

**National Cancer Institute
Lung Cancer and Upper Aerodigestive Chemoprevention
Working Group Retreat**

Bethesda Marriott
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Meeting Summary

Presenters

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Vladimir Kuznetsov, Ph.D., National Institute of Child Health and Human Development
Gary G. Liversidge, Ph.D., Elan Drug Delivery, Inc.
Spyro Mousses, M.D., National Human Genome Research Institute
James Mulshine, M.D., Chief, Intervention Section, Center for Cancer Research, NCI
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Targeted Therapy, From Bench to Bedside: Are We Ready?

Ivan Horak, M.D., Pharmacia Corporation

Industry shares with academia the desire to cure cancer, and its goal is early market entry with minimal expenses and the best labels.

In 1998, Pharmacia Corporation decided to shift its focus from discovery to targeted therapy. Since then, the company has made major progress in the identification of kinases, as homology in the kinase domain provides pharmacological opportunities and challenges. In 2001, Pharmacia identified 500 kinases as platforms for targeted therapy that will make it possible to develop very selective and specific compounds. Pharmacia is also working intensively on cell cycle inhibitors and is hoping to bring some of these to the clinic within a year or two.

Cancer physiology is important from the pharmaceutical perspective, as an understanding of what the target does in cancer biology (pathogenesis, biochemical targets, etc.) is needed. Products with specific cancer targets have absolute specificity but are niche products. Those that address basic mechanisms result in broad tumor coverage, but may have safety tradeoffs. The major challenge is how to identify targets whose validity can be demonstrated relatively quickly.

Drug discovery requires a logical hypothesis about physiology and pathophysiology, biochemical mechanism of action, validity for *in vitro* screens, chemical feasibility, and strategic fit. Before exploratory drug development can start, the following must be demonstrated:

- Biomarkers are available for mechanism of action (MOA), efficacy, and toxicity;
- Proof of efficacy in tissue culture and animal models;

- Acceptable toxicity profile;
- Target population known; and
- Diagnostic test available.

Pharmaceutical companies also require that the product candidate have biomarkers before entering exploratory drug development, as biomarkers can be used for patient selection, target modulation, efficacy markers, and imaging.

A preclinical plan addresses what must be accomplished before the product reaches the clinic. The plan addresses protein kinase metabolism, *in vivo* efficacy, toxicology, and biomarkers. Dose is based on proof of target (which is the lowest effective dose), proof of mechanism, proof of efficacy, and maximum tolerated dose.

The pharmaceutical industry faces a challenge in translational oncology research. Preclinical and basic science research can easily identify and quickly validate targets. But translation takes much longer, so the challenge is to bring the compound to patients more rapidly. The old paradigm (target, validation, lead compound, models, lead optimization formulation, phase I trials, phase II trials, phase III trials, etc.) is changing. The new paradigm involves literature searches, tissue analysis pivotal studies, patient selection based on the target, preclinical models and biomarkers, etc.

Discussion

Pharmacia's policy of requiring at least 75 percent efficacy for compounds might miss many potentially efficacious compounds. Pharmacia's preclinical models are therefore not suited for identification of chemoprevention agents. However, this strategy ensures that compounds given to cancer patients are safe.

Imaging studies may help measure the duration of the biological consequences of inhibiting given targets. Head and neck cancer may provide a good model for this. Tissue biopsy, pharmacokinetics, and pharmacodynamics in tissue would be helpful because results in plasma might be irrelevant. This is one way to approach hematologic malignancies.

Angiogenesis plays a different role in hematologic than in other malignancies. Some antiangiogenic compounds can be measured on the surface of circulating leukemia cells but it is not clear whether this will translate into clinical benefit in solid tumors.

Pharmaceutical companies establish the label for a compound before developing the strategy. At a very early stage, a target candidate profile and even the package insert can be built before the product enters the clinic. If the label is not developed first, too many important points may be missed by the time the product is developed. Label development is a joint venture among clinical and preclinical, regulatory and commercial representatives, and is initiated many years before a compound reaches the market.

NanoCrystal[®] Colloidal Technology

Gary Liversidge, Ph.D., Elan Corporation

NanoCrystal particles are small particles of drug substance, typically less than 1,000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet-milling technique of Elan Corporation. By decreasing particle size (which increases surface area), NanoCrystals increase the dissolution rate of poorly water-soluble compounds.

Poor oral pharmacokinetics can result from dissolution, solubility, stability, transport, and first-pass loss. NanoCrystal technology can increase bioavailability, dose proportionality, and rate of absorption of compounds for oral delivery. The technology also reduces fed/fasted variability.

Many poorly water-soluble compounds are formulated with harsh vehicles for parenteral administration. NanoCrystals can modulate distribution of pharmacokinetics, serve as a platform for targeting, enhance efficacy/disease toxicity, and administer large doses in small volumes. NanoCrystals can be given safely to humans intravenously, and they stay in the vasculature longer than conventional formulations—5 minutes for nanopaclitaxel versus 3 hours for Taxol, for example. Other benefits of NanoCrystals for poorly water-soluble oncologics include improved safety, comparable or improved efficacy over conventional formulations, no evidence of hemolysis, prolonged residence in blood pool and tumor, potential for higher maximum tolerated dose, administration as a simple bolus, and no necrosis at the injection site.

When NanoCrystal formulations are injected subcutaneously, they migrate through the vasculature and can be used to image lymph nodes. Two clinical trials are assessing the use of NanoCrystals to deliver steroids into the lung with different types of nebulizers. With concentrated dispersion, very high drug loads can be delivered in very short times.

Discussion

There is no [data about the kinetics of how quickly evidence](#) that NanoCrystal formulations can cross the intact epithelium. If short peptide sequences could substitute for stabilizers, this could yield organ-specific delivery. Elan would like to foster collaborations with NCI and others to study this type of issue.

To reduce barium sulfates for imaging, Elan looked at tissue dispersion of NanoCrystals and found that they accumulated on the mucus surface, some migrated into the epithelium, and some of those entered the tissues. The company has studied this using highly water insoluble agents and the material does migrate.

The Role of Cooperative Research and Development Agreements (CRADAs) in Drug Development at NCI (or, CRADAs and What They Can Do For You)

Suzanne Frisbie, Ph.D., Technology Transfer Branch, NCI

The Cooperative Research and Development Agreements (CRADAs) arose under the Federal Technology Transfer Act of 1986. CRADAs are collaborations between a Federal laboratory

(including NIH laboratories) and any company for any type of research (including basic, preclinical, and clinical).

Under materials CRADAs (MCRADAs), the Federal laboratory cannot accept funds from the private company, but private companies can sponsor research by the Federal partner under standard CRADAs. In 2001, NCI received \$5.3 million from CRADA collaborators for its approximately 100 CRADAs (not including its 100 MCRADAs).

CRADAs can be used for any or all steps in the drug development process. When researchers use NCI resources alone, they can:

- Use the Developmental Therapeutics Program (DTP) 60 cancer cell line screen—easy, little or no expense
- Use NIH animal facilities and NCI expertise in other laboratories to conduct animal and preclinical studies—could be costly, expertise might not be available
- Use the contractor facility in Frederick to produce clinical-grade drug for preclinical and/or clinical studies—could be costly, have to wait in queue
- Conduct clinical trials on their own, or use Cancer Therapy Evaluation Program (CTEP) resources—very costly, especially if the investigators file their own investigator-sponsored investigational new drug application (IND) with the U.S. Food and Drug Administration (FDA)

Under a CRADA, a collaborator can:

- Conduct preclinical toxicological/pharmacokinetics or provide funding or expertise to do this at NCI
- Produce bulk preclinical grade drug for preclinical and “ancillary” studies
- File or may have already filed an IND with the FDA
- Provide personnel or funding for personnel

To establish a CRADA, NCI staff should identify companies that they think might be interested in the technology in question based on a review of the literature and the companies’ Web sites. The Technology Transfer Branch (TTB) can also advertise for potential collaborators. Once a staff member identifies a collaborator, he or she should contact TTB before talking to the company, and TTB will set up a confidential disclosure agreement.

Discussion

For examples of existing CRADAs, staff should telephone TTB. ~~For NCI PI’s~~ Anyone interested in tapping into an existing CRADA should contact Dr. Frisbie, who will ask the lead investigator on the CRADA and the company if they agree to an amendment to the CRADA. Otherwise, the staff person can develop his or her own CRADA.

A letter of intent can be executed quickly, often within a few days of the investigator’s contact with a company about establishing a CRADA. The formal agreement takes longer, usually a few months. All NIH investigators on the CRADA must indicate ~~if that~~ they have ~~no~~ conflicts of interest on a form, which Dr. Frisbie forwards to the Ethics Office for its approval. Once the research plan and draft budget are complete, they are sent to the company and TTB negotiates

the agreement. The agreement is reviewed by both the company and TTB, and must be approved by the NIH CRADA subcommittee, which meets monthly. The NIH scientist and technology transfer specialist make a brief presentation to the subcommittee during its monthly meeting and respond to questions. The subcommittee verifies that the CRADA corresponds to NIH policy and may make comments to which the investigator must respond. Several signatures are required before the CRADA is finalized.

Small companies often seek help from NCI to test new drugs for new enzymes, but are concerned about rights to inventions. NCI gives very good royalty rates to companies, and rights are usually split in the event of co-invention. The CRADA can specify that the company has first option for exclusive license to prevent competitors from using the same technology. NCI can obtain a research use license, so that its investigators can research the compound in their own laboratories.

Intramural Drug Development Toolbox

James Mulshine, M.D., Center for Cancer Research, NCI

For drug development, intramural translational investigators should:

- Focus on compelling targets or large public health needs,
- Understand the road to FDA approval (for the indication, not the drug),
- Use the CRADA mechanism as a win/win strategy to complement intramural drug development capabilities,
- Support greater resident experimental pharmacology strength,
- Create an ongoing forum to catalyze progress, and
- Re-establish referral patterns to allow for rapid drug evaluation.

Intramural investigators are welcome to attend monthly meetings of the CTEP/FDA working group. Although both groups have similar goals, their perspectives are different. Understanding the FDA's regulatory pathway can help NCI laboratories identify the appropriate direction to take.

About 400 cancer drugs are in the pipeline, but none is a prevention drug, even though 90 million people are at risk for lung cancer. All current chemoprevention drugs were originally developed for applications other than cancer.

Disincentives for pharmaceutical firms to become involved in chemoprevention include:

- The long trials process thwarts return on investment, which is further exacerbated by the short remaining patent life by the time FDA approval is obtained;
- Unpredictable out-year risk for liability;
- High-volume, low-margin market model (like that of over-the-counter, consumer products); and
- Lack of successful precedents.

Challenges for drug development at NCI include:

- Limited preclinical pharmacology/toxicology expertise,
- Limited formulation expertise,

- Limited good manufacturing practice (GMP) production capability,
- Limited regulatory expertise—intramural researchers often fail to consider how a drug will be used ultimately and how it will be reviewed by the FDA, and
- Limited drug lifecycle planning expertise—many agents can be recycled in creative ways that would be win/win for NCI and private companies.

Spiral computerized tomography (CT) could be very important as a monitoring tool. New spiral CTs can distinguish a change in volume on serially acquired studies of less than ~~product~~ a 1 mm when the volumes are reconstructed ~~edion and~~ and render it in three dimensions. The computer can measure this volume very accurately. Spiral CT can be used for serial imaging at baseline and after drug exposure to measure differences very precisely. Virtual colonoscopy using spiral CT appears to provide much better information at a much lower cost than standard colonoscopy, and is safer and quicker.

Future needs for chemoprevention include:

- Drugs selected for both safety as well as efficacy;
- Informatics system that links cohorts in disparate locations to allow for rapid trial completion;
- More efficient trial designs to accelerate drug evaluation; and
- Objective, robust, economical intermediate endpoints to allow for rapid trial completion.

Discussion

Mutations are necessary, but not sufficient, for clinical cancer. The transformed cell must expand clonally to threaten the host's livelihood. Current chemoprevention trials are attempting to prevent this clonal expansion often through targeting mechanisms of tumor promotion. - Strategies aimed at changing mutation rates are less effective clinically.

Potential toxicity should not stop the development of drugs for chemoprevention. As we enhance our understanding of the pathways and downstream effects, the side effects may decrease. What is important now is to identify agents with some promise of prevention activity in lung cancer, as none has been found to date.

Molecular profiling might be used to identify people at greatest risk, and experimental approaches could be used with them to develop chemoprevention and other prevention strategies. Hopefully, the targets will be tailored to deliver the compound effectively at low cost and low morbidity. An enormous need exists for risk stratification, to identify whom to target and what level of side effects can be accepted, depending on level of risk for lung cancer.

Integrative Statistical and Computational Tools in Analyzing Complex Datasets in Drug Discovery

Vladimir Kuznetsov, Ph.D., NICHD

Systems biology can help solve some drug discovery and drug relation problems. Drug discovery using systems biology must:

1. Integrate genome, transcriptome, and proteome databases; and

2. Decipher complex and incomplete biological data by statistical analysis, constructing and fitting models of biological systems and their responses to treatment agents.

How can we identify “critical” therapeutic targets with low-copy numbers (e.g., rare regulatory molecules, rarely expressed transcripts) and determine their biologic function? Few genes are present in high levels of abundance. Problems with these rarely expressed genes include:

- Current large-scale gene expression technologies provide too many large-molecule targets to be studied by standard methods;
- Thousands of genes are expressed at less than one copy per cell, making it difficult to identify them and determine their functional roles; and
- Noise and ambiguity make identification difficult in more rare transcriptions.

Associated statistical problems must be addressed:

- How many genes in a given cell type are expressed at any possible expression level, including genes expressed at less than one copy per cell, on average?
- How many genes are reliably expressed in a single cell or population of cells?
- How can we separate functional transcriptions from noise errors?

Progress in drug discovery is dependent on the reliability of biological markers used for target gene identification. New bioinformatics tools and statistical modeling techniques are needed to improve the accuracy and reliability of large-scale methods. The probabilistic statistical model helps to remove sequencing errors and redundancy, which is critical in the analysis of large datasets.

The serial analysis of gene expression (SAGE) method has the following limitations:

- Tag sequences are much shorter than corresponding genes,
- Databases contain erroneous tags due to construction and sequencing errors (“non-genome” erroneous tags),
- Some tags match noncoding DNA regions (“genome-associated” erroneous tags),
- No tags exist for some genes, and
- Tags may match more than one gene.

Statistical tools can separate these kinds of tags, and make it possible to analyze more complicated data.

Discussion

The simplest way to assess low-expression genes that might be valuable targets for therapy is to use a normalization technique to amplify the genes, and then analyze them in an artificial reaction. The answer to the problem lies in biological experimentation, not statistical methods.

Integration of Microarray Technologies for Functional and Translational Genomics

Spyro Mousses, Ph.D., National Human Genome Research Institute

With the human genome project and the advent of technologies for gene expression analysis, massive data have been generated. The efforts to translate these genomic data into scientific knowledge have produced a bottleneck effect.

Scientific experiments generate information on how genes relate to phenotype, drug response, and disease. Scientific knowledge, however, is derived solely from hypothesis testing. Data generation should be treated as a discovery tool, and controlled experiments following proper scientific methods are needed to generate scientific knowledge. But such experiments are not possible on 10,000 observations, as they would require hundreds of years to complete.

A parallel and high-throughput hypothesis-testing platform is therefore needed, and microarrays provide such a platform. Microarrays allow massively parallel analysis and are high content, high throughput, and (if experiments are done correctly) produce rich, multidimensional information from which discoveries can be made and hypotheses generated.

Many types of cancer have chromosomal alterations. Conventional comparative genomic hybridization (CGH) microarray can be used to identify chromosomal region. cDNA and CGH microarrays can be used to find genes immediately that are overexpressed and amplified. Genes so identified can be hybridized, and fluorescence *in situ* hybridization (FISH) can be used to see if a match exists. Tissue microarrays are unique in maintaining tissue integrity. Subpopulations within tumors can now be stained and identified.

Once some of the candidate genes are identified, full-length expression vectors can be printed onto glass slides and used for functional endpoint analysis. This allows the translation of association observations into causal observations, which are closer to scientific knowledge.

To develop cell microarray technology beyond prototype into practice, the following issues related to development and standardization of hardware, software, reagents, and methodologies need to be addressed:

- Biological reagents,
- Manufacturing,
- *In vitro* experimentation,
- Assays for endpoint detection,
- Image acquisition,
- Image processing and analysis,
- Information\data management systems,
- Data analysis, and
- Extracting biological information.

Analysis of these data requires new analysis tools. Several groups are trying to form networks of associative gene information, which requires mathematical modeling.

Discussion

Most laboratories have difficulty achieving sufficient sensitivity with classical CGH to discover what is driving amplification.

Integromics: Melding Molecular Data From the DNA, RNA, Protein, and Pharmacological Levels for Cancer Drug Discovery

John Weinstein, M.D., Ph.D., Laboratory of Molecular Pharmacology, NCI

Since 1990, more than 70,000 compounds have been tested against 60 cancer cell types to identify potential candidates for animal studies and, eventually, clinical trials. Many laboratories, including the NCI Laboratory of Molecular Pharmacology, have looked at the characteristics of cells one—or a few—at a time. By looking at the protein or DNA level and then adding additional cell types, one can obtain the pharmacological value of characterization without testing all 60 cell types.

Analytic techniques that can be used for this purpose include:

- Partial sequencing methods (like SAGE);
- Differential display, restriction display, etc.;
- Flat surface hybridization (microarrays);
 - Oligonucleotide chips (length of the oligonucleotide is a big question);
- Light-directed synthesis (Affymetrix); and
- Ink jet, capillary-stamped.

Generic tasks in analyzing gene expression or other “omic” data include:

1. Establish hardware/software/personnel infrastructure;
2. Convert image in pixels to raw expression levels;
3. Examine the image;
4. Preprocess the data (normalize, standardize, filter);
5. Analyze and visualize “high-dimensional” data;
6. Search the literature on genes;
7. Integrate expression data with other databases; and
8. Design the study (replication, controls, internal standards).

Types of bioinformatics include:

- Applied bioinformatics (which is the province of biologists)
 - Exploration of public databases
 - Data analysis
- Developmental bioinformatics (development of statistical theory and computer science algorithms)
 - Statistical procedure development
 - Algorithm and software development

MedMiner software streamlines the search and organization of biomedical literature. It allows the user to make single gene, gene/gene, and gene/drug queries and produces key sentences from abstracts with links to the abstracts. The system speeds up literature searches by a factor of 5 to 10.

In contrast with clinical materials, cultured cells are reproducible, homogeneous, available in large quantities, and can be manipulated. However, cultured cells do not truly represent clinical tumors because they have been taken out of their natural environment.

Discussion

Evolution is a single elimination tournament, and someone will win the biological niche. Even if systems are incoherent, the chance that one will work and still be there in billions of years is unity. This shows why the difficulty of integrating the various levels of concern would not exist if the systems were engineered.

Use of SAGE to Generate Molecular Profiles of Non-Small Cell Lung Cancer

Jin Jen, M.D., Ph.D.

Non-small cell lung cancer (NSCLC) accounts for 80 percent of all lung cancers, which are the most common cause of cancer death in the United States. No specific gene per se is known to be the lung cancer gene, and the genes associated with lung cancer are shared with many other cancers.

The SAGE technique allows the rapid analysis of transcripts present in the system of interest. Essentially, it provides a genetic bar code. To identify genes unique to NSCLC tumors and not present in the normal lung, Dr. Jen's laboratory used SAGE to sequence 18,000 clones from 9 libraries representing 374,000 SAGE tags, each representing a different transcript. The NSCLC cells were compared to cells from the lung, small bowel, liver, and lung cancer.

The laboratory found, using immunohistochemistry, that PGP9.5 was expressed in very few lung epithelium cells, but was highly expressed in cancer cells. In addition, the adenocarcinoma cells were less likely to express this gene protein expression than squamous cells, and were more likely to express it in later stage than earlier stage cancer cells. These findings were statistically significant. Several studies have since shown that PGP9.5 is one of the most commonly occurring markers in lung cancer, but its role in tumor development is not yet clear.

Dr. Jen's laboratory used cluster analysis to evaluate the difference in expression patterns, or calculate the "distance," between genes or samples using data generated from the SAGE analysis. They found that normal tissues clustered together and cancer tissues clustered together. Results were similar for small epithelial cells and large airway epithelial cells, and squamous cells and adenocarcinoma cells. These SAGE results appear to represent the underlying signature that distinguishes tumor and tissue type.

To determine which genes provide this distinct profile, Dr. Jen used P-chance analysis to compare the differences between tumor and normal cells and assess the likelihood that these differences occur by chance. She narrowed 4,000 genes down to 115, and found the same pattern with the 115 as with the 4,000. Most of the genes present in the squamous cell carcinoma of the lung were those commonly associated with smoking and related to immunoglobulin. Perhaps these proteins are the consequences or cause of the immunological reaction that is often associated with adenoma.

Limitations of this research include that all of the data studied so far were generated from nine primary tissues and tissue cultures, and the tumors were very heterogeneous. Dr. Jen used GeneChip[®] expression array to screen another 40 primary tissues to determine the reproducibility of the data and found the same clustering patterns.

Several challenges remain. The observed tumor specificity can depend on the type of control tissue used. The utility of a particular marker depends on the clinical endpoint measured. Finally, the technique requires large cohort samples with fresh tumor materials, and complete case histories and follow-ups.

In conclusion:

- Using only few samples, the molecular profile generated by SAGE can distinguish between neoplastic states as well as cancer cell types of the lung.
- Genes associated with a particular tumor type can be grouped in biologically meaningful clusters reflecting the biological characteristics of the cancer.
- Identification of these genes could provide potential markers for tumor detection as well as rational targets for drug therapy.

Discussion

The field of detecting markers in serum is very young and technical issues need to be resolved to identify markers in a way that is reproducible for assay. The many protein markers will open up this field.

The tumor-associated genes that could be expressed in tumor but not in normal cells were typically very low-copy number genes. Dr. Jen's research focused on the more overexpressed rather than the low-copy genes.

Intermediate Endpoints in Cancer Prevention Clinical Trials

Eva Szabo, M.D., Division of Cancer Prevention, NCI

The minimum essentials for successful cancer prevention trials are:

- Efficacious agent—used at a pharmacologically appropriate dose for a sufficient amount of time,
- Appropriate cohort—with intraepithelial neoplasia (pre-malignant lesions) or at very high risk for cancer development, and
- Primary endpoints—surrogate markers vs. cancer incidence (typically done in phase III, which require thousands of people and much time).

Some differences between treatment trials and prevention trials are presented in the following table.

	Treatment trials	Prevention trials
Phase I	Maximum tolerated dose, dose and schedule, pharmacokinetics	Dose and schedule, pharmacokinetics (this step can be skipped if a simultaneous treatment trial is conducted)
Phase II	Therapeutic effect (specific tumor types)	Intermediate endpoints (preliminary efficacy), which can serve as surrogates for the ultimate endpoint—cancer incidence
Phase III	Therapeutic effectiveness (compared to standard of care)	Cancer incidence

Because prevention trials do not include cancer patients, they cannot assess preliminary efficacy. Instead, such trials identify short-term endpoints that are predictive of patient-specific outcomes, such as blood pressure or elevated cholesterol, which are predictive of cardiac disease.

For an intermediate endpoint to be reasonable for a prevention trial, it must meet the following requirements:

- 1) Predictable relationship between endpoint and cancer risk:
 - High association with cancer development,
 - Low spontaneous reversion rate,
 - Differential expression between normal and premalignant or high risk, and
 - Reduction in marker correlates with disease control.

- 2) Detection and characterization must be reliable and consistent:
 - Feasible in clinical setting,
 - Easily available tissues/body fluids, and
 - Can be modulated by interventions.

- 3) Must be validated via measurement of relevant clinical outcome:
 - Cancer incidence (less ideal), or
 - Cancer mortality (ideal).

Cancer-related biomarkers that can serve as endpoints include histology, processes deregulated in cancer (such as proliferation), and regulatory/signaling pathways crucial to carcinogenesis.

Partnerships are needed between basic science and clinical trials. Basic scientists need to work out the pathways and develop good preclinical models, and clinicians must then determine how the agents are used, identify proper cohorts, and ultimately reduce cancer mortality from these diseases.

Discussion

Spiral CT shows much promise for finding precursor lesions and following them volumetrically. Patients could be scanned at diagnosis, and given a drug during the 3-4 weeks before surgery. The specimen could be resected and CT repeated just before surgery. This type of design is needed to obtain information about early targets. The intermediate endpoint would be change in growth on spiral CT. However, 20 to 50 percent of individuals will have nodules. Those with growth probably already have cancer, and it is not clear which opacities are neoplastic or preneoplastic as opposed to infectious.

Positron electron tomography (PET) and magnetic resonance imaging (MRI) spectroscopies might be used to look relatively easily at metabolic indices of cell health in these lesions. But until a measure of validation is available, the utility of these as an endpoint is only moderate.

One approach is to use drugs with another approved indication, such as celecoxib. These drugs can be used in the setting of actual cancer, as long as doing so does not interfere with appropriate care. Patients can take the drugs during the few weeks while they are waiting for surgery.

Interest Group Business Meeting

Participants were asked to share ideas for this group's name with Drs. Jim Mulshine or Len Neckers.

The Need for This Group

NCI needs an interdisciplinary group of investigators studying tobacco-related malignancies. Such a group is critical for exploring new therapeutic approaches; efforts to combine informatics, analysis of tissue, and tumor specimens; and bridge the gap between basic biologists and clinicians.

NCI used to have vibrant clinical representation in this area, but none of its investigators can do this on their own any more. Unless they join forces, they cannot do state-of-the-art translational research, because setting up a trial takes so long. Finding some way to "piggyback" patient referral would be much more efficient than the "one-hit" efforts that investigators currently undertake.

Full-time clinicians at NCI often do not know that someone in the laboratory across the street is conducting research in the same specialized cancer. Forming a faculty or working group would make it possible to coordinate such efforts. But the number of clinicians devoted to this field is limited.

Lung cancer accounts for one-third of cancer mortality in the United States. Its 5-year death rate is almost 90 percent. Yet last year, only two patients in the NCI HMO program entered lung cancer trials. The need is extraordinary.

Faculty vs. Working Group

At NCI, working groups and faculties do not differ in terms of what they can do. Which type of organization this group forms depends on what projects the group wants to take on, what it wants to work toward. Becoming a faculty does not require a long submission, but only a simple declaration of what the group is about.

According to Carl Barrett, Ph.D., Director of the NCI Center for Cancer Research, faculties are mandated from the top down, whereas working groups are typically grassroots, formed by a group of people with a shared interest. But training is a major part of being a faculty, and having faculty status would enhance this group's reputation with outside speakers.

If this group formed a faculty, this might improve the chances of hiring a full-time clinical lung cancer researcher and forming a small, devoted clinical effort in lung cancer for prevention or treatment.

Potential Collaborations

The tobacco control group is building a clinical facility to do tobacco control activities off the NCI campus. Dr. Mulshine has discussed with Dr. Barrett the possibility of putting a spiral CT unit in this new center to start screening a cohort. NCI might work with Elan to improve diagnostic yield, and could start identifying lesions, developing protocols, doing drug exposures, and obtaining materials. Instead of using cell lines, the investigators could obtain some very early lesions. A major common sentiment from the last meeting was the need for access to tissue, and working with the new facility could start providing this access. Moreover, this small volume of tissue could be leveraged into many types of diagnostic platforms. The NCI intramural program must "get its foot in this population-based medicine door" or it will lose its edge as a vibrant, trend-setting body for upper autodigestive chemoprevention. Too often, NCI intramural researchers only talk about such possibilities, while others do the research.

Dr. Mulshine plans to meet with the tobacco control group to discuss this idea. Having a phase I/II site off campus makes it much easier for patients to participate in the trials. Prevention patients do not want to travel to campus to participate in phase II trials because this can be very time consuming. These individuals would be more comfortable at a satellite facility.

Now is Specialized Program of Research Excellence (SPORE) renewal time, and the SPORE investigators are seeking to add new activities to their portfolios. Therefore, this might be a good time to approach them. In fact, SPORE principal investigators were invited to attend this meeting.

With the amazing array of chip technologies, perhaps this group could form a win/win relationship with respect to the chip's move to the clinic. If some interesting chip or imaging technology turned out to be robust, having it available to this group might be very useful. Going through all the trouble of developing an imaging tool to study 25 patients does not make sense. But if five trials were going on in which the investigators could use their new tool, this would yield data much more quickly. Shared interactions would be useful in this area.

Elan's current management is very comfortable with working with government institutions. NCI could develop a finite number of pilot molecules, have Elan process the molecules using their technology, and then use the results for its analyses.

Next Steps

Perhaps this group should meet every 6 months. The next topic might be CRADA development in depth. Participants in this meeting should e-mail any ideas about future meeting topics to Drs. Mulshine or Neckers. They want to base the forums on what group members want to know for their own personal research.

Phillip Dennis, M.D., Ph.D., is involved as a clinician with a preclinical working group on animal models for lung cancer. All of the members of this group struggle with how good or how poor different animal models are for lung cancer. Obtaining human specimens is difficult for many, so good models need to be defined for lung cancer and other upper aerodigestive cancers. There would be broad interest in preclinical models of efficacy, coupled with preclinical evaluation of toxicity, etc. Perhaps the group could spend half a day on this topic next time, and the rest of the day on another topic.

Because many members of this group belong to more than one group, carving out time for this particular group can be challenging. But instead of carving out time, this group could hold joint meetings with other groups that are doing something that is similar or of interest.

Approximately 40-60 people were expected to attend this meeting, and this is an appropriate number. If the group became too big, it might find it more difficult to accomplish anything, as the number of interests would be larger. Staying small makes the group more focused, and makes it easier to accomplish its goals.

This group will be compelling only inasmuch as Drs. Mulshine and Neckers hear passion from group members that if they obtain the resources, they will do the work.

The leaders of this group will try to meet again in late April to revisit these issues. In the meantime, Dr. Mulshine will discuss with Dr. Hanley-Hyde the write-up required to apply for faculty status. The group will make presentations at the SPORE meeting, regardless of whether it is a working group or a faculty. Dr. Neckers will present at the SPORE meeting on his drug work.

To apply for faculty status, this group needs a mission statement. If it wants to promote an idea, such as using spiral CT for experiments in the new satellite facility, it should write a two-page proposal and justify the request. The proposal should provide a succinct description of what the group wants to do and why, and why this is a reasonable thing on which to spend money.