. In principle, co-funding should leverage funds from other sources and hasten the transition of fundamental research to commercial application. In practice, co-funding can exact a debilitating toll on the research community.

Inevitably, co-funding steers resource allocation, as dictated by the partner entity, which may be to the detriment of some of the best science. In particular, co-funding is often biased against fundamental research that is far from commercialization and so at odds with the short-term goals of industrial partners. The vicissitudes of most co-funding sources also severely compromise the sustainability of long-term research platforms. Co-funding is more easily obtained by well-connected investigators able to draw on resources and contacts inaccessible to many of their colleagues, thereby greatly restricting the pool of eligible science. Moreover, the mega-scale mandate of many co-funding initiatives virtually eliminates the individual researcher or small teams in favor of larger, sometimes artificial, consortiums. Perhaps most troubling from a scientific perspective, the criteria for eligible co-funding are inherently subjective.

A recent example illustrates the latter point. Genome Canada, the primary Canadian funding agency for genome-scale projects, has winnowed its latest round of team applications solely on the basis of the perceived financial suitability of the co-funding source. To this end, each application required up to 10 times more pages of budgetary justification than the scientific proposal itself. Of ~120 initial proposals, ~30 were culled at an early stage without review at all. Of the 93 full proposals allowed to go forward, almost one-third were eliminated by a panel of accountants based on ambiguous financial criteria and without any consideration of scientific merit, with many of the remainder placed in a financially suspect category.

The conclusions to be drawn are obvious: In general, grants are best awarded solely on the basis of scientific peer review, and funded in full without matches, strings, or contingencies that depend on outside agents. By eschewing scientific excellence as the primary consideration, co-funded programs imperil scientific credibility.

By eschewing scientific excellence as the primary consideration, co-funded programs imperil scientific credibility...

—Tyers et al.

Issues in Biosecurity and Biosafety

A 2004 report, Biotechnology Research in an Age of Terrorism, recommended that Institutional Biosafety Committees (IBCs) review research for biosecurity and “dual use” potential, to prevent nefarious applications such as bioterrorism or biowarfare (1). To discuss this recommendation, we convened a group of IBC chairs, scientists, and administrative staff from our six universities on 11 May (2). We hope that the fruits of our deliberation will be considered by the National Scientific Advisory Board on Biosecurity (NSABB), which will meet for the first time on 30 June.

NSABB’s first task is to formulate criteria for “dual use,” starting from the seven “experiments of concern” in the 2004 report. Yet the much deeper problem is what to do once concerns are identified. There appears to be little consensus.

Some believe that secrecy is the best policy to stop proliferation. Others believe open science is the best long-term policy; misuse is a risk, but secrecy hinders advances toward drugs, vaccines, and detection methods. There is some agreement between these frameworks, however: Most agree that security measures and the location of dangerous materials should remain secret and that most research results should be published. But experiments reconstituting synthetic polio and the Australian experience with interleukin-4 in mousepox (3, 4) exposed areas of conflict. Many scientists believe publication was appropriate, but it is far from clear that the case for “open science” has been made successfully with the general public, law enforcement officials, or elected officials.

Last year, as the Policy, Ethics, and Law Core of the Southeast Regional Center of Excellence for Biodefense and Emerging...
Infections, we reviewed a few experiments that might inadvertently enhance pathogen virulence, similar to protocols IBCs may face. We found little to guide us. Journal editors made a statement committing to vigilance (5), but many questions remain for investigators and their institutions: Should they destroy stocks of pathogens? Swear post-docs and graduate students to secrecy? Notify NIH? What should be told to local public health officials? A “new” agent must be registered, but what does this mean?

Adding review of proliferation of bioweapons to the existing biosafety (mitigating biohazard) mandate for IBCs is a big change. IBCs have gotten little attention and few resources over the past two decades. A 2003 survey found only 21% of IBCs reported that their members had training in biosafety review; 64% had less than one full-time equivalent staff member (6). Last year’s “Sunshine Project” report on IBCs, although strident and sarcastic, further documented this dearth of attention (7). We are concerned that IBCs today might face a situation similar to resource-starved Institutional Review Boards (IRBs) in the late 1990s. IRBs received attention only after human research was conspicuously shut down at major research institutions.

NIH recently gave welcome guidance to IBCs (8). The big new task of biosafety review is nonetheless fraught with ambiguity. Federal guidance to IBCs now comes from NIH’s Recombinant DNA Advisory Committee (RAC), focused on biosafety; NSABB will address biosecurity. Sorting out the respective roles of IBCs, RAC, and NSABB will clearly be a challenge. NSABB will not review individual protocols; instead, it will respond to requests for guidance. Protocol review will thus be left to IBCs, at least initially. Are institutions prepared to shoulder this burden?

The stakes are high: Biodefense is a prominent and hotly contested field that has grown immensely in the past 3 years. It is juggled in many different directions, as previous correspondence in these pages testifies (9–11). Biosecurity review is yet another battleground. IBCs will need resources, training, and guidance to ensure that resources devoted to research on biodefense and emerging infections are used effectively, and that public trust and accountability are preserved.

**LETTERS**

Problems in Patenting Human Genes

I read with interest the Policy Forum “Patents on human genes: an analysis of scope and claims” (J. Paradise et al., 11 Mar., p. 1566). There is no doubt that patents have been issued with claims that may be exaggerated in scope and would ultimately be held invalid if attempts were made to enforce them. There are a number of instances where
letters

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responses

our study did precisely what Murashige is calling for. We applied the statutory requirements of 35 U.S.C. § 100 et. al. to gene patents. This contrasts with what practicing attorneys routinely do, which is to claim aggressively for their clients, even though some claims might later be invalidated in litigation.

Rolla assumes that we have overestimated utility problems by including patents granted before the USPTO in 1999 issued new utility guidelines. However, because we limited our analysis to gene patents related to specific diseases, the patents we analyzed were not of the offensive expressed sequence tag variety, which the guidelines addressed. The pre-1999 patents we analyzed had a potential use in diagnosing diseases, and the policy change did not affect their patentability.

Rolla criticizes us for not analyzing the file history of the patents we examined. The Federal Circuit, however, has noted that an analysis of the specification [the portion of the patent where the invention is described (1)], and not the file history, is usually “dispositive” of any claim construction issues (2). That is what the investigators meticulously did in this study. The file history is not relevant in assessing the adequacy of the patent’s disclosure and the utility of the invention.

The juxtaposition of Rolla’s claim that “the invention is the chemical compound, not “the information” ” and Murashige’s “recognized practice” of using a protein sequence to claim exclusive rights to undis-
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**Letters**

covered, hypothesized DNA sequences, underscores our point that inventions in this area relate to data, not compounds. Moreover, traditional composition of matter patents cover a chemical composition with a particular function, such as a drug, which can be designed around. A genetic sequence—the alphabet of ATCGs—is strictly information that has no function until it is linked to an intervention such as a method of diagnosis. Yet allowing a patent on that information allows the holder to prevent others from using the basic sequence, even in research (3), and one cannot design around a human nucleotide sequence if one wants to study, diagnose, or treat the genetic disease at issue.

Murashige cites *In re Wallach* (4), where the court said in dicta, which is not binding precedent, that it “may” (not necessarily, would) in a future case find that knowing the protein sequence alone would allow the patent applicant to claim all DNA sequences coding for that protein. Such a comment conflicts with the holding in *In re Deuel* that knowledge of a protein sequence does not necessarily put the inventor in possession of the DNA sequence, because of the redundancy of the genetic code (5).

We were careful to state that our findings represent our team’s application of the statutory guidelines and do not necessarily predict what a court would do. In the United States, unlike in Europe, there is no formal mechanism for third-party intervention in the decision to grant a patent, so studies such as ours may be the only way for the larger community to weigh in on the legal appropriateness of gene patent claims.

**CORRECTIONS AND CLARIFICATIONS**

**News of the Week:** “With domestic program at issue, House votes to hold up funding for ITER” by E. Kintisch [3 June, p.1395]. The amendment by Rep. Sherwood Boehlert (R-NY) to delay any spending on ITER until March 2006 was offered in support of the position of the Department of Energy that funding for some domestic fusion energy experiments may need to be cut to finance ITER. “Unless we can get agreement that the U.S. participation in ITER will require changes to the domestic program, then the U.S. should not sign on to ITER,” Boehlert says. His position contrasts with the views of many fusion scientists and with the House Appropriations Committee, which recently declared that supporting ITER at the expense of domestic fusion research is “unwise” and “shortsighted.” Boehlert’s amendment was attached to a 2006 spending bill for the Department of Energy that passed the House 24 May.

**Reports:** “ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex” by J.-H. Lee and T. T. Paull [22 Apr., p. 551]. The Biomolecular Interaction Network Database (BIND) accession codes given in reference 21 are incorrect. The correct codes are Z16040 to Z16045.


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**TECHNICAL COMMENT ABSTRACTS**

**Comment on “S-Nitrosylation of Parkin Regulates Ubiquitination and Compromises Parkin’s Protective Function”**

Stuart A. Lipton, Tomohiro Nakamura, Dongdong Yao, Zhong-Qing Shi, Takashi Uehara, Zezong Gu

Chung et al. (Reports, 28 May 2004, p.1328) reported that S-nitrosylation of parkin inhibits its ubiquitin E3 ligase activity and neuroprotective function. Concomitantly, we found that S-nitrosylation first increases E3 ligase activity. This initial increase may contribute to the formation of Lewy bodies, ubiquitinated inclusions of misfolded proteins which are a hallmark of sporadic Parkinson’s disease.

Full text at www.sciencemag.org/cgi/content/full/308/5730/1870b

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**RESPONSE TO COMMENT ON “S-Nitrosylation of Parkin Regulates Ubiquitination and Compromises Parkin’s Protective Function”**

Kenny K. K. Chung, Valina L. Dawson, Ted M. Dawson

Further experiments carried out in our laboratory confirm the finding that S-nitrosylation of parkin enhances its E3 ligase activity at earlier time points, but inhibits its ligase activity at later time points. We suspect that this biphasic response plays a more important role in regulating the physiologic E3 ligase activity of parkin and the ubiquitination of its substrates.

Full text at www.sciencemag.org/cgi/content/full/308/5730/1870c

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**Letters to the Editor**

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