EDITORIAL

INTERDISCIPLINARY EQUILIBRIUM

Continuing our experiment of creating the right environment for interactions between disciplines, the first Horizon Symposium gave us the chance to tackle key issues in protein folding and disease.

Anyone familiar with this page will be well aware that we seek to encourage interdisciplinary cross-fertilization. We approach our subject driven by the belief that at least some of the shortfalls worrying the industry can be laid at the door of its compartmentalized culture. Grouping researchers by technique or by therapeutic indication can have the effect of making it too easy to ignore information from outside one's 'area'. "Get out more", we've been saying, "you never know what you might find".

So, since our launch in January, we've been attempting to create a sort of 'cocktail party' in print. By mixing up the very best of each branch of the subject, we hope that readers might just bump into that unexpected, but engaging, piece of information that changes the way they think about their problem. Last month saw an extension of this concept into face-to-face interactions, with the inaugural meeting in our new series of Horizon Symposia. Given that there are already multiple meetings at which we have the chance to listen to each other give what is too often the same old speech, these meetings, created in partnership between the Nature Publishing Group and Aventis, hope to offer something different. They seek to give people from related but separate disciplines that rarest of opportunities — the chance for lengthy discussion of a topical problem in drug discovery.

The theme for our first three-day meeting was protein folding and disease, and specially written summaries of some highlights of this event have already been posted on our dedicated website (http://www.nature.com/drugdisc/horizon/home.html). The formula for the meeting was simple; put a small group of the field's leading exponents (also listed on the web site) together and give them the goal of discussing the key outstanding questions in each branch of the subject, from structural biology through cell biology and on to disease. Giving this progressive structure to the discussions helped to focus what might otherwise have been 'Brownian motion', and ensured that each topic was given due attention. As the highlights testify, the formula worked.

To illustrate the sort of theme that emerged from the meeting, take the problem of what actually constitutes the cytotoxic species in a protein-folding disease, such as Alzheimer's disease. For many years, researchers have tried to determine whether amyloid deposits are themselves neurotoxic, and therefore causative features of the disease, or merely by-products of the condition. Then, earlier this year, a couple of papers presented evidence that smaller aggregates of misfolded proteins, presumably on their way to becoming fully formed amyloid deposits, were more damaging than their larger brethren, indicating that these might therefore be better targets for intervention. The discussions at the meeting emphasized just how very little idea we have of how these entities relate to each other. Furthermore, the energy landscape linking the pathway between native protein and fully formed aggregates is highly dependent on surrounding conditions and the concentration of each intermediate state. So, before rushing in to develop therapies, it needs to be noted that any intervention will disrupt the balance between many interacting species. For example, it seems possible that amyloid deposits act as 'sinks' for smaller, more toxic misfolded aggregates, and so should actually be preserved as a 'good' feature of the disease. By the end of the meeting, a feeling had emerged on all sides that, lacking a sufficiently clear idea of what the correct therapeutic target species is, we should concentrate considerable effort on understanding the energetics of the misfolding and dimerization of the monomer that sets this cascade in motion.

In passing, many would have readily acknowledged this fact, but how many act on the basis of it? In the headlong rush from meeting to meeting, we often find ourselves dealing with cross-disciplinary questions that briefly make us question our assumptions, but the few minutes allowed for discussion means that we seldom need to engage very deeply with the issue. We acknowledge the problem, and then move on to the next talk. Achieving a consensus view at the Horizon Symposium took time to achieve, requiring people to live with the issues for a day or two. So it seems that achieving a useful interdisciplinary balance in the flesh needs not so much of the cocktail party atmosphere, but rather the allowance of enough time for equilibrium to be reached.

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