S7. Can Laboratory Studies Help in Selecting Specific Compounds for Prevention Trials?

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Only 25 years ago, the notion of preventing cancer seemed unlikely – even untenable – for most organ sites. Since that time, we have gained new insights in the molecular genesis of cancer, developed preclinical models for human neoplasia, and completed the first generation of human chemoprevention trials, all of which have raised public and professional expectations that cancer is preventable in many instances. Nevertheless, making progress in cancer prevention has been difficult because our mechanistic insights remain limited, the available tools for decision-making are poorly validated, and the ethical, temporal, and fiscal demands of clinical prevention research have proven exceptionally challenging. Preclinical data are an essential component of the process of identifying and prioritizing new agents for entry into the clinic. Some of the earliest clinical trials in cancer chemoprevention were developed using agents (e.g., beta-carotene) premised largely on observational data, with little preclinical testing for effects against cancer. Because of surprising data arising from these experiences, researchers now identify and prioritize compounds based on a broad spectrum of efficacy data that arise from in vitro, in vivo, and observational settings wherever possible. The usefulness of preclinical data in selecting and prioritizing agents for clinical trials can be demonstrated by trans-model correlations evaluating: 1) molecular carcinogenesis; 2) agent pharmacokinetics; 3) pharmacodynamic biomarker modulations; and 4) changes in "definitive" endpoints, such as precancer incidence/regression or cancer incidence/regression. In order to perform these sorts of assessments with adequate attention to critical issues of accuracy and reproducibility, however, we must take advantage of data from well-controlled phase III trials both positive and negative. No single agent or model completely satisfies this level of scrutiny, but the usefulness of preclinical data in identifying and prioritizing agents for clinical trials has been amply demonstrated. For example, tamoxifen in breast cancer prevention, and nonsteroidal antiinflammatories, selenium, or calcium in colorectal cancer prevention present compelling data that invite correlations across preclinical and clinical studies. Of course, preclinical models and the data that arise from them have important limitations. Cross-model correlations of dosing and pharmacokinetics are crude and inexact, thus the selection of an optimal dosing regimen or target serum concentration for early phase clinical trials remains challenging. In addition, several agents with promising efficacy in preclinical models have not shown similar efficacy in clinical trials; examples include fiber supplements or ursodiol in colorectal neoplasia prevention. Because of these challenges and potential confounding by false-positive results, wherever possible, the selection of compounds for clinical prevention trials should be based on a broad, consistent, and mutually corroborative set of data.