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BEP Programme

To the editor:

The fascinating article "European exploitation of biotechnology—do government policies help?" (*Nat. Biotechnol.* **18**, 605–608, 2000) had one noteworthy omission. This is the "Biotechnology Exploitation Platform" (BEP) Programme, a successful scheme funded specifically by the UK Department of Trade and Industry to improve the protection and commercial exploitation of biotechnology arising from UK academic research.

The BEP Programme was designed to overcome two perceived obstacles to successful exploitation of academic research in the biosciences. To enhance the knowledge and expertise of university technology transfer offices in the modern biosciences, funding is provided to allow the recruitment of additional staff with qualifications and expertise in some area of the biosciences and (hopefully) some experience of industry or technology transfer; and to overcome the suboptimal nature of much technology arising from individual academic institutions or departments, the program requires the formation of consortia of universities who will work together to package and exploit their combined technology.

The program started in 1997 with a pilot scheme that made a total of £2.45m of funding available. Awards were competitive, and to a maximum of £250k over three or four years. Private matched funding had to be provided by the participants. Awards to eight consortia were made during the pilot scheme. Some of these consortia were regionally based, and others focused their activities on specific areas of bioscience, for example, cancer.

Bearing in mind the fact that the program has been running over only a short time scale in technology transfer terms, it has been very successful in stimulating the protection and exploitation of intellectual property. At the last count six months ago, 80 patent applications had been filed, 25 spinout companies formed, 20 licenses signed, and significant revenue from industrial research and development contracts secured (all numbers approximate).

The success of the pilot program led to the announcement of a full BEP Programme in August 1999 with a total of £6.5m funding available. The first six successful bids under the new scheme will be announced shortly.

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Ubiquitin/proteasome system

To the editor:

Dantuma and colleagues[1] have recently proposed the use of engineered green fluorescent proteins as substrates for the quantification of the ubiquitin/proteasome-dependent proteolytic system in living cells. Because of the critical involvement of this pathway in many essential processes, this effort is greatly appreciated and the development of new assays urgently needed. However, what Dantuma et al. have really developed is an assay representative of only a limited fraction of the ubiquitin/proteasome system. In fact, it is well known that the ubiquitin–protein ligases (E3s) responsible for substrate recognition can be grouped in at least four subtypes with regard to structure and degradation signal recognition[2]. The fusion proteins described by Dantuma et al. utilize only one of such pathways (the N-end rule) that in addition has a yet unknown function and thus cannot be considered representative enough to be used in high-throughput screening programs of compounds that selectively modify proteolysis in vivo. Furthermore, the UFD (Ubiquitin Fusion Degradation) pathway is also in search of a defined function in mammalian cells. The only possible implication for UFD1 in humans appears to be the DiGiorge syndrome in 22q11.2 deletions[3].

Huang and colleagues[4] have reported that expression of a green fluorescent protein in transgenic mice causes cardiomyopathy. Thus the accumulation of the reporter cannot be considered without consequences for the cell, making the suggested correlation between ubiquitin/proteasome-dependent proteolysis and toxicity difficult to evaluate with confidence. Finally, green fluorescence proteins constructed to be a substrate for the N-end rule pathway seem instead to follow the UFD pathway, at least in *Dictyostelium discoideum*[5].

In conclusion, the green fluorescent protein reporters described by Dantuma et al. are certainly of interest but do not yet provide an informative tool useful in the screening of inhibitors that may interfere with the multiple steps (ubiquitin tagging, unfolding, and proteolysis) of the ubiquitin/proteasome pathway. We believe that the ubiquitin/proteasome pathway is involved in so many cellular processes that it could not be properly described by a single model substrate and that the minimal requirement should be the availability of substrates recognized selectively by the four subtypes of ubiquitin–protein ligases.

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Maria Masucci and Nico Dantuma reply:

In response to Prof. Magnani, it is well established that the ubiquitination cascade exhibits a hierarchical organization, where a single ubiquitin-activating enzyme (E1) interacts with a large family of ubiquitin-conjugating enzymes (E2), which in turn cooperate with even larger groups of ubiquitin ligases (E3). Furthermore, current knowledge suggests that substrates targeted for degradation converge to a common proteolytic machine composed of the catalytic core of the proteasome (20S) and different regulatory subunits[1]. Thus, the reporters described in Dantuma and colleagues[2] may allow the identification of inhibitors acting at the early stages of ubiquitination, by selective inhibition of E1, as well as downstream of ubiquitination, including protein unfolding and proteolysis. It is true that the reporters will not detect inhibitors specific for a multitude of E2s or E3s. Yet, reporters recognized by different families of ubiquitin–protein ligases would suffer the same type of limitations—being of no use in the identification of inhibitors targeting individual enzymes. The easy establishment of stable GFP transfectants in numerous model systems suggests that the long-term toxicity of GFP in transgenic animals has no direct bearing on the use of the reporters in screening assays.

The accumulation of processed GFP in HeLa cells expressing Ub-M-, Ub-L-, or Ub-R-GFP confirms that these chimeras are efficiently recognized by ubiquitin hydrolases and are therefore bona fide N-end rule substrates in vivo. The observation that similar chimeras are recognized as UFD substrates in the slime mold *Dictyostelium discoideum* does not detract from their applicability in mammalian cells. Finally, it seems unlikely that highly conserved recognition strategies, such as the N-end rule and UFD signals, would have limited biological significance. We hope that the reporters described in Dantuma et al. will be useful also in dissecting this conundrum of regulated proteolysis.

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