Development of Novel Combination Therapies

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Innovative drug development requires science and regulation to advance in concert. Nowhere is this need more apparent or urgent than in the development of combination therapies. Advances in genomics and cell biology have increased the opportunity for rational design of targeted drugs to inhibit the function of specific molecules, including those contributing to the proliferation of cancer cells and pathogenic microorganisms. Although targeted therapies may offer enhanced efficacy and improved selectivity (and therefore less toxicity), most often their effects are not durable when they are used alone.

Cellular pathways operate more like webs than superhighways. There are multiple redundancies, or alternate routes, that may be activated in response to the inhibition of a pathway. This redundancy promotes the emergence of resistant cells or organisms under the selective pressure of a targeted agent, resulting in drug resistance and clinical relapse. For this reason, combination therapies are often needed to effectively treat many tumors and infectious diseases.

Yet traditionally, new drug development has been pursued one agent at a time, even for diseases for which combination therapy is necessary, such as mycobacterial diseases and many other chronic infections. For those diseases, many investigational drugs are tested for efficacy in add-on trials in which the new drug added to a standard regimen is compared with the standard regimen alone.

Successful development of future targeted therapies will require modernizing this paradigm to provide the flexibility needed to rapidly evaluate combination regimens involving new targeted agents in a single development program. Increasingly, tumors will be screened for pertinent pathway dependencies, as is currently done for breast cancer, and patients will be treated with drug combinations on the basis of screening results and experience with patterns of resistance. Similarly, combination antimicrobial therapy will increasingly be targeted, and susceptibility determined, at a molecular level. For example, the antiretroviral drug Selzentry (maraviroc), in combination with other antiretrovirals, is indicated only to treat strains of human immunodeficiency virus type 1 that rely on the CCR5 protein receptor to infect cells. Development programs evaluating combinations of targeted
agents, including investigational agents, are an essential part of this evolving paradigm.

Concern has been expressed that the policies of the Food and Drug Administration (FDA) on the development of combination therapies, which heretofore have focused primarily on fixed-dose combinations (i.e., combined in the same tablet or vial) of already-marketed drugs, are a barrier to the development of novel combination regimens using targeted therapies. FDA regulations for fixed-dose combinations require demonstration of the contribution of each component of the combination to the treatment effect. Often, a large clinical trial, using a multigroup factorial design to demonstrate that the combination is superior to each of the individual components alone, is needed to meet this requirement. For example, a factorial study for a two-drug combination could have four groups so that the combination can be compared with each of the individual components alone, as well as with either the standard of care or placebo.

The FDA recognizes that for diseases in which innovative targeted combination therapies are likely to be used, such studies will often be unethical because of the potential for promoting the development of resistance and rendering a new therapy ineffective. For instance, hepatitis C virus (HCV) can develop resistance to antiviral monotherapy within only days, so a factorial study of sufficient duration (24 to 48 weeks) to demonstrate the efficacy of the individual new drugs in an anti-HCV combination would not be possible and could not be required.

To ensure that the regulatory expectations are clear, the FDA has drafted guidance about testing and developing two or more novel agents together in a single development program (termed "co-development" in the guidance). The guidance provides general recommendations for all facets of co-development, including preclinical testing for proof of concept and safety, clinical pharmacology studies, phase 1 safety studies, and phase 2 and 3 clinical efficacy studies. It also makes clear that the FDA’s regulations and policies pertaining to the amounts and types of data needed to demonstrate the contribution of each drug to the overall effect provide adequate flexibility to facilitate the development of novel targeted therapies for use in combination regimens in diseases for which a large factorial study (requiring monotherapy treatment groups) would not be possible. And it emphasizes that a range of potential data sources could be used to help establish the contribution of the individual drugs and provides examples of potential alternative study designs, including the use of data from in vivo models and pharmacodynamic studies.

Although co-development of innovative drug combinations directed simultaneously at multiple therapeutic targets has the potential to dramatically improve the response to treatment and survival rates among patients with difficult-to-treat diseases, it does introduce additional uncertainty. Because it will usually not be possible to fully characterize the effects of the individual components of the combination, co-development may yield considerably less information about the safety and effectiveness of the drugs than would be obtained if they were developed individually. For this reason, co-development should be used only for therapies intended to treat serious and life-threatening diseases for which there are no satisfactory alternatives — a situation in which patients and physicians tend to accept heightened uncertainty — and only when there is potential for an important effect on human disease. There should also be a compelling biologic rationale for use of the combination, evidence of substantial in vivo or in vitro activity, and strong reasons why the components cannot be developed as individual agents.

Because co-development results in greater uncertainty about the performance of the individual agents, it will be important to ensure that the risks, benefits, and appropriate uses of the combination are communicated to prescribers and that those risks are effectively managed. The FDA’s guidance recommends that companies developing novel drugs for use in combination devise pharmacovigilance plans to address these risks, including the potential for the use of the drugs individually or in combination with different therapies. For example, if it is essential that the drugs in the combination be used only together, there should be careful consideration of ways to ensure that the individual agents are not misused.

To date, interest in combination development has focused primarily on cancer and infectious diseases. However, the FDA intends the guidance to serve as a roadmap for co-development in any appropriate therapeutic category.

A clear regulatory path is a prerequisite to successful co-develop-
Obesity Prevalence in the United States — Up, Down, or Sideways?
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Americans are continually bombarded with statistics on obesity. The media are filled with news reports celebrating the possible shrinking of our waistlines or lamenting their ongoing expansion. Some recent studies have suggested that U.S. obesity rates are continuing to increase. For example, state- and national-level data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) of the Centers for Disease Control and Prevention (CDC) showed increases between 2007 and 2009 in the reported prevalence of obesity among adults — a 1.1% increase nationally, or an additional 2.4 million or so obese adults. Such data have led some investigators to suggest that by 2050, an enormous percentage of Americans — perhaps approaching 100% — will be overweight (defined in adults as a body mass index [BMI, the weight in kilograms divided by the square of the height in meters] above 25 but below 30) or obese (BMI ≥30).

Other reports, however, suggest that the U.S. obesity prevalence, though very high, has stabilized. Results from the CDC’s 2007–2008 National Health and Nutrition Examination Survey (NHANES) suggest that the prevalence of obesity among women (35.5%) and children 2 to 19 years of age (16.9%) has remained stable over the past 10 years and that the prevalence among men (32.2%) has not changed significantly since 2003. These conflicting reports have led to confusion regarding the prevalence of, and secular trends in, obesity in the United States.

Why do the reported rates vary so markedly (see graphs), even though the data all come from government agencies? If obesity rates are stabilizing, why are they doing so? And what do these trends and prevalence rates mean for the current and future health of the U.S. population?

One key reason for discrepancies among the estimates is a simple difference in data-collection methods. The most frequently