Executive Summary

Rare cancers are difficult to study because of the low incidence. Rare cancers pose many challenges for detection, diagnosis, prognosis, treatment and technology development. Rare cancers are included in the Rare Disease Act of 2002 (HR 4013), and the U.S. Orphan Drug Act defines a rare disease or condition as one that effects less than 200,000 persons in the United States.

Recently a workshop was held on Rare Cancers\(^1\) to discuss the issues and challenges associated with rare cancers and to facilitate collaborations among the participants. Approximately 200 participants including scientists, clinicians, industry, government, and patient advocates met for the workshop. The day and a half workshop was structured with plenary sessions for the first half-day followed by three Breakout Groups for facilitating discussions among the participants. The Breakout Groups were divided into the following areas: A) Building a Knowledge Base – Biology, Epidemiology, and Etiology; B) Facilitating Clinical Studies in Rare Cancers; and C) Development of New Detection, Prevention Methods/Strategies, and Therapies. On the second day, the moderators of each Breakout Groups presented a summary for discussion to all participants. All three Breakout Groups identified similar issues and challenges in the study of rare cancers and common themes for addressing these challenges. This report outlines the outcome of this workshop and the recommendations provided by the participants of this workshop.

Recommendations for the Study of Rare Cancers:

- Biospecimens
- Centers of Excellence for Rare Cancers
- Funding
- Comprehensive Knowledgebase
- Animal Models
- Technology: Current and Development of New Detection, Prevention Methods
- Increased role for Patient Advocacy Groups

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\(^1\) Rare Cancers: Challenges for Cancer Prevention and Treatment on December, 10-11, 2009, in Bethesda, MD. The workshop was sponsored by the NIH Office of Rare Diseases Research and the NCI Division of Cancer Prevention.
**Meeting Summary**

**Biospecimens**
The most pressing issue in the study of rare cancers remains the availability of high quality, well annotated biospecimens. Rare cancers pose major problems in the coordination of sufficient numbers of samples from the large numbers of centers required to access a statistically adequate number of biosamples. The small numbers of the rare cancers often constrain the ability to perform statistically significant studies. Well annotated biospecimens are necessary for discovery and verification, if the community is to take advantage of 21st century “–omics” technology. Databases need to be developed with research, translational, and clinical data on rare cancers. In addition, investigators need to access, in a searchable manner, biospecimen banks.

The paucity of epidemiologic studies underlies the inability to apply risk assessment to rare and lethal cancers. Epidemiological studies will provide fundamental characterization and delineation of heterogeneity in populations. Case control and cohort designs can identify environment and molecular risk associations. Leveraging existing large cohort studies (e.g. Health Professional Cohorts, HMO based cohorts) can provide rich data sets and biosamples for defining molecular heterogeneity. Case control studies provide the detailed exposure and outcome data. In addition, many rare cancers do not have specific etiologic agents. Ethnic variation and racial disparities provide can provide insight into etiology.

**Centers of Excellence for Rare Cancers**
Centers of Excellence for Rare Cancers can provide vertically integrated resources spanning the entire continuum from basic discovery to translational research to clinical care. Seed infrastructure funding for such Centers may galvanize institutions to invest in specialized centers out of self interest (patient referral resource, unique patient populations, etc.). Centers of Excellence can provide tissue and bioinformatics infrastructure and serve as coordinating centers for national and international efforts to collect biosamples, pool scientific expertise, train new investigators, link to advocacy groups, and share novel insights. In addition, clinical practitioners have limited experience identifying and caring for patients with rare cancers, a specialized center of excellence would help train clinical investigators.
Furthermore, large consortia with international collaborations are likely to be required to address the research continuum of low incident cancers. In certain geographic areas and in specific populations, there may be a high prevalence of specific rare cancers. International collaborations are essential for collecting biospecimens, early detection trials, developing new treatments for patients, and performing therapeutic trials. Also rare cancer forums need to be established where scientists, clinicians, the pharmaceutical industry, and patient advocacy groups can discuss and plan joint global studies.

International collaborations are important and an example is nasopharyngeal carcinoma, a rare cancer in the United States but the fifth most common cancer (and seventh greatest cause of cancer death) in Southern China. A set of biomarkers for active Epstein Barr viral infection have a high degree of sensitivity and specificity for nasopharyngeal cancer in men ages 40-60. They also have predictive value for response when biomarkers are assessed prior to anticancer treatment (radiation, cytotoxic therapy). These data suggest that biomarkers for early detection of a regional cancer endemic to China may be applicable to other parts of the world. The approach of tailoring biomarkers to specific populations as a cancer risk assessment or early detection biomarker was considered a useful paradigm.

**Funding**

Current funding mechanisms can be used to create and support investigators and Centers of Excellence or new funding mechanisms need to be developed. Review committees focus on science that addresses major health problems that will have the most impact in reducing mortality and suffering in a population and addresses high incident, high mortality cancers. Grant proposals addressing rare cancers have been reported to face barriers in review due to concerns that support of such research may have a minimal impact on the overall mortality from cancers. Investigators dedicated to the study of rare cancers are needed. Without a more robust investigator pool, progress will be limited for the development of diagnostics and interventions for rare cancers.
**Comprehensive Knowledgebase (Genome/phenotype linked)**

There is value in studying rare cancers because rare cancers can inform about common cancers by identifying genetic events that are likely to be involved in carcinogenesis in other malignancies. For example, in renal cell carcinoma there are four different histologic subtypes, all rare cancers. Genetic mutations/events were identified that appear to be causal or requisite events in each of these subtypes. The molecular defects in each of these histologically different neoplasms have molecular pathway commonality; they all are related to metabolic disorders in iron, oxygen, or nutrient sensing.

For early detection, cost effectiveness will likely dictate that rare cancers can only be screened for in the general population when “bundled” with more common cancer types. Differential diagnosis must therefore be emphasized. In addition, the approach of tailoring biomarkers to specific populations as a cancer risk assessment or early detection biomarker was considered a useful paradigm.

**Animal Models**

Animal models for cancer prevention need to be representative of the human carcinogenesis process (both initiation and promotion models). Major progress with transgenic models appears evident and continued investment in these models will allow comparison between the molecular events in rare cancers and those of common cancers by leveraging high throughput technologies. Animal models also allow for acquisition of post therapy biosamples, not possible from patients.

In using animal models, a variety of platforms merit exploration. For example, the heterograft transplant model that grafts human tumors into rodents while preserving the original biology of the tumor. In addition, there is a transgenic mouse model for gall bladder cancer. This model was presented in the context of common genetic alterations in human gall bladder cancer as well as the signaling cascades most likely for pathogenesis. A major feature of this model was the finding of oncogene addiction and the polyclonal evolution of lesions.
**Rare Cancers: Challenges for Cancer Prevention and Treatment**  
**December 10-11, 2009**  
**Bethesda, Maryland**

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**Meeting Summary**

**Technology: Current and Development of New Detection, Prevention Methods**

State of the art high-throughput methodologies, such as nextgen sequencing or array-based approaches (of the genome, transcriptome, and methylome, and of genetic variation) need to be applied to the study of rare cancers. These strategies have a very high likelihood of providing key insights into not only the underlying biology of these tumors, but also of identifying biomarkers and “druggable” targets. Examples are the kinome, which is providing targets, and bcr-abl/Gleevec, a prototypic molecular therapeutic agent identified from studies of a rare cancer.

Efforts to utilize novel high throughput technology to identify small molecules that inhibit the activity of the protein products of the genetic abnormalities that underlie some rare forms of cancer was presented. These studies highlight the necessity for external collaborations, and industry collaborations to develop large libraries of compounds that may be bioavailable and efficacious in the treatment of the rare cancers.

The lack of large sample cohorts of rare cancers and the relative paucity of material in any one case have precluded extensive proteomic studies of rare cancers. An innovative adaptation of MS-based proteomics, illustrated the implementation of a simple strategy for the analysis of proteins from formalin-fixed paraffin-embedded tissues in a form of human malignant lymphoma. The study illustrated the discovery of potential therapeutic targets in lymphoma and highlights the advantage of exploitation of existing samples for discovery work facilitated by novel technologies.

Pharmaceutical industry and biotechnology company interest in rare cancers is minimal. The challenges that attend collaborative ventures with individuals in the academia include; intellectual property protection of agents by the companies and restrictive agreements between the academic investigator and the pharmaceutical concern. In addition, the major pharmaceutical industries have not prioritized research and development in the area of rare and lethal cancers because of the “small market share” amongst all diseases. To incentivize pharmaceutical industry to engage in research centered on rare and lethal cancers, consideration strategies such as extension of patent rights for rare cancer indications and tax releases for the pharmaceutical concern were proposed.
**Patient Advocacy Groups**

Patient advocacy groups are important in generating philanthropic resources and educating patients. These groups can be involved in the research process by providing resources and knowledge on a rare cancer; identify research efforts across multiple institutions and disciplines. They provide an important interface with patients to collect clinical data, biospecimens, and recruit patients for clinical trials/research. In addition, patient advocacy groups can provide outreach to help develop international contacts and potential resources for the study of rare cancers. Patient advocacy groups are an important partner for increasing the pace and productivity of research on rare cancers.