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Inducing apoptosis: mind the natural killer cells ▼

The elegant and timely review by Los *et al.* [1] lists numerous novel apoptosis-related drug targets, many of them seemingly suitable for further development as anticancer drugs. The list is expected to continue growing as data mining of the published human genome sequence continues to yield potential drug target candidates. Yet, one wonders how to select the most likely to succeed anticancer candidates among so many new apoptosis targets for further research and development. After all, the cost of drug development for an entirely new drug target is often prohibitive. Moreover, failures during advanced phases of clinical trials could create serious financial problems even for larger biotech companies.

We would therefore like to use this platform to offer a word of advice for the creative minds in academia and in the pharmaceutical industry who are looking for premium new anticancer targets. When searching for apoptosis-inducing anticancer drug targets, look for those that are least likely to obstruct the performance of the human immune system. Above all, beware of possible interference with the immune system's most vital innate cancer-fighting counterpart, the natural killer (NK) cells [2,3]. Indeed, inhibition of NK cell activity has often been linked to tumor development. For example, it has been suggested that stress-induced inhibition of NK cell activity is a key player in metastasis [4], and appears to involve the release of catecholamines from the adrenal glands [5].

The reason for this concern is that numerous apoptosis control pathways are apparently implicated in the intricate and delicate regulation of immune responses, fine-tuned by evolution to ensure accurate control of self-immunity. The drug-induced activation of some of these pathways in immune cells of cancer patients might inhibit the native immune attack on their cancer tissues, thereby potentially causing more harm than benefit at certain stages of the battle against cancer.

Moreover, identifying the novel apoptotic pathways employed by NK cells during their intrinsic attack on cancer cells, and harnessing these signals so that they can be enhanced by apoptosis-promoting anticancer drugs, might be a key approach for developing this innovative class of drugs. For example, activation of nitric oxide synthesis was implicated in cancer-cell-killing by NK cells [6]. Thus, it is likely that anticancer drugs capable of enhancing this particular activity in cancer cells could be particularly beneficial in battling cancer. In conclusion, while the long list of apoptosis-related drug targets implicated in killing cancer cells keeps growing, only selected targets might be activated without interfering with the patients' innate immune system. Moreover, only a handful of anticancer drugs might have the added benefit of augmenting NK cell action *in vivo*, and such drugs seem to have a potential advantage for cancer pharmacotherapy.

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Taking the lead? ▼

None of us needs reminding that the spiraling costs of bringing a drug to the market are primarily due to the alarming attrition rate of new drug candidates, a failure rate that few other research-based

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industries can tolerate and still remain profitable. Indeed, it is questionable how long this level of failure can be sustained. The identification and elimination of the causes of this attrition rate are of vital importance to the pharmaceutical industry, and Gilbert Rishton's review [1] makes an excellent contribution to this debate. By highlighting the differences between screening based on biochemical assays and the previously used biological assay systems, Rishton clearly identifies a major and potentially preventable cause of erroneous decision-making in appropriate lead selection. Furthermore, several criteria are suggested that are likely to be useful in removing compounds that will not be tractable for optimization.

A note of caution should be expressed, however. Although there is little argument in defining what is 'non-leadlike' (compounds that display non-productive or artifactual activity, owing to the nature of biochemical screening), positively defining what is 'leadlike' (compounds that have a higher chance for development to a drug) is far more open to question. Turning a lead into a drug is a mixture of many separate, often poorly understood processes, and is also highly prone to chance events, and I am not convinced that the physical properties of 'leadlikeness' are, or need to be, so very different from 'druglikeness'. In particular, the physicochemical definition of leadlikeness given by Rishton will result in a considerable loss of property diversity, likely to lead to a reduction in the hit-rate, particularly over an expanding range of biological targets. The 'weak-lead' strategy proposed by Teague and colleagues [2] could easily require more optimization work than a larger compound with fewer structural options, and thus greater potentially wasted effort to attain sufficient data for a go/no-go decision. For diversity alone, a proportion of compounds defined by Rishton as leadlike should be included, but I feel it far from wise to use it as a straitjacket for the entire collection. Furthermore, I would suggest that a practical concept of 'leadlikeness', to assemble a compound collection for use in lead generation, should include additional non-physicochemical factors such as novelty (that there will be fewer later constraints), ease of synthesis (that follow-up work can be quickly carried out) and diversity (that the compound has a chance to generate activity in the first place, or is this 'hitlikeness' – the probability that a compound will produce hits?). Applying Rishton's 'leadlike' parameters might place constraints on these factors, unlike his already widely-used 'druglike' parameters.

In fact, the real issue is not the appalling attrition rate of drug discovery itself, but the cost of research that has no marketable products. Increasing the use of filters and predictive methods to reduce the attrition rate is obviously important to target the expenditure more effectively, but it must not detract from the pressing need to reduce the costs of obtaining experimental data, in order to make the high attrition rate acceptable ('fail fast, fail cheap'). Unproductive failure is the consequence of poor decision-making based on low quality and inadequate data, and thus the key to solving the attrition problem is to provide both more and higher quality data efficiently.

The debate of what makes a good lead will continue until serendipity ceases to play a role in drug discovery, which will probably only occur when all the '-omics' can be effectively combined. Until then, success will be achieved by pragmatism, and although it is sensible to use empirical conclusions from historical data as guidelines for compiling compound collections, a proportion of non-compliers or compounds assembled according to alternative rationales must be retained to enhance that serendipity. So, in the end, what makes a good lead? Gilbert Rishton gives us several clear signposts as to what makes a bad lead, but I think we have to be honest and admit that we don`t have similar signposts to fill our compound collections only with leads, just yet.

References

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