ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Targets in Oncology Drug Development

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H&O How has molecularly targeted therapy changed the landscape of cancer drug research?

JV Over the past 15 years we have seen a paradigm shift from targeting DNA directly by, basically, poisoning the cell to molecularly targeted treatment. These targets include transmembrane proteins, which can be targeted from outside or inside the cell, through downstream signals, and through RNA and DNA transcription. This shift—from targeting the nucleus to targeting the membrane—has been very successful.

H&O What conclusions have been made so far with regard to targeting transmembrane proteins?

JV To date, it appears that all of the above-mentioned approaches are potentially effective strategies for targeted therapeutics. Monoclonal antibodies, for example, target receptors from outside the cell, and already there are several effective such agents, including trastuzumab (Herceptin, Genentech), bevacizumab (Avastin, Genentech), cetuximab (Erbitux, Bristol-Myers Squibb/ImClone), and rituximab (Rituxan, Genentech/Biogen Idec).

The most striking example of targeting a receptor from inside the cell thus far is the drug imatinib mesylate (Gleevec, Novartis), for treating of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs).

There is still a great deal to be learned, and there is much ongoing research to better understand the mechanisms behind these targets. For example, targeting the outside of a receptor has so far proven to be more effective than targeting the inside with synthetic drugs, and we do not yet understand why. Effectively targeting the inside of a receptor apparently requires the receptor to be mutated, which is not the case with antibodies.

H&O What downstream effects of the signaling pathway are being investigated as part of current molecularly targeted therapy research?

JV The Akt and mTOR pathways appear to be essential elements in downstream signaling of transmembrane proteins. There is already evidence that targeting the more downstream events of the signaling pathway could be effective. However, positioning these agents at the right spot is difficult, and also the toxicity associated with these agents has sometimes proven to be too severe. Development is continuing, and certainly there will be drugs in the near future that target signaling pathways downstream.

H&O What other targets appear promising?

JV Another target is transcription inhibition. There have been some very interesting developments in this area, although agents in development are still very far from clinical reality.

Cell cycle inhibition is a very active and promising area of research that entails interfering with cell cycling, as the name implies. Although investigations of cell cycle inhibition have been ongoing for many years, it is only in the last couple of years that some agents have come into the clinic. These agents have shown very interesting effects, without the side effects that were initially observed. The various checkpoints in cell cycling are now potential targets that can be explored for clinical benefit.

H&O Is there an advantage to targeting pathways upstream or downstream?

JV Initially, investigators believed that upstream inhibition was less selective, and therefore the potential for side effects was greater, and that inhibiting downstream would be more selective. In reality, upstream inhibitors have not been observed to cause insurmountable challenges with side effects. However, we have also found that upstream targets must be mutated in order for a synthetic drug to be of benefit. If the target is not mutated or overexpressed in a way that is important for cell growth, the drug has no therapeutic activity. This finding was not known when upstream target inhibitors were initially developed.

H&O With so many potential targets being explored, has anything become clear about how the search for effective agents might be narrowed down?

JV There have been some limited efforts to narrow down this research. Over the past decade, we have learned that laboratory findings in animal and cell culture models are not always indicative of clinical activity. There are transmembrane factors that may be present for no clear reason and are unrelated to actual tumor growth. In order to narrow the focus of research, we need to learn what factors are related to tumor growth. Identifying these factors will enable us to develop more agents that inhibit cancer cell growth without affecting normal cell growth. From the development of agents such as imatinib we know that it is necessary for the receptor to be mutated in order for the drug to be of benefit. The development of agents that target the epidermal growth factor receptor has also confirmed that the greatest benefit is seen among those patients who harbor mutations of this receptor. The nonmutated receptor may not be that relevant to tumor growth.

H&O What has been learned thus far about the development of resistance?

JV In the early development of targeted agents, we were simplistic in hoping that resistance would not occur; we can now see that it does occur with all of these targets. Imatinib was the first example of an effective signal transduction inhibitor. Yet, resistance to this agent occurs among both CML and GIST patients; additional mutations of the receptor develop, making it no longer sensitive to the drug, thus enabling the tumor cells to escape the inhibitor. It appears that the development of some form of resistance will always need to be a consideration in the research and use of molecularly targeted agents.

H&O What are some of the most promising agents now on the horizon?

JV There are indications that cell cycle inhibitors could be the next class in which active agents are found. Some agents are already in the clinic, and although it is still early, hints of activity have been observed, with patients experiencing benefit in early clinical trials, and there is reason to be optimistic about this class of drugs. The cell cycling process is also closely controlled, and interfering with that control is another possible way to affect tumor growth.

H&O What is needed in order to speed up the development of molecularly targeted agents?

JV There are a few important considerations with regard to quickening the pace at which effective agents enter and proceed through clinical trials. First, close collaboration between academicians and clinicians in university hospitals and pharmaceutical industry employees is needed. There is a great deal of knowledge in the clinic that industry could make use of, and there is a great deal of knowledge in industry of which clinicians could make use. Optimal collaboration is key. Industry should not try to develop drugs without the input of physicians in the field; otherwise, companies run a greater risk of developing ineffective agents and also wasting money. Second, it is essential to improve the level of international communication and collaboration, which is already very good but could be improved further.

A major problem that we are currently facing is the plethora of regulatory rules that are inhibiting and delaying the process of developing these agents. The European Union Clinical Trials Directive, recently implemented in all EU member states, is extremely rigid and is impeding clinical development and clinical trials. The United States is also fraught with regulatory guidelines that do not have a positive impact on the speed of clinical trials. There certainly is a need for regulations; however, it appears that there is an overcompensation in this area. There needs to be a balance between maintaining essential regulatory rules and doing what is needed to speed the development of agents that could be of benefit to cancer patients. The current regulations could be greatly simplified.

Suggested Reading

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