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Rapid Access to Preventive Intervention Development (RAPID) Program in the Division of Cancer Prevention of the US National Cancer Institute: An Overview

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As a 17th century English preacher stated: “Prevention is much better than healing because it saves the labor of being sick” [T. Adams, *The Happiness of Church*, 1618, p146]. The term “chemoprevention” was coined by Sporn and coworkers in the 1970s (1) and articulated through numerous publications ever since. It refers to cancer prevention which aims to disrupt oncogenesis by chemical, biological, or nutritional intervention and thereby prevent, reverse or delay the development or recurrence of cancer. The importance of prevention in the war against cancer has also been very recently echoed by a prominent cancer researcher, Dr. Vogelstein: “One interpretation of our work is that the proportion of effort and funding devoted to other ways of managing cancer, such as prevention and early detection, should be greatly increased...as they may have much more success in minimizing cancer deaths”¹. There are other significant, ongoing efforts in cancer prevention, but primarily in the areas of behavior modification such as smoking cessation, diet, and exercise. However, the pharmaceutical industry emphasis in the cancer area is on treatment as opposed to prevention. Therefore, there are minimal opportunities to develop cancer preventive interventions that could be applied clinically. The RAPID Program (November 1 annual submission deadline)² has been initiated as a public health service initiative within the Division of Cancer Prevention (DCP) of the National Cancer Institute (NCI) to address this deficiency. Acceleration of progress in cancer prevention including support of a robust cancer prevention agent development program to identify the most promising synthetic and natural agents to prevent or delay cancer onset are components of strategic objectives of the NCI Strategic Plan³ in the “War on Cancer”.

The Rapid Access to Preventive Intervention Development (RAPID) Program⁴ is an applied translational research program whose purpose is to stimulate, enable, facilitate and expedite movement of novel cancer preventive chemical or biological agents from the lab bench to clinic. It is unique in at least two different respects. First of all, it supports the development of cancer preventive agents. While there is a huge global effort by the pharmaceutical industry to develop cancer therapeutic agents, the effort by such industries is minimal or virtually absent for the development of cancer chemopreventive agents. Secondly, this program is targeted at academicians and academically-affiliated investigators worldwide who may have conceived a rational idea for a promising candidate chemopreventive agent and performed initial efficacy

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¹<http://www.bio-itworld.com/pb/2008/09/25/gbm-vogelstein.html>

²<http://prevention.cancer.gov/programs-resources/programs/rapid/appinfo>

³<http://strategicplan.nci.nih.gov>

⁴<http://prevention.cancer.gov/programs-resources/programs/rapid>

screening in their laboratory but lack the necessary resources, know-how and expertise to bring it to clinical testing.

The RAPID Program supports the entire drug development process from scale-up synthesis through the initial testing in humans. The support of specific tasks varies from project to project and can include any and all tasks from bulk agent acquisition through Phase 1 clinical trials. The Program aims to provide the materials for proof-of-principle clinical testing and satisfy requirements for Phase 2 clinical efficacy studies. It differs from more common grant and contract support mechanisms. The RAPID Program utilizes the expertise and resources (existing contracts) of the Chemopreventive Agent Development Research Group, CADR⁵ within the DCP⁶ to perform the required studies and provide the required regulatory documentation and support for the Investigational New Drug (IND) filing with the US FDA leading to Phase 1 clinical trials. The Intellectual Property Rights remain with the RAPID awardees. Utilizing CADRG existing contracts, RAPID carries out the tasks which are required for IND application submission to the FDA (e.g. preclinical toxicology and efficacy studies, etc.) on a case per case basis on behalf of the successful applicants. All the tasks are performed by CADRG prequalified contractors in the respective areas and the resultant data and documents are given to the awardees and used for regulatory filings. In a few instances when the awardee has some unique expertise not readily available outside his laboratory, that part of work could be subcontracted to him. The support continues without need to re-apply as long as specific milestones, as agreed on between the awardee and DCP, are met. RAPID support ends with completion of Phase 1 but promising candidates may be recommended to DCP Clinical Organ Groups for their interest in further development of these agents.

Examples of drug development tasks that are commonly supported by the RAPID Program are shown in Table 1. Support for these and other tasks is based on specific needs of each drug development project (e.g. scale-up synthesis, preclinical toxicology and efficacy studies, etc.), prioritization within the DCP program and the available resources to the CADRG group. While the RAPID Program is unique in several respects (as described above) and to our best knowledge the only chemoprevention program of this kind globally, it is only one of the programs within the CADRG. Other programs supported within CADRG include identification of molecular targets and intermediate endpoints, *in vitro* and *in vivo* preclinical efficacy screening and testing, preclinical pharmacology and toxicology testing, and identification and development of chemopreventive agents from sources other than RAPID. Therefore, in order to utilize our limited resources most effectively, individual drug development projects in the RAPID and other programs are prioritized according to their needs and their relative importance and cost to the overall goals of the CADRG and DCP. The drug development involves applied as opposed to basic sciences and thus is not commonly supported by investigator initiated grants. Consequently, many promising ideas in academia may never be tested or come to fruition. Also many of the tasks are beyond the scope of academic laboratories. For example, laboratory syntheses commonly generate small mg or g quantities of synthetic chemicals or natural product extracts. While these amounts may be adequate for *in vitro* cell culture work or *in vivo* experiments in few animals, they are several orders of magnitude short of quantities needed for the actual drug development (e.g. preclinical toxicology and efficacy studies and clinical trials). This is especially the case for preventive agents which by their nature are and need to be relatively free of adverse effects. As a result, large quantities are needed, for example, for preclinical toxicology studies which are intended to test doses showing toxicity (up to 2 g/kg body weight). Therefore, for a relatively nontoxic preventive agent, almost 10 kg may be needed just to carry out studies for minimal FDA requirements to qualify the agent for a 28-day clinical trial. However, if chronic treatment is anticipated in a prevention

⁵<http://prevention.cancer.gov/programs-resources/groups/cad>

⁶<http://prevention.cancer.gov/>

clinical trial this would require much longer term animal studies and thus even much larger quantities of candidate agents would be needed. Obviously, such large quantities are way beyond capabilities of most academic institutions. In addition, clinical trials would require a GMP (Good Manufacturing Practice) grade material, i.e., manufacture in an FDA-approved facilities under the GMP guidelines, typically not feasible in academic laboratories. Preclinical toxicology studies also need to be carried out in FDA-approved facilities under GLP (Good Laboratory Practice) guidelines, also not typically found in academic laboratories. Therefore, many drug development tasks are well beyond the scope and scale of academia. The RAPID Program strives to provide the means for testing and developing promising academic leads in cancer prevention intervention.

A few representative cancer preventive agents which have received RAPID support in the past are presented in Table 2. They include synthetic products, extracts of natural products and vaccines, have different purported mechanisms of action and are targeted for different organs. The first 3 agents listed in Table 2 are in clinical trials. Se-Methyl-Seleno-L-Cysteine and 9-cis-UAB30 are both in Phase 1 clinical trials for prostate and mammary cancer prevention, respectively. SR13668 is in a Phase 0 clinical trial aimed to identify optimal formulation which would optimize its bioavailability. Several other agents are nearing completion of their preclinical testing at which point a decision will be made based on the compiled data whether to proceed or not to IND filing and clinical trials.

The studies supported by the RAPID Program have also resulted in number of publications in different areas, including *in vitro* and *in vivo* screening, efficacy, preclinical toxicology, analytical methodology and drug metabolism (2–13)

Therefore, the RAPID Program provides unique opportunity for academically-affiliated investigators to translate their promising ideas into candidate cancer chemopreventive agents and which may subsequently have a major impact in cancer prevention.

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Table 1

Examples of drug development tasks supported in the RAPID Program

AREA	SPECIFIC EXAMPLES
MANUFACTURE (GMP)	Scale-up chemical synthesis or isolation from natural sources; characterization; purification.
PRECLINICAL TOXICOLOGY (GLP)	Genotoxicity battery (bacterial mutagenesis, <i>in vitro</i> chromosomal aberration, <i>in vivo</i> chromosomal aberration); 28-day rat and 28-day dog studies including clinical observations and examinations, weight, weight gain and food consumption monitoring, ophthalmic and electrographic examinations, clinical chemistry, hematology, coagulation, urinalysis, toxicokinetics, and gross pathology and histopathology; other as needed.
ANIMAL CHEMOPREVENTION EFFICACY MODELS	Organ and cancer based carcinogen-induced or transgenic animal models, including those in respiratory tract, gastrointestinal tract, mammary gland, prostate, bladder, skin, cervix and ovary.
PHARMACEUTICAL DEVELOPMENT	Formulation for non-invasive dosing (oral, topical or inhalation); stability and dissolution testing; packaging and labeling; distribution.
REGULATORY SUPPORT	Preparation and submission of Investigational New Drug (IND) application
PHASE I CLINICAL STUDY	Escalating single dose safety and pharmacokinetic evaluation; escalation repeat dose safety and pharmacokinetic evaluation.

Table 2

Examples of Agents in the RAPID Program

AGENT	PROPOSED MECHANISM	TARGET ORGAN(S)	SOURCE
Se-Methyl-Seleno-L-Cysteine	Cell cycle, caspase modulation	Prostate, breast, colon, lung	Synthetic (also found in garlic, onion, broccoli)
9-cis-UAB30	Rexinoid agonist	Breast	Synthetic
SR13668	PI3K/AKT inhibitor	Breast, lung, ovary, cervix, prostate	Synthetic (rational drug design based on naturally occurring indole-3-carbinol)
ISY16	Cell cycle	Colon, lung	Mushroom extract
Tricin	COX-2, PI3K Inhibitor	Colon	Synthetic (naturally occurring in brown rice)
HPV vaccine	HPV	Cervix	
Glucoraphanin	GST induction, Keap1/Nrf2/ARE	Colon, stomach	Broccoli seed extract
Antitumor B	Apoptosis, cell cycle	Lung	Chinese herbal mixture extract
QW1624F2-2	Deltanoid, CYP24 inhibitor	Prostate	Synthetic
Pentamethylchromanol	Antioxidant, antiandrogen	Prostate	Synthetic