Inaugural Starr Cancer Consortium Workshop

November 16, 2006, New York City, NY

Workshop Summary

Over 90 scientists and clinicians from the five participating institutions of the Starr Cancer Consortium (The Broad Institute of MIT and Harvard, Cold Spring Harbor Laboratory, Memorial Sloan-Kettering Cancer Center, The Rockefeller University, and Weill Cornell Medical College) participated in the inaugural Starr Cancer Consortium (SCC) workshop.

After opening remarks by Eric Lander and Harold Varmus on behalf of the SCC executive committee and by Hank Greenberg, founder of the Starr Foundation, as well as Eli Broad, benefactor of the Broad Institute, the workshop was divided into the following sessions: i) genomic, chemistry, and animal model technologies, ii) disease / clinical examples that illustrated the application of technologies and iii) examples of areas of basic biology that could benefit from the application of these technologies. Finally, the workshop closed with a brainstorming discussion about next steps and alternative processes to move forward.

The major topics and key discussion points are described below:

Genomic characterization of tumors. Cost-effective genome-wide characterization of tumors for changes in copy number and loss-of-heterozygosity are now feasible using technologies such as CGH, ROMA and SNP arrays . Costs of mutation detection through sequencing have continued to fall, allowing sequencing of targeted genes sets. Genome-wide sequencing of tumors is currently still cost prohibitive. The potential for collaborative genomic studies was illustrated by the Broad-MSKCC Sarcoma collaboration that has carried out genome-wide SNP array and focused sequencing analyses of 140 matched tumor-normal sample pairs.

Discussion points:

- Large sample sets are required to detect changes and their correlation with phenotype - for example, a sample size of 250 is required to reliably detect a 5% frequency variant. Larger numbers may be required for the analysis of specific patient subsets.
- A dialogue between clinicians and genomics scientists is needed to define the critical clinical questions that genomic projects can address.
- Systematic analyses of known oncogene and tumor suppressor mutations are lacking. Different technologies and performance criteria are required for discovery of novel mutations vs. characterization of known mutations.
- Mixed cell populations within tumor samples are a challenge for these studies - strategies to address this include high % tumor sample selection, immuno-sorting, single-molecule sequencing, and tagged riboprotein expression profiling.
- Large, well-annotated sets of clinical sample sets collected under appropriate consent are critical for these studies.
- Appropriate policies for data sharing and release are needed to satisfy regulatory requirements, patient confidentiality while enabling dissemination and analysis in the research community. Developing common approaches will facilitate collaboration and accelerate genomic research.
- Common data structures are needed to facilitate sharing and integration of data from different technologies.

RNA interference. The institutions of the Starr Consortium encompass many of the leading labs in RNAi research and technology development. The RNAi resources and screening capabilities available to the Consortium include the genome-wide human and mouse shRNA libraries constructed at CSHL and The Broad, the siRNA resources at MSKCC as well as the arrayed and pooled screening capabilities across all these institutions. Genome-wide cell-based screens are feasible now and can be used to dissect almost

any cellular cancer trait.
Discussion points:

RNAi technology still needs to be improved - validation of reagents, improved design, inducible systems, systemic delivery for in vivo screening.

While genome-wide screens are increasingly feasible and cost-effective, a clear strategy for following up and validating screening hits has yet to be developed.

Combination of RNAi screening with other approaches such as genome characterization may be effective ways of identifying key cancer genes.

Beyond its use as an in vitro genetic tool, RNAi has application in animal models, and potentially therapeutics.

The role of RNAi itself as a biological process in cancer is another focus for RNAi research including profiling of miRNAs and their targets.

Animal models The technologies for constructing genetically engineered mouse models are well established. They provide powerful tools for studying all aspects of cancer biology from initiation through metastasis. These models have yet to be fully leveraged for cancer therapeutic discovery and development. Imaging technologies extend the utility of animal models allowing non-invasive assessment of tumor progression and drug response through a variety of imaging modalities such as MRI, CT, bioluminescence.

Discussion points:

Pharmacodynamic biomarkers are needed to augment the utility of animal models to allow rapid measurement of drug effect at molecular level.

Chemistry & screening efforts should be directed towards discovery of improved imaging reagents.

Chemical Biology. Synthetic chemistry, high-throughput screening, and medicinal chemistry capabilities available across the Consortium institutions can enable collaborative projects for small molecule discovery and development for a variety of purposes: as a research tools for modulating targets and pathways in vitro or in vivo, as imaging reagents, and as candidates for therapeutic development. Combining these technologies with genomic technologies such as gene expression profiling provides an opportunity to systematically characterize the effects of small molecules in cells at the molecular level as has been recently demonstrated in the Connectivity Map project at Broad.
Discussion points:

Genomic and chemistry technologies provide a clear opportunity to identify drug candidates for traditionally accepted "undrugable" targets such as transcription factors.

Synthetic chemistry around "privileged structures" has proved productive for identifying small molecules target to known target classes.

Structural biology and rational design can complement screening approaches

Experimental Therapeutics There is a critical need for biomarkers to accelerate therapeutic development - for patient selection, rational dose/schedule selection, measuring functional effect, and rapid assessment of treatment effectiveness. In some cancers (CML, GIST, EGFR-positive lung cancer), the implementation of such biomarkers is proving effective, but for some biomarkers (e.g. B-raf, Flt3) the relationship with drug response is complex. Genomic technologies should be applied towards discovering and evaluating more biomarkers. The value of immunotherapy for cancer was demonstrated with the presentation of the clinical success of anti-CTLA4 antibody therapeutic strategy.
Discussion points:

shRNA screening aimed at identifying enhancers/suppressors of drug response to identify biomarkers

Deep targeted gene re-sequencing of responders and non-responders to identify mutations related to drug response

Access to tissue is critical - communication and collaboration with clinical trials is key

Need blood-based biomarkers from circulating tumor cells or serum protein readouts.

Defined mouse models may be an effective discovery tool for biomarkers

Molecular imaging will be a key modality for biomarker measurement

Need tools to assess therapeutic effects beyond tumor shrinkage e.g. cytostatic effect.

Basic biology. A few basic biology projects were presented as examples of areas of interest and to foster a discussion of possible connections between these types of projects and the technology development and large-scale application projects discussed earlier. Presentations covered angiogenesis, metastasis, telomeres, inflammation.
Discussion points:

An example of a potential inter-institutional collaboration was presented focused on the dissection of the ALT pathway for telomere maintenance. The genomic characterization projects could be adapted to identify candidate loci involved in this pathway. These would provide starting points for basic biology projects using existing cell-based models for telomere maintenance.

In general, by identifying basic biology collaborators for genomic characterization projects, a clear path forward for functional analysis of candidate genes can be established.

Starr Cancer Consortium Process. A brief brainstorming at the end of the workshop identified possible mechanisms to move forward beyond this first workshop. Some key elements that were raised:

The participants in the first workshop represent only a small fraction of the investigators at the five institutions potentially interested in getting involved. The process needs to reach out to the wider group.

It is important to provide sufficient opportunity to identify and define the key biological, disease, and clinical questions before we focus on the mechanisms of project solicitation and review.

Two distinct but parallel processes to address different potential project types could be implemented:

For major technology/disease areas, focused smaller workshops may be the most effective way of identifying and articulating the major challenges and opportunities. These may then lead to specific collaborative project proposals

A combination of web-based forums and inter-institutional meetings could facilitate the identification of a broader range of potential collaborations between individual labs across institutions.

It is important to keep the bureaucracy of the funding allocation process to a minimum while ensuring that funded projects are consistent with the goals of the consortium and of the highest quality.