As risk increases, with greater attention being paid to rare diseases and difficult and uncertain molecular targets and strategies, so must the involvement of biotech and academic laboratories, which are less risk-adverse by their natures. This seems especially true for NIH-funded academic laboratories whose mandate must be to provide the taxpayer some measure of return on their tax dollars in the form of drug discovery research in diseases areas that are neglected by large and small pharmaceutical companies.

In the specific case of neurodegenerative disease, market risk increases from Alzheimer's disease to Parkinson's disease to Huntington's disease, while discovery risk increases from tried-and-true enzyme inhibition programs, such as those exemplified here by β- and γ-secretase inhibition, to inhibition of the protein–protein interactions that control the polymerization of proteins such as α-synuclein, tau and huntingtin. At the LDDN, we have chosen to aim at high-risk targets when we are focusing on a low-risk disease and, likewise, to aim at lower risk targets when we focus on a high risk disease (Fig. 2). With such a strategy, it is our hope to complement the discovery activities of industry in the arena of neurodegenerative disease.

To ensure the success of this new strategy, the pharmaceutical industry, financial community and government must work together with academics to develop innovative ways to fund organizations that are involved in high-risk drug discovery efforts. Only in this way will our society be able to meet the urgent needs of patients suffering from rare diseases.

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Letting biology do the work ▼

Cancer drug development is in transition. We are moving out of an empirical era of blunderbuss cytotoxics used at their most tolerable toxic dose to a far more sophisticated molecular-mechanism-based approach to cancer. The drugs are already there in the laboratory – over a 1000 such projects are recorded as being in the preclinical phase. They target cell-cycle control proteins, apoptosis systems, cell invasion and metastasis, angiogenesis, signal transduction, inflammation and differentiation. But there is a missing link – how best to measure their effect, which was the subject of a recent review [1].

Biomarkers that reliably quantify the effect of a drug on its molecular target are now becoming essential. The high cost of clinical development has made the cost of identifying a relevant marker before going on to clinical testing seem like peanuts. Translational research – bridging the gap between discovery and clinical operations – is here to stay. Furthermore, such biomarkers might also act as surrogate endpoints of successful treatment for cancer, which is ultimately judged by the effect of a therapy on long-term survival. Two other tools are also being intensively investigated. Functional imaging using magnetic resonance (MRI) and positron emission tomography (PET) allow us to follow in real time the subtle effects of a drug on cellular biochemistry whilst gleaning detailed anatomical information to search for differential effects between normal tissues and tumour. The fourth tool is the molecular subclassification of disease, which divides apparently homogenous groups of patients into new categories with different natural histories and likely responses to therapy.

Personalised medicine for cancer is the final goal. Currently the technologies used are holistic, searching for needles in

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the haystack to identify tumour subtypes. Genomics, proteomics, methylomics (DNA methylation patterns) and metabonomics are highly information-rich technologies that have spawned the new science of bioinformatics.

How will it all look in ten years time? By then biomarkers and early surrogates for tumour response will be an absolute requirement to take a drug into man. Holistic approaches will disappear as novel, effective indicator molecules are identified. Healthy volunteers will be used for Phase I cancer studies using pharmacodynamic endpoints, and Phase II studies will be completed in months using well validated surrogates of response. For some agents with clear mechanisms of action, Phase III randomized trials could be omitted. The global regulators will have the confidence to accept a new drug based on comparisons between new and old drugs of the same class, using biological markers only. Novel methods of pharmaco-vigilance will pick up any disturbing trends early, setting alarm bells ringing.

The studies reviewed in the article by Nicolette and Miller will radically change cancer drug development forever. However, realigning the R&D departments of the global pharma industry to meet this brave new world is going to be a significant challenge.

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Nuclear transport as a target for cancer therapies ▼

Currently in the literature there are at least a dozen tumor suppressor proteins and oncogene products known to be regulated at the level of nuclear–cytoplasmic shuttling. In a recent issue of *Drug Discovery Today*, an article by Kau and Silver outlined potential anticancer strategies based on the premise of targeting the localization, and hence activity, of cancer-linked proteins, including p53 and NF-κB, and also the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [1]. The discovery in 1994 of the first known nuclear export signal in HIV-1 Rev led to the realization that hundreds of cellular proteins actively 'shuttle' between the nucleus and the cytoplasm [2]. Perhaps as many as half of all known nuclear proteins can exit the nucleus. Here, I briefly address two other cancer-associated shuttling proteins, adenomatous polyposis coli (APC) protein and β-catenin, whose localization might provide future therapeutic targets.

APC is a tumor suppressor that is inactivated by the presence of truncating mutations in its encoding gene in patients with colon cancers. Many of these mutations prevent the phosphorylation and consequent proteasome-mediated degradation of β-catenin, an oncogenic transcriptional activator and a key transducing molecule of the Wnt signaling pathway. Overexpression of β-catenin is observed in numerous cancers, including colon cancer, melanoma, breast cancers and hepatocellular carcinoma [3]. Both APC and β-catenin are regulated by nuclear–cytoplasmic shuttling. APC contains five different chromosome region maintenance-1 (CRM1)-dependent nuclear export signals (NESs). By contrast, β-catenin exits the nucleus either via its association with APC or through a CRM1-independent mechanism [4]. The APC protein can shuttle in and out of the nucleus even when it is severely truncated in diseased cells. Preliminary evidence from studies in our laboratory suggests that trapping APC in the nucleus can induce tumor cell death, and thus this finding might provide a future direction for the development of anticancer agents (i.e. specific inhibitors of APC nuclear export). Of course, as with all small-molecule inhibitor treatments, selective host cell targeting is a major consideration.

The oncogenic effects of β-catenin require its nuclear localization and transcriptional activity, both of which provide potential therapeutic targets. There has been progress in resolving the structure of complexes between β-catenin and certain key binding partners such as APC and E-cadherin, as well as T-cell factor (TCF) transcription factors, which it binds to and activates in the nucleus. Such information should assist the development of specific peptide inhibitors that prevent the cancer-linked transcription-activating function of β-catenin *in vivo* [5]. Disrupting the interaction of β-catenin with nuclear transcription factors should also indirectly stimulate the nuclear export of β-catenin and its subsequent degradation in the cytoplasm [4].

In terms of reducing nuclear accumulation of β-catenin, cadherin fragments have been used to trap β-catenin at the plasma membrane, and one could envisage several types of NES-containing peptides that exclude β-catenin from the nucleus. Further study of the transport signals and pathways that facilitate β-catenin import and export are required to fully exploit this idea.

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