

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Creating an Infrastructure for Pediatric Oncology Drug Development

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H&O What is the impetus behind creating an infrastructure for pediatric drug development in oncology?

WE In 2005, the Institute of Medicine (IOM) for the National Academy of Science issued a report entitled *Making Better Drugs for Children With Cancer*, which is available to the public (<http://www.iom.edu/CMS/28312/4935/26453.aspx>). The premise of the report is that the oncology community has entered the period of targeted therapies for cancer, which will have profound effects on the way cancer in children is treated. Using insights from the human genome and proteome, it is possible today to understand more precisely than ever before what is wrong in a cancer cell as compared to a normal cell. Most types of cancers are due to a relatively small number of abnormalities in disease-specific pathways. With this understanding of the biology of cancer, it is possible to identify potential targets for therapy, and using new approaches such as high throughput screening methods, highly targeted therapies can be developed. Such agents will theoretically affect only the tumor and not cause severe toxicity. The problem, however, for pediatric oncology is that pediatric tumors are quite distinct in terms of molecular abnormalities from adult tumors, as the IOM report notes. A targeted therapy that is active against breast, lung, or prostate cancer, or most other adult tumors, is unlikely to be effective in pediatric tumors, which are often in the muscle, bone, or brain, or are leukemias that differ molecularly from adult leukemias. In the past, oncologists have used nonselective adult

anticancer drugs in the pediatric population, experimenting to find how exactly to make these drugs effective in this population. Because the drugs were nonselective, they were effective in many pediatric malignancies. The belief is that the same will not be true with highly selective anticancer agents.

Another significant problem facing the pediatric oncology community is that there is not enough financial incentive for major pharmaceutical companies or even many biotechnology companies to pursue pediatric drug targets because the number of new cases per year ranges in the thousands rather than the hundreds of thousands as in adult populations. The pharmaceutical business model is more attuned to the common tumors in adults, for which the doses and numbers of cases are larger, leading to higher profitability. The IOM report thus recommended that a viable approach to pediatric cancer drug development will require a partnership between private and public, or academia and government, ideally with industry involved as well. If major pharmaceutical companies are unwilling to commit an entire program to this field, it is hoped that some of their resources can be committed to ensure that progress is made. For example, this commitment could be in the form of giving pediatric-cancer investigators access to a library of candidate anticancer agents that are not otherwise planned to be screened in the pediatric population. In this case, if an agent is found to be promising, the corporation would be given first right of refusal. If an agent turns out not to be potentially efficacious, and profitable, at least it would not have been left on the shelf and never tested against pediatric tumors.

H&O What steps have been taken to implement the recommendations of the IOM report?

WE The IOM held a follow-up meeting last year, which I co-chaired with Dr. Peter Adamson from Children's Hospital in Philadelphia, Penn. The meeting brought together representatives from academia and industry, as well as from other organizations that work on orphan diseases such as cystic fibrosis. In many cases, these types of diseases face the same problems as pediatric cancer in terms of limited funding available from industry for research and drug discovery. We gained some valuable insights from these organizations. A follow-up committee was appointed to begin to develop a business plan, with representatives from Pricewaterhouse Coopers giving assistance in strategizing on securing grants and combining industry and academic participation.

H&O In terms of strategizing oncology drug development for children, are there differences between neonates, children, and adolescents?

WE The problems already mentioned with profitability affect drug development across the entire pediatric age range. Furthermore, there are molecular differences in malignancies affecting neonates as compared to older children. For example, childhood leukemia in neonates has a different molecular signature from the most common form of childhood leukemia, which occurs most commonly at ages 4–6 years. In contrast, osteosarcoma is a common bone tumor that occurs primarily in adolescents and teenagers. Thus, all three pediatric age groups differ from adults, but within the three groups there are different tumors and tumor subtypes that further divide the potential attention and investment of those involved in pharmacodevelopment.

H&O What other challenges must be faced with drug development in this setting?

WE I believe the industry historically has had a certain amount of nervousness about conducting drug studies in children because the consensus belief is that this population is more difficult to study than adult populations. One major concern that has been apparent is that if a drug were being developed for an adult cancer and it were tested in children and found to be problematic, this could lead to cessation of research in both markets. An unusual toxicity, for example, that occurred in children but would never occur in adults could lead to apprehension on the part of regulatory agencies. Another concern has been that if a drug were found not to work in adults but did work in children, it would be necessary to make a business

decision whether to continue the program or abandon it. From the perspective of ensuring a return on its investment, a corporation might abandon the program, but from a public health perspective, this decision to cease investigation because a drug would be insufficiently profitable would be unfortunate and a potential public relations concern for the company. Therefore, in order to avoid facing such a decision, pharmaceutical companies may elect not to investigate novel agents in children at all, and not only for cancer. In response to this perceived nervousness, the US federal government created incentives to encourage pharmaceutical companies to test their drugs in children, at the very least to conduct dose-finding studies. The incentive was that if drugs were tested, in order to let pediatricians and pharmacists know what the right dose would be and what toxicities they would face, the patent on the drug would be extended by 5 years. As it turns out, this incentive has been quite effective in inducing companies to study many drugs in children.

It is important to be aware of challenges posed by the pediatric population, but I believe that conducting clinical trials in children is just as easy as, if not easier than, conducting trials in adults. Looking at the way pediatric cancer is treated in the United States, approximately 80% of children are treated according to a research protocol, whereas the number of adults on research protocols is closer to 5%. The pediatric oncology community decided 40 years ago that given the relatively small number of cases, it was imperative to work together in order to make progress against pediatric malignancies. It was decided that if children were not treated in a uniform fashion, using protocols to determine which agents are effective and which are not, progress would be difficult.

H&O Are there specific examples of molecular targeted agents that have been entered into research since the IOM report?

WE To my knowledge no agent has yet entered research in a coordinated fashion through a consortium in response to the IOM report. However, there have been ad hoc multi-institutional consortiums to test new targeted agents in pediatric cancers. One example is a *FLT3* inhibitor in childhood leukemia. It turns out that *FLT3* mutations occur in some pediatric leukemias, and some companies that were developing *FLT3* inhibitors for adult cancers began to work with the pediatric oncology community. As a result, we have been able to open clinical trials to test this agent. We have begun to show that such cooperative work is possible. It has not yet been systematically organized and facilitated in order to ensure that the research occurs in a timely fashion, but we are making progress in this regard. The *FLT3* inhibitor is an example

of this progress; this agent had been under investigation in adult clinical trials for many years. We hope to shorten the time between identification of a novel agent and its investigation in the pediatric population.

H&O In what other ways has the pediatric oncology community responded to the IOM report?

WE The community is attempting to integrate pharmacogenomics and pharmacogenetics; once a genetic abnormality is discovered in a tumor or in normal tissues, there are situations where treatment decisions should be based on genetic differences among patients in terms of the intensity of treatment, what dose to use of certain medications, and the risk of toxicity, based on inherited differences in drug effects. Institutions have begun new programs to address some of the issues raised in the IOM report. At St. Jude Children's Research Hospital, we have started a new department Chemical Biology and Therapeutics. This program uses high throughput screening, robotics, and combinatorial chemistry to screen molecule libraries against pediatric cancer targets that are identified in the laboratory. We have constructed and equipped a special building to house 10 million vials of candidate drugs, which are robotically picked and plated so they can be screened. This sort of research is what the pharmaceutical industry has in place for screening against adult tumor targets, but we have initiated this program for pediatrics. Of course, our institution is not intending to become a drug company; rather, we are oriented toward drug dis-

covery. If we find a molecule that appears promising in preclinical studies, we might be able to proceed with clinical trials, but ultimately, we would hand the agent off to a drug company. We feel this approach will be attractive to some drug companies because we will have done the early evaluations of safety and efficacy for the agent. Therefore, even though the return on investment for a pediatric agent is smaller than it would be for an adult agent, the company would have to invest less money as a result of our work. We are attempting to show that it is possible to set up a hybrid of pediatric drug development and drug discovery in an academic, nonprofit institution. If successful, I believe this model will be replicated at other institutions (many of which already undertake similar work for adult agents). Our institution has made a great investment in people, equipment, and expertise toward this goal, and we are hoping to exploit the institution's knowledge about pediatric malignancies in order to create a drug discovery and development process driven both by knowledge and technology.

Suggested Reading

Adamson PC, Weiner SL, Simone JV, Gelband H; Committee on Shortening the Time Line for New Cancer Treatments. *Making Better Drugs for Children with Cancer*. Institute of Medicine and the National Research Council The National Academy of Science; 2005.

Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. *Nature*. 2004;429:464-468.

Boklan J. Little patients, losing patience: pediatric cancer drug development. *Mol Cancer Ther*. 2006;8:1905-1908.