Cofactor-mediated protein promiscuity

To the Editor:

The review article by Nobeli *et al.*[1] in the February issue creates a conceptual framework for protein binding and functional promiscuity and delineates its significance for biotech. As the interpretation of protein promiscuity in the literature is itself promiscuous, this timely review comes to clarify important features of this phenomenon. The authors have proposed a comprehensive classification of the mechanisms responsible for protein recognition and functional promiscuity. We believe, however, that an important additional mechanism for protein promiscuity could be added to this classification.

Heme (ferroprotoporphyrin IX) is an ubiquitous macrocyclic compound present in all kingdoms of life, predominantly in a protein-bound form. The proteins that use heme as a cofactor are referred to as hemoproteins; these have pleiotropic functions not limited to redox chemistry[2]. Heme is able to bind with a relatively high affinity to a great variety of proteins—from 'typical' hemoproteins, such as hemoglobin, myoglobin, peroxidases and cytochromes, to 'untypical' hemoproteins, such as albumin, prion protein[3], amyloid beta (Aβ) peptide[4], myosin[5], growth hormone[6], orphan nuclear receptors[7] and many others. Indeed, it is a challenge to define a protein that is not able to show any heme-binding activity. The remarkable binding promiscuity of heme is broader than the promiscuity of any other organic compound of a similar size. What is most intriguing, however, is that the promiscuity of heme is not limited only to the molecule itself, but it could also spread to the proteins to which heme binds. This 'contagious promiscuity' is obvious in the case of hemoglobin—a protein that is able, thanks to its heme groups, to interact with diverse gaseous molecules—oxygen, carbon monoxide, nitric oxide, hydrogen sulfide, among others. In addition to recognition promiscuity, heme endows hemoglobin with a functional promiscuity, explaining its well-known activities in gas transport, in the reduction of the oxygen molecule as well as its peroxidase activity. An even more striking example is the interaction of heme with the Aβ peptide, which not only prevents the formation of amyloid plaques by conformational rearrangement of Aβ but also endows the same peptide with peroxidase activity. We have recently, documented yet another example of heme-mediated protein promiscuity concerning protein-protein interactions[8]. Approximately 20% of human antibodies bind heme as an interface cofactor, and the intrinsic binding promiscuity of this bound heme confers substantial antigen-binding promiscuity that could well be important for antibodies' role in the defense against pathogens.

The prominent promiscuity of heme may be useful in biotech. Looking carefully at the properties of heme as a prototype promiscuous molecule could help in understanding what determines the binding promiscuity of different compounds and could thus selectively guide drug designers in creating less promiscuous drugs—a challenge that was discussed in the Nobeli *et al.* review.

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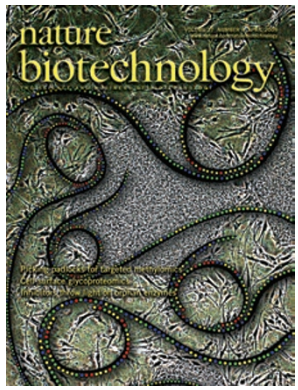
Healthcare-biotech symbiosis

To the Editor:

A Commentary by Scangos[1] in the May issue raises concerns about the future of biotech research at a time when both healthcare and medical research are under pressure. Despite criticism about research bias, a considerable number of breakthroughs in the treatment of diseases and prolongation of lives have come about through research backed by the biotech and pharmaceutical industries[2]. For instance, 92% of drugs approved by the US Food and Drug Administration in the early 1990s were developed by industry[3]. Healthcare, at present, is more technologically driven than ever; however, recent cuts in research funding are threatening to hamstring both technological and pharmaceutical innovations in medicine[4].



In addition to securing a baseline healthcare level, the international biotech and pharmaceutical industries have an established role in philanthropic actions in developing countries[5]. Moreover, in western European countries, pharmaceutical industry financing accounts for ~50% of the continuing medical education (CME) activities for healthcare professionals. CME is closely linked to specialist recertification and aims to validate continuing fitness of the practitioners. Specialist recertification can ensure patient safety and is in the process of development and implementation worldwide[6].

The key aspect of a flourishing health system is dynamism of healthcare research in terms of safe medical practice. This can be secured through a progressively increased allocation of finances in the right direction. In his Commentary, Scangos correctly highlights the potential for reduced capital