How to stay out of a BIND

To the editor:

Your very sympathetic editorial in the February issue (*Nat. Biotechnol.* **23**, 215, 2006) regarding the demise of the Biomolecular Interaction Network Database (BIND) assigns the blame for this resource's passing to "...bureaucratic delays [and] government fiscal nitpicking...." and calls on science funding agencies to provide more long-term funding for databases. Worthy as your crusade to better direct my tax dollars may be, I don't find BIND to be a particularly suitable poster child for the effort.

According to your account, BIND, via the Blueprint Initiative, burned through $25 million in about two years. Even in Canadian dollars that burn rate is nothing short of shocking, especially given BIND's relatively modest scope, and the ease with which its data were to be 'scraped' from a relatively small number of scientific publications (I have quite a bit of professional experience in this domain, so I say this with some insight.) Personally, I admire Genome Canada's decision to stop the bleeding.

I'm sure there were, and are, those who have found BIND useful. Whether or not it was another $20.8 million worth of 'useful' or a total of $46 million worth of useful, given all the other worthy scientific uses to which that sum could be put, was the question, and Genome Canada decided this in the negative, citing concerns regarding management, budget justification and financial plan—concerns your editorial brushed aside without comment.

A happy consequence of Genome Canada's decision is that BIND is now where many such efforts belong. . . in private hands (albeit under the same management), where the rigors of the marketplace can impose upon its owners some deep regard for efficiency and utility. If BIND is truly valuable, then Christopher Hogue can charge users a modest access fee; perhaps research funding agencies will view their grantees' carefully justified requests for these small sums with favor. He may then use such hard-won revenues prudently to sustain and improve the product. If, on the other hand, BIND isn't a particularly important resource, then users won't be willing to pay, and it will pass on. This is as it should be.

Much the same may be said for the Alliance for Cellular Signaling's Molecule Pages, which never really amounted to much (numerically, at least). Now under Nature Publishing Group's cost- and profit-conscious guidance they will, no doubt, either flourish or fold.

Rather than arguing for the importance of long-term database funding by granting agencies, BIND's saga in fact argues for greater caution and more demanding oversight when these agencies elect to fund a database's initial development. Realistic plans for long-term sustainability must be demanded, as must some basic enterprise management ability on the grant recipient's part. Such expectations are anything but fiscal nitpicking; they are a fiduciary responsibility. I have no bone to pick with researchers who bemoan the intermingling of capitalism and scientific research (if, in this Bayh-Dole era, there's anyone left who can still do so with a straight face). But those who feel this way should be prepared to make every precious tax dollar go as far as it possibly can. Those who fail at this should be quicker to blame themselves, and slower to blame 'bureaucrats'.

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The dog as a cancer model

To the editor:

The dog has long been used as a model in drug discovery and development research because of its similarities to human anatomy and physiology, particularly with respect to the cardiovascular, urogenital, nervous and musculoskeletal systems. Compared with other animal models, it may also prove invaluable in research and development on cancer drugs, because dogs naturally develop cancers that share many characteristics with human malignancies. The completion of a high (7.5×) coverage canine genome[1] now paves the way for the development of critical resources that will allow the integration of naturally occurring canine cancers within the mainstream of cancer research. To initiate and facilitate collaborative efforts and leverage the opportunities provided by the dog in cancer research, scientific and clinical leaders from both human and veterinary oncology have come together to form a multidisciplinary consortium, the Canine Comparative Oncology and Genomics Consortium (CCOGC).

Cancers in pet dogs are characterized by tumor growth over long periods of time in the setting of an intact immune system, inter-individual and intra-tumoral heterogeneity, the development of recurrent or resistant disease, and metastasis to relevant distant sites. In these ways, dog cancers capture the 'essence' of the problem of human cancer in a manner not possible with other animal model systems. Compared with other large animals commonly used in biomedical research, such as pigs and nonhuman primates, an additional advantage offered by pet dogs is that they are cared for into the ages

commonly associated with the highest risk for cancer. This risk, coupled with their large population size (>70 million in the United States), results in a cancer rate sufficient to power clinical trials, including assessment of new drugs. Using crude estimates of cancer incidence, in the United States alone, there are ~4 million new cancer diagnoses made each year in dogs[2]. Examples of these cancers include non-Hodgkin lymphoma, osteosarcoma, melanoma, prostate carcinoma, lung carcinoma, head and neck carcinoma, mammary carcinoma and soft-tissue sarcoma. For many of these cancers, strong similarities to human cancers are seen, including histological appearance, tumor genetics, biological behavior and response to conventional therapies. The compressed course of cancer progression seen in dogs allows timely assessment of new cancer therapies.

With the recent release of the canine genome sequence, the dog is now also amenable to comparative genomic analysis. Indeed, preliminary assessment of the canine genome suggests that the dog and human lineages are more similar than the human and rodent lineage in terms of both nucleotide divergence and rearrangements. The CCOGC initially plans to take advantage of these opportunities through the following actions:

- Develop a robust and well-annotated biospecimen repository of canine cancers and tissues—funding of a large, accessible biospecimen repository is difficult using existing resources.
- Improve opportunities to link the efforts of veterinary and comparative oncologists with the work of basic cancer researchers and clinicians.
- Initiate non-clinical trials using pet dogs with cancers that are integrated into the development path of new cancer drugs. Mechanisms for review of these non-clinical trials by regulatory bodies should be developed such that information from these studies, where appropriate, may help to focus the scope of early human clinical trials.

To date, non-clinical studies in dogs with cancer have answered questions that would have been difficult or impossible to answer in either mice or humans. The lack of gold-standard veterinary treatments also provides the opportunity for the early and humane evaluation of new therapies for dogs with cancer. Following institutional review of trials, pet owners would be given the option to enter their dogs into clinical trials and in so doing receive access to novel cutting-edge treatment options for cancer, many of which are less toxic than conventional treatment options currently available. Accordingly, studies in pet dogs offer opportunities in both human and animal healthcare.

The 2.4-billion-bp (7.5× coverage) sequence of a female boxer dog (pictured) published in December 2005 (ref. 1), together with that of a poodle sequence released in 2003, should facilitate the use of dogs in cancer studies.

First, pet dog trials will help better define the safety and activity of new anticancer agents. They may also assist in the identification of relevant biomarkers associated with response or exposure to these drugs. Furthermore, these studies may allow rational development of combination strategies that will improve the success of these new drugs in human clinic trials. These data may be useful before the filing of an investigational new drug application (IND) at the US Food and Drug Administration (FDA; Rockville, MD) and as means to optimize the development of anticancer agents currently in early human trials.

Second, data generated through such studies may inform the development of new cancer treatments for animals. Research and development of new anticancer treatments is increasingly recognized as an area of need in the field of animal health. In this way, pet dogs with cancer will be directly helped through access to new these new drugs; results may be translated and extended to the development of better cancer drugs for humans and other pet dogs.

An opportunity window now exists. With the realization of the need for more useful animal models in human cancer drug development, the organization of a number of consortia and collective groups, the completion of the canine genome sequence, the increasing availability of dog-specific biological reagents and investigative methodologies, (e.g. antibodies specific for dog proteins or dog-specific oligonucleotide arrays) and the interest of the animal health biotech and drug industry, the CCOGC hopes to further stimulate efforts to fully exploit the many advantages of the dog in cancer drug research.

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