The Drug Development Process

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The chemopreventive agent development process is a science in its infancy. Developers of chemopreventive agents face the same regulatory hurdles as do therapeutic drug developers. As in all drug development, chemoprevention scientists must demonstrate both safety and efficacy for an agent to be approved for marketing to the public. Historically, this has meant that developers must demonstrate reduced cancer incidence or mortality in order to show effectiveness. Needless to say, this would be a lengthy process given the 20 to 30-year trajectory of carcinogenesis. This requirement has been modified in recent years. The notion of targeted prevention of cancer is now based on the discovery of surrogate endpoint biomarkers, signal transduction pathways, and the ability to promote or inhibit specific molecules in those pathways with new molecular entities (NME) or drugs (O'Shaughnessy, Kelloff et al. 2002).

In the United States and internationally, the development and manufacture of drug products is regulated by government entities in order to protect general populations as well as research participants. In the United States (U.S.), the Food and Drug Administration (FDA) has this regulatory responsibility, while in Europe and Japan, the responsibility falls to individual governments using standards established and maintained by the International Conference of Harmonization (ICH). The regulatory agencies and the developers of drugs must balance the benefit of new drugs to the population as a whole against the risk to individuals participating in clinical trials and eventually to the general public. In the development of chemopreventive agents, the risk must be very low and the benefit very high, as, in order to be effective, large at-risk populations would need to use the drug, possibly for life, in order for a drug to be effective in preventing cancer (Anonymous 1999).

The process of developing chemopreventive agents consists of several systematic steps. First, NMEs are chosen based on basic science findings. Promising agents then undergo preclinical testing in animal models. Before human testing can begin, the science must be reviewed by the FDA or other regulatory agency. After the completion of clinical trials and prior to marketing, findings must be evaluated and communicated to the scientific community. This chapter outlines the process of developing chemopreventive agents and the standards that guide such development.
Selecting New Molecular Entities for Development as Chemopreventive Agents

New molecular entities are the focus of scientific study in cancer therapeutics as well as cancer prevention programs across the world. However, the selection of new molecular entities (NMEs) for development is not a random or serendipitous process. Rather, specific important criteria apply to the selection of NMEs for clinical development as potential chemopreventive agents. The major criteria include evidence of activity in preventing cancer at the target site, low toxicity to allow for potential use in large populations, the identification of the biomarkers associated with the effectiveness of the NME, and the availability of a pertinent population for clinical testing. The focus of these criteria is the real feasibility of giving a drug prophylactically to large populations at risk for a particular type of cancer (Kelloff, Hawk et al. 1996).

There are significant precedents for the notion of developing drugs that lessen the risk for a disease or the recurrence of disease and that can be given on a large scale. An example of such a precedent is the development and FDA approved marketing of lipid lowering drugs that aim to reduce the risk of cardiovascular disease. The process included research on cholesterol lowering and modulation of other markers. Lowering of cholesterol emerged as a definitive risk reduction marker and development of cholesterol lowering drugs followed. In the case of cancer chemopreventive agents, early associated biomarkers discovered by basic scientist must also form the basis for development. Examples of such markers are proliferation antigens [e.g., proliferating cell nuclear antigen (PCNA)], inhibition of growth factors [e.g., epidermal growth factor receptor (EGFR)] and apoptosis.

Discovery of related biomarkers is followed by research to demonstrate activity against proliferation of pre-cancer or intraepithelial neoplasias (IEN). Demonstration of activity is performed in vitro in cell lines and later in vivo in animal models. Satisfactory activity in both models can then be evaluated as justification for proceeding to clinical trials. In addition to peer review by other scientists, the FDA performs the function of approving clinical trials in humans using NMEs. The criteria used by the FDA to evaluate proposed drugs for development and marketing are safety and effectiveness viewed in a risk-benefit balancing framework.

An important requirement for chemoprevention agents is that while they must be highly effective, they must also be safe enough to be given to large populations at risk for a particular cancer. This is a marked departure from the usual thinking about therapeutic cancer drugs where the toxicity, unless major, is an expected fact that is mitigated by the effectiveness of the drug in treating the cancer. Therapeutic clinical trials, therefore, tend to seek the highest effective dose for which the toxicity can be justified by its effectiveness, while chemoprevention studies seek to find the highest safe dose that is also effective.

An important consideration for selecting a NME for development as a chemopreventive agent is the availability of the agent in quantities needed for all phases of testing. A supply can be assured by either synthesizing the drug, provided no patent rights are contravened, or acquired in bulk from the manufacturer or wholesaler of known compounds. Synthesis can be a computer assisted process in which a compound is simulated using enzymes that attach to the disease related target site on the cell membrane. Synthesis of a drug for research also requires attention to documenta-