

**State of the Science (SOTS) Implementation Working Group Meeting
For Myeloproliferative, Myelodysplastic, and Marrow Failure Syndromes**

Four Points Sheraton Hotel, Bethesda, Maryland
March 3, 2003

Co-chairs: Henry Chang, M.D., Assistant to the Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI); Roy S. Wu, Ph.D., Chief and Program Director, Clinical Grants and Contracts Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI)

BACKGROUND

Congress has identified myeloproliferative disorders (MPD), myelodysplastic syndromes (MDS), and marrow failure syndromes (MFS) as diseases that are understudied and underserved and directed that NCI and NHLBI report on their responses to this problem. The congressional mandate of January 15, 2003, states:

Chronic myeloproliferative disorders—Polycythemia vera, idiopathic myelofibrosis and essential thrombocytosis are malignant diseases of the bone marrow that are underserved with respect to research funding, considering the number of people they strike. These disorders are chronic and can transform into acute leukemia. They offer great research promise with respect to insights into the behavior of blood cells, since the cells that they affect appear normal but behave abnormally. The major obstacle to research into the causes and the treatment of these disorders has been the lack of Federal funds designated for this purpose.

The Committee strongly believes that the NCI should expand research into these disorders, and it expects the NCI to report to Congress by April 1, 2003, about existing efforts, as well as planned future efforts, to better understand these disorders.

Myeloproliferative disorders and myelodysplasia—The Committee urges the NHLBI to work with the NCI to develop new research initiatives into the causes and targeted therapies of myeloproliferative disorders and myelodysplastic syndromes. These disorders are characterized by an overgrowth of often abnormal cells in the bone marrow which may lead to leukemia.

PROPOSED JOINT ACTION BY NCI AND NHLBI

Dr. Roy S. Wu, NCI; Dr. Henry Chang, NHLBI

The purpose of this meeting was to develop an action plan in response to prior input from the scientific community as described in:

1. NHLBI - Critical Research Issues in Myelodysplastic Syndromes, April 30, 1999
<http://www.nhlbi.nih.gov/meetings/workshops/myelodys.htm>
2. NCI – SOTS Meeting on Myelodysplastic Syndromes, October 30-31, 2000
<http://www.webtie.org/sots/html/Leukemia%20Home.htm>
3. NCI - SOTS Meeting on Myeloproliferative Disorders and Mastocytosis, April 29, 2002
<http://www.webtie.org/sots/html/Leukemia%20Home.htm>
4. NCI Strategic Plan to Address Recommendations of the Leukemia, Lymphoma, and Myeloma PRG, 10/02
<http://prg.nci.nih.gov/llm/llm.pdf>

Because these prior recommendations were not coordinated with each other or among the respective Institutes, the NCI and NHLBI staff presented at this meeting a draft proposal for combined support of research on these diseases (see flow chart in Appendix A). The simplest approach of supporting research activities may be guided by how patient samples should be handled to expedite research and improve characterization of patients in clinical trials. The rationale is that multiple extra- and intramural programs supported by the Institutes may compete for biological material from these relatively rare disorders, and the study of these conditions requires similar methodologies.

The clinicians are the gatekeepers, and have an important role in the characterization of phenotypes. In addition, it will be necessary to standardize sample handling across centers. During the consent process, for example, it may be possible to obtain permission to harvest bone marrow from perimortem patients for delivery to a specimen bank for cell sorting and molecular profiling. In the area of -chromosome analysis, there is much to do in detection of mutations beyond obvious aneuploidy and translocations. Progress in this area requires participation of clinicians to deliver samples as the disease evolves.

The NCI and NHLBI are currently supporting research activities in the three disease areas through intramural as well as extramural programs. Existing NCI resources include the Director's Challenge and the Cancer Genome Anatomy Project. NHLBI has cooperative agreements for Programs for Genomic Applications, and 6 of 10 newly funded proteomics projects are funded by a Broad Agency Announcement (BAA) mechanism. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) also supports stem cell and stromal cell databases. An implementation strategy should rely first on these resources and those surveyed in the scientific community to generate new hypotheses, with funded studies serving as models for successful applications. New resources will be created where the need is identified, e.g. areas that are not addressed in the proposed approach include immunologic causes and occult infectious diseases.

A Review of Existing NCI/NHLBI Resources

1: The NCI Director's Challenge: Toward A Molecular Classification Of Cancer

James W. Jacobson, Ph.D., Chief, Technology Development Branch, Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis

The NCI Director's Challenge was designed to:

- challenge the cancer research community to demonstrate the power of comprehensive molecular techniques by developing profiles of molecular alterations in tumors;
- develop strategies for analyzing tumor specimens in the context of a clinical or biological question;
- address data management and data analysis; and
- consider approaches to public release of the large, complex data sets resulting from analyses.

Four projects address hematopoietic research. It has been shown that subgroups of diffuse large B-cell lymphoma (DLBCL) have distinct clinical outcomes; 17 genes have been correlated with outcome; and a mathematical predictor has been developed to cluster subgroups by prognosis.

The Director's Challenge has a web site and database for microarray data (<http://dc.nci.nih.gov/index.html>) and a gene-expression data portal. Data in the web site are raw, not processed. It is the first DNA database to be "mammal compliant," that is, consistent with international standards for microarray data for mammals. Unfortunately, bioinformatics resources are not available now to help grant applicants design good database programs or aid existing databases to interface with the Director's Challenge databases.

Discussion

Annotation and data integration Annotation is a problem with all data sets; it can be hard to identify which experiment, which time point, which chips, and which genes are significant. The Director's Challenge is working on annotation issues (e.g., correlation of probes to genome location), but these problems will remain. For this reason, data should be used in hypothesis-generation mode. Data integration is also an issue. The Director's Challenge web site hopes to include results of some of the commercial efforts to integrate data.

Gene expression profiles and histology Gene-expression profiles are interesting but virtually useless without correlating histological profiles, especially with new World Health Organization classification of these disorders. The international pathology community reviews all cases arrayed; clinicians are involved in classification of all these cases, working together with pathologists. Descriptive research grant applications generally score poorly; the importance of supporting descriptive research needs to be conveyed to the review community rather than to the National Institutes of Health (NIH). The culture of the study sections needs to change.

Lack of data and samples Most researchers are aware of the tools that are available; however the lack of data is a problem. The Director's Challenge database is of little benefit to MPD researchers because the diseases are underserved, and resources are not available to generate relevant data for this website. As a consequence translational researchers and hematologists lack the motivation to harvest needed samples. This might be a fruitful area for stimulation.

HIPAA issues related to access to patient histories are another impediment. MPD clinicians want to provide tissue, but cooperation is hindered by government rules and regulations that may not allow or encourage collaboration. Although the HIPAA criteria are onerous, they are not insurmountable. NIH is trying to develop guidance in this area.

2. Cancer Genome Anatomy Project

Lynette Grouse, Ph.D., Scientific Project Manager, NCI

The Cancer Genome Anatomy Project (CGAP) is an interdisciplinary program created by NCI in 1997 to generate information and technological tools needed to decipher the molecular anatomy of the cancer cell. Its goal is to determine the gene-expression profiles of normal, pre-cancer, and cancer cells, leading eventually to improved detection, diagnosis, and treatment.

The CGAP database (<http://cgap.nci.nih.gov/>) is organized by genes, tissues, chromosomes, SAGE (serial analysis of gene expressions) data, pathways, and tools. Genes and tissues are the most popular portals. Tissues are totally anonymous, with no links to clinical data.

The CGAP pipeline generates large numbers of expressed-sequence tags (EST), which are deposited into dbEST and incorporated into the UniGene and HomoloGene databases. Gene-based, manual annotations may also be added via an interface to LocusLink. UniGene partitions EST data into clusters, each representing a unique gene. The database also has a SNP (single nucleotide polymorphism) finder and viewer and cDNA libraries in which a gene has been expressed. Through a link to the OMIM (Online Mammalian Inheritance in Man) database, users can see the diseases in which the gene of interest is expressed. CGAP contains links to a protein database and other public databases as well.

If researchers transfer some funds to CGAP, they can use the existing CGAP infrastructure and its competitive costs to build similar libraries for these three underserved disease areas. CGAP has negotiated a good price from private contractors to build its libraries. Although full-length sequencing is still costly, EST sequencing can be useful and is well priced. Standard libraries cost about \$9,000 each; specialized libraries can cost \$11,000. CGAP has some 2,000 sequences to survey at approximately \$5 per read.

A donation of biological material to CGAP waives all rights to whatever is generated from that material (researchers can obtain aliquots). After sequencing and annotation, all

CGAP data go directly from the contractors that perform the sequencing to GenBank, where they are publicly available. Companies are allowed to sell the libraries; there are no intellectual property issues.

A demonstration of the CGAP database was performed. A search of the CGAP database for the EVI1 gene, a major transcriptional repressor associated with leukemia, yielded only two GenBank accession numbers and very limited data overall.

Discussion

Standards and quality control CGAP quality control depends on the RNA received. Participants in this SOTS meeting may want to create standards and protocols for collection and handling of biological materials (e.g., putting aspirates directly into dry ice). Quality control issues may be addressed by splitting samples—sending half to CGAP and half to the researcher’s own resource.

Use of CGAP’s structure NIDDK is supporting work on gene-expression profiles of zebrafish and wants to use the CGAP structure. The NIDDK provided CGAP with the necessary funds. CGAP then contacted the NIDDK investigators to facilitate transport of tissue from the principal investigator to the company that builds the libraries.

Utility and access Although NCI is seeking novel translational cancer grants, on several occasions staff members did not believe polycythemia vera was in the scope of the NCI. An R21-like mechanism is needed because a PI can use CGAP only if already funded. MPD is not in the CGAP database under current circumstances. The CGAP policy of waiving rights to donated samples and commercial desires to get exclusive rights to them may hamper submissions. Expanding CGAP will require government support. \$100,000 is a relatively modest amount to spend and could fill CGAP with MPD data.

Recommended action: request at least five sequence collections be allocated for these diseases in CGAP.

Role of clinicians and pathologists Challenges involve determining how best to gather and store samples effectively and how to get clinicians and pathologists, who are central to specimen issues, to correlate clinical data with specimens.

Funded Studies as Models

1. Inherited Bone Marrow Failure Syndromes Study

Blanche P. Alter, M.D., M.P.H., Clinical Genetics Branch, NCI

NCI is sponsoring the largest North American study to focus on people with rare inherited bone-marrow-failure syndromes (IBMFS) and their family members. The primary hypothesis is that study of rare cancer-prone syndromes can provide information about the development of cancer. The study also has several secondary objectives, which include verification of diagnosis from medical records and by laboratory testing.

The IBMFS study includes people with Fanconi's anemia, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, severe congenital neutropenia, thrombocytopenia with absent radii, amegakaryocytic thrombocytopenia, Pearson's syndrome, and non-acquired bone-marrow failures. An estimated 1,000 or so people in the United States have these disorders. Opened approximately a year ago, the study has enrolled about 100 families, for a total of 500–600 people. Only 100 or so have been seen to date, however, and it is a highly resource-intensive effort. Because some diseases are dominant and some are recessive, all family members must be seen.

Fanconi's anemia can present in older patients as MDS and only later be identified as the cause. If this potential is not recognized, MDS data can be inaccurate.

In this study, the data are not stripped of patient identifiers. The study itself is publicized on listservs of patient support groups, presentations at meetings, and through a web site, www.marrowsfailure.cancer.gov.

Discussion

Study data Data are made available to the public through presentations and publications. Collaborators receive raw data. Extramural investigators receive data without identifiers. An investigator who has a question that requires clinical information can ask Dr. Alter, who heads the IBMFS study, and she will check that information and provide an answer.

Study budget The annual budget is more than \$1 million, excluding salaries, and some salaries are funded at 100 percent for this work. When both technical and laboratory support, covered by contracts under a different budget, are considered, the annual study budget is between \$20 million and \$30 million. By contrast, for a program project or SPORE, a typical budget ranges between \$1.5 million and \$2 million per year in direct costs. Capturing all relevant data will cost \$5,000–\$20,000 annually per patient.

Patient accrual Although MDS, MPD, and marrow-failure syndromes are all blood diseases, they involve different biological questions. Basic translational models are common to all three, and advocacy is very important. For productive clinical research, both a national and an international effort may be needed to accrue enough patients.

2. International Consortium For Myeloproliferative Disorders

Ronald Hoffman, M.D., Director, UIC Cancer Center, University of Illinois, Chicago

Although these disorders are becoming more common, in total numbers they remain rare. Large numbers of patients are needed for clinical trials to yield molecular and cellular information that might improve treatment. In polycythemia vera, for example, many basic questions can be answered only through large clinical studies.

The consortium began with U.S. researchers working with Italy's Instituto Mario Negri, which has clinical and scientific expertise in this area, a registry of more than 1,600 patients with polycythemia vera, and access to a European polycythemia vera study. In

addition to the 1,600 Italian patients, 20-50 patients are enrolled in the United States. All patients in Europe can be entered into the trial, and Mario Negri manages the database. The Italians are funded through the European Union and a private foundation. The hope is that, after initial funding, basic science projects will feed into clinical trials using novel compounds in these disorders.

Several support “cores” have been considered for the consortium, including a tissue-bank core, which may be one bank with sites on both sides of the Atlantic. Translational research associated with clinical projects and the cores is anticipated. Although the group does not have a hemopathology core for budgetary reasons, it could be incorporated in the first clinical project. All cores would be both U.S. and Italian. All investigators who participate are funded and want to work on MPD.

Discussion

Funding Enormous funds would be needed to characterize large numbers of patients. Although the Italian collaborators have some European Union funding, and the Mario Negri Institute is a private foundation with three sites: Milano, Bergamo, and one near Rome (the latter is the newest and is capable of doing microarrays). This Consortium has initiated talks with NCI and NHLBI staff to submit a P01 grant on the model of the CLL Research Consortium funded by a NCI P01 grant (CA81534)

Smaller studies International studies are important for large randomized patient studies but are not essential for pathology work. Phase I and II pathogenesis studies can accrue enough patients for meaningful results. Organizations of U.S. scientists and clinical researchers can get together to perform valuable cooperative research in the absence of the sizeable funding needed for larger studies. Meeting participants might consider seeing what can be accomplished within their own community via collaboration. Many domestic resources have not been organized and used.

3. MDS Center, Rush Cancer Institute

Azra Raza, M.D., Professor of Medicine, Charles A. Weaver Professor of Cancer Research, Director, Section of Myeloid Diseases and MDS Center, Rush Cancer Institute, Rush-Presbyterian St. Luke's Medical Center

Rush Cancer Institute is one of the largest centers in the United States devoted to MDS. It sees approximately 350 new MDS patients and 200 follow-up patients annually, referred from a large network of hematologists in five midwestern states. The MDS Center has nine ongoing therapeutic protocols. Planned collaboration is expected to increase the patient base to some 1,000 patients per year.

The tissue repository contains roughly 40,000 samples from 5,000 patients. These samples come from different stages of disease and have the benefit of uniform pathology, surface markers, and cytogenetics, and companion laboratory and clinical data. This computerized data bank can be used for epidemiologic and correlative studies. Such specimens can be used for molecular, immunological, and genetic studies in MDS and

AML; Northern, Southern, and Western blots; PCR and RT-PCR; DNA microarrays; genomics and proteomics; FISH and multiplex FISH; and protein-expression studies.

The MDS Center's computerized database has the following information for approximately 2,000 MDS patients: detailed information on history of toxic exposure, family history, social history, medical history, and medications; course of the disease and response to therapy; duration of response; and overall survival.

Discussion

MDS Hubs Within the United States, MDS research hubs can be identified, along with nodes to connect them. Modest seed money in this effort would go a long way.

Patient accrual Hematologists are willing to contribute patients to centers that are studying and treating MDS. NCI funding can support development of a large patient base that can be used to propose basic research in the future. This effort must include education through web sites, public service announcements, and other means.

Budget A clinical database with a technician devoting 50–100 percent effort to the project and a refrigerator for storing samples would cost about \$250,000 per year. Enrollment of 300 patients per year would generate a lot of data. Entering data for only one patient could take all day. The MDS Center has had longtime NCI funding and additional support from foundations and industry. Industrial support is usually provided in the context of therapeutics development and clinical trials.

4. An NCI-funded Study Of Juvenile Myelomonocytic Leukemia

Peter D. Emanuel, M.D., Associate Professor of Medicine, Wallace Tumor Institute, University of Alabama at Birmingham (1R01CA095621-01A1)

A proposal to study juvenile myelomonocytic leukemia (JMML) did not reach the payline the first time but was funded in a later submission (2003) because it was supported by strong signal-transduction science. This study involves the Children's Oncology Group (COG) and is an example of what can be done through cooperative groups and competitive funding from NCI.

JMML has an estimated incidence in North America of 40–50 cases per year. It is linked to two inherited disorders. About 20 percent of patients with JMML have N-ras and K-ras point mutations; 25 percent have inactivated neurofibromatosis (NFM) genes (the NF1 signal turns off ras); 10–25 percent have clinically active NFM. Noonan's syndrome has been associated with the PTPN11 gene. All mutations appear to be mutually exclusive and are somatic, not germline.

Two mice models are available for JMML: an NF1 knockout mouse and an NF1 non-SCID mouse. With these models, it is possible to investigate targeted treatment (e.g., to GM-CSF, which turns on growth, and NF1, which turns off growth). The current COG Phase II trial includes a tissue repository and analysis for NF1, ras and PTPN11

mutations. The study has accrued 30 patients in the first year and a half, and data will be mined from this group of patients. Laboratory staff work all hours (24/7) because of the unscheduled arrival of samples.

Discussion

COG clinical trial This Phase II study (COG #P9920) is evaluating farnesyl transferase inhibitor (R115777) followed by 13-cis retinoic acid, cytosine arabinoside, and fludarabine plus transplantation of hematopoietic stem cells.

Correlative studies COG does not have funding to build into the protocol all the correlative biological studies needed for targeted therapeutics development. Some seed money is available, but scientists need to acquire funding from industry and other sources on their own. The attendees questioned whether this is only a matter of money or whether this is due to a lack of representation on the clinical trials protocol development groups. Although the Cooperative Groups look more favorably on a clinical trial if biological correlative studies are included, the problem is finding the funding to support these correlative studies. Molecular profiling is important to characterize patients in a trial. Large granular lymphocytic (LGL) leukemia is a neglected disease that requires correlative studies but is too low a priority for the Cooperative Group.

Translational scientists It would be valuable to identify translational researchers across the country who are interested in these diseases and identify resources available in their areas.

Recommended action: Form a consortium of strong clinical and basic researchers that would be supported by NCI with basic seed money. The group can apply for SPORE funding later.

Clinical collaboration M.D. Anderson Cancer Center would like to be part of other groups (has now joined SWOG). Most correlative studies are done through foundations and industry. It is much easier to work with AML and CML than with MPD and MDS. Memorial Sloan-Kettering Cancer Center puts very few resources into this area (one faculty member in bone-marrow transplantation and one doctor in leukemia). It is difficult to interest research fellows in these diseases because they see that discoveries are unlikely. Clinical collaboration is needed; the only way to do this is through small groups that are comfortable working together. Unlike CML or CLL, there are no approved drugs for MDS. Most therapeutic agents come from industry. Because these diseases are heterogeneous and very difficult to study, this group needs an impetus to collaborate. Sometimes, continuity is a problem. When a postdoc leaves, the new one may refuse to continue the work because the samples saved are not good enough.

Recommended action: From the expertise available at this meeting, reach consensus on what materials should be stored and how to process and store them.

FUNDING MECHANISMS

In addition to R21/R01/P01 grants there are three other funding mechanisms available:

- supplements, which require an existing grant;
- Broad Agency Announcement (BAA), which operates somewhat like a contract but has more leeway in implementation (used often at NHLBI; less so at NCI); and
- U01 cooperative agreements.

Because the BAA's goal is to increase knowledge, this mechanism addresses a broad research area rather than specific investigations. NIH outlines basic areas of interest, but each applicant proposes an investigation to address one or more specific aspects outlined. Selection is based on importance to NIH programs, merit, and available funds. BAA applications undergo peer review.

NCI will continue to support investigator-initiated research. Through supplements, existing grantees can receive seed money to jump-start work on new ideas. In the current budgetary climate, it will be hard for the NCI and NHLBI to set aside large amounts of new funds for these diseases.

Discussion

Clinical trial costs Funding for Cooperative Groups is well below the true cost of accruing, treating and following a patient through a clinical trial. Additional internal resources are needed to supplement these NIH funds. Exclusive of corollary studies, Phase I-III studies cost on average \$5,000 per patient in direct costs. Patients accrued to phase I cancer trials cost about \$7000-10,000 per patient. Free standing institutions, Cooperative Groups, and other organizations have access to large patient bases controlled by physicians or university programs that can publicize a new program quickly. The plan for basic studies should be incorporated into the initial design.

NCI's Cancer Trials Support Unit (CTSU) is a pilot project for the support of a network of physicians (domestic and foreign) to participate in NCI-sponsored Phase III cancer treatment trials. <http://www.ctsu.org> Currently only Canadian physicians are participating in this pilot project but European physicians will be allowed to participate in the near future. CTSU also provides a mechanism for collecting samples. There is a movement to put rare diseases within the purview of CTSU.

Collaboration with Cooperative Groups Collaboration requires dollars. Significant funds would attract response in the Cooperative Groups. Small or large consortia, such as the CLL Research Consortium, could encourage work within and attached to Cooperative Groups. Requests can be very specific (e.g., tissue repositories, molecular diagnostics). Cooperative Groups work because they examine common diseases. Rare, adult hematological disorders are much more difficult. Scientists cannot rationally identify drugs or therapeutic approaches because they lack a basic understanding of these diseases. Participation in Cooperative Group trials is driven by good studies. Good science draws participants. However, the nature of these patients—older people, cared

for by community-based clinicians and often under treatment with chemotherapy—makes many of them ineligible for other studies. An MPD web site can be a recruitment resource.

[After the meeting, Dr. Peter Greenberg at Stanford commented that he would be willing to make available the forms used for the International MDS Risk Analysis Workshop (IMRAW). In addition, he chairs the MDS Panel for Practice Guidelines of the National Comprehensive Cancer Center (NCCN), which could be connected to the NCI Clinical Trials Cooperative Group and other institutional protocols.]

A barrier to collaboration is that many people are competing for the same funds to support their research. Collaborative projects can mask the contribution of individuals who collaborate and can affect their chances of independent funding.

Consortium approach A consortium of leading scientists—clinicians who are passionate about these diseases rather than those who are absorbed in a broad range of clinical trials—would have a better chance of funding. Larger consortia better serve the pathobiology of these disorders, although there is an important role for single-institution studies, and some centers already have track records in these diseases.

Recommended action: Set up consortia with hemopathologists, clinicians, and research scientists for collaboration and sharing of resources.

Private funding The pharmaceutical industry and foundations provide financial support for some research in these diseases. The Leukemia and Lymphoma Society vacillates about whether MPD fits its mission; it has funded MPD research before but has not funded research at multiple institutions for this disease. The Leukemia Research Foundation, a Chicago-based grassroots organization, gives more than \$1 million per year in \$50,000 grants. Its research support has expanded beyond leukemia. The MDS Foundation has funds to carry out an expansive program of clinician and patient education but provides no funds for clinical trials or pilot studies. The Aplastic Anemia and MDS International Foundation has limited research funds and has a large program in patient oriented/related efforts (education, registry, on-going clinical trials).

Recommended action: Consider partnerships with the Leukemia and Lymphoma Society, and the Leukemia Research Foundation and other non-profits as well as for-profit organizations.

TRAINING FUNDS

Mechanisms are needed to lure postdocs to these understudied diseases. However, training grants are of limited utility because they:

- support mainly the trainees, but they require considerable investment of time from mentors who already should have grants
- cannot assure trainees of career development in a poor funding environment

There are many ways to pay for trainees. The issue is the research money to cover the experiments, especially in molecular biology (e.g., tests for gene expression are costly).

Discussion

Career opportunities MDS does not offer young researchers a sense of optimism that their time and effort will yield a lifelong career. Seed money is needed to build an infrastructure of knowledge, and collaborators to tempt junior researchers. Industry is not interested because the MDS field has not produced approved therapies.

Novel ideas Cooperation in clinical trials is greatly needed, but innovative ideas are equally important, both to interest young fellows—especially those interested in translational work—and to move the entire field forward. In the 1970s, MPD was a hotbed of research, with clonal assays for hematopoietic progenitor cells. The loss of interest is partly the result of the lack of funding and novel ideas. Few people being trained have the experience with the natural history of these disorders needed to work with clinical and research scientists to design studies. There is a shortage of young people in the pipeline to work on MPD.

Seed money to develop infrastructure The only way to get seed money from NIH is to write an application and submit it for review. The NCI-funded CLL Research Consortium application did not initially reach the payline as a P01 grant. Instead, it received one year of seed money as a planning grant (P20) and later competed successfully for a P01 award. NCI is willing to consider any submission that receives a priority score close to the payline. The Institute has some leeway for areas of interest, given the congressional mandate.

RECOMMENDATIONS

A relevant model will have a good database, patient profiles, and a repository of samples to support the genomics and proteomics work. This, in turn, can lead to insights that support translational work and grants.

Recommended actions:

- Develop a broad, national database with open access for data mining.
- Focus on small numbers of highly selected and well-defined cases of each of these diseases, that are well-characterized and made publicly available.

Many grant applications have stimulated interest but received low priority scores. Researchers do not want to continue to waste their time. They want assurance that their applications will be reviewed favorably.

Recommended actions: Eventually, some funds will have to be set aside. Focus on studies with excellent correlative resources, especially basic science.

An important issue is how to compete with diseases that are far easier to study and more advanced in research. All initiatives compete widely with other diseases and initiatives. Also, a tension exists between clinical and basic science because of the cost of clinical studies. There are ways to fund clinical trials; what is missing is the basic science support structure. All correlative work is driven by clinical trials, but money is needed

for translational science, and to develop ways to utilize biologic samples (e.g., industry will not pay for storage of CD34 cells).

Action item: Subcommittees of experts will be formed to work out details in specific areas (patients, adjudication, cellular, molecular, software, database, diagnosis, treatment, resources).

NHLBI's interest in stem cell biology should justify an interest in MPD, as well as research in thrombocytosis. Also, cancer presents a paradigm for the study of chronic disorders. In the past 20 years, MDS has moved far ahead in translational research, and the Rush MDS Center's large patient base has brought many offers from industry.

Recommended actions: In various geographic locations across the country, identify investigators and universities interested in these areas. Put data together, organize into groups, and present proposals to NIH.

Are MDS and MPD researchers competing against each other? Should NIH initiatives be split between these two areas? Given patient numbers, MDS is likely to overwhelm MPD. Although there is some overlap, the congressional mandate lumped together three groups of disorders. Some biological questions are different, and there may be as many as 20 understudied agents for treatment of MDS but nothing comparable for MPD. Although it may be desirable to split MDS and MPD, clinical and basic research should not be separated. Resources are essential for researchers in this field to be competitive for R01 grants.

Recommended actions:

- Create a web page for deposit of information and ideas, so that in 3 years, the field could meet and know what is available.
- Enthusiastically endorse the study of MDS and MPD from clinical and basic research perspectives without excluding either. Proceed through organization of new consortia as proposed, cooperative groups, or other mechanisms, perhaps internationally.
- Give basic science a "leg up" through dedicated set-aside funds for these diseases, and let researchers compete for that pool of funds.
- Create a method to organize (e.g., the Italian consortium model). Have government endorse the importance of a national registry, tissue bank, and database (which will have to take into account final HIPAA requirements). Clinicians will then participate, attracting industry and basic scientists, who will be more competitive for grants because of this resource.

NHLBI has a tissue bank relevant to the preceding item but does not have an extensive phenotype database. Doing a tissue bank properly requires a major effort (e.g., clinical descriptions, flow cytometry, lab work, quality assurance, central cytogeneticists to validate chromosome data, and pathology review for diagnosis), but this could be set up.

Final recommendations:

- Provide supplements to existing resources and foster collaboration.

- Issue an RFA for MDS and another for MPD. For each of these disease categories, look favorably on potential consortium proposals, whether they are independent or involve an existing group.
- Form subcommittees to standardize approaches, if possible, and assess progress.

A sign-up sheet was circulated for planning committees to address the following areas:

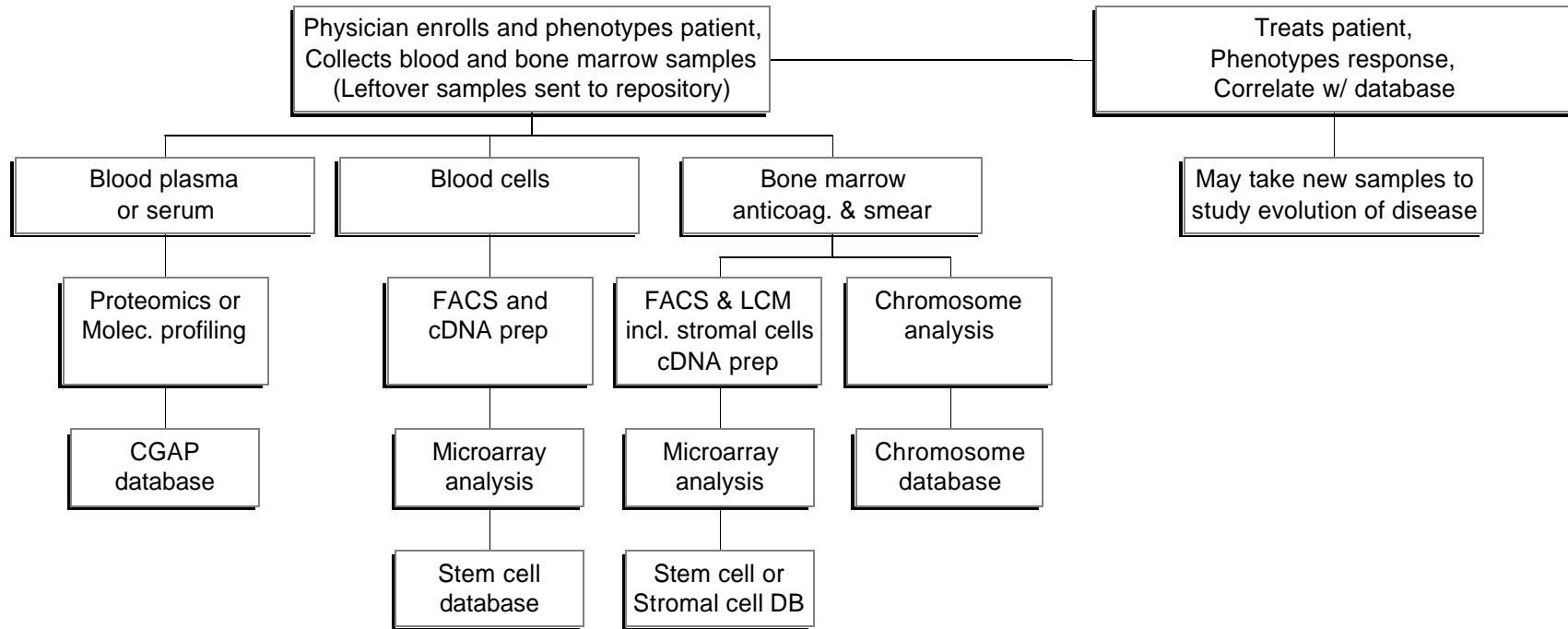
1. Patients:
 - What are the existing sources for patients and how to recruit more?
 - What repositories exist to collect samples, including postmortem ones?
 - How best to correlate the changing phenotype of the disorders with lab data?
2. Diagnosis and adjudication (a quality assurance function):
 - Should initial classification by morphologists be blinded to molecular data?
 - What additional resources would help to classify these disorders?
3. Cellular and molecular diagnosis:
 - What is the availability and need for cell-sorter facilities, cytogenetic facilities, microarray facilities, and proteomic facilities?
 - What technologies are needed to find occult infectious or immunological causes?
 - If funds are available, who can share or provide them?
4. Software and database curation:
 - What are the best platforms for data collection and analysis?
 - Who will curate the results?
 - Who will set priorities for non-exclusive access to data and samples?

In lieu of these four topics, meeting participants might choose to consolidate into Diagnosis (RBC, WBC, megakaryocytes, stroma, mast cells) and Treatment (chemotherapy, transplant, and immunotherapy) Subcommittees, which would increase participation and facilitate communication.

APPENDIX A. FLOW CHART

APPENDIX B. ROSTER

APPENDIX A. FLOW CHART



Roster

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