A Quantitative Assessment of the NIH Bench-to-Bedside Program: Accomplishments of the First 100 Projects, 1999-2006

Charles R. Sherman, Ph.D.
Program Evaluation Consultant
July 2007

Abstract

The NIH Clinical Center's Bench-to-Bedside program's purpose is to encourage innovative projects that involve both laboratory and clinical researchers for the purpose of accelerating the achievement of NIH's principal mission. To assess the performance of the Bench-to Bedside program, information was solicited and summarized to document the breadth of NIH participation, the accomplishments of each project, investigators self-reports of the programs process and funding, and to focus on the benefits of the recent extension of the program to encourage intramural-extramural collaboration. It was observed that the record of accomplishments is tangible and growing, although some individual projects have not been successful. Collaboration between individuals with bench science and clinical skills has been stimulated and led to new research protocols. Collaboration between intramural and extramural investigators stimulated enthusiastic expectations of synergistic accomplishments. The level of funding awarded is generally insufficient to cover the entire project costs; while it supports the seeds of translational ideas and initial growth, supplemental funds and subsequent grant support is frequently sought. Continuing program support from sponsoring offices looks promising. From the responses of principal investigators, it can be inferred that encouragement and support from Scientific Directors of various Institutes and Centers is not uniform and may be an appropriate subject for further exploration and discussion.

Background

Program and goals

The NIH Clinical Center's Bench-to-Bedside (B2B) program purpose is to encourage innovative projects that involve closer collaboration between laboratory and clinical researchers for the purpose of accelerating patient-oriented research for the diagnosis and therapeutic intervention of medical disorders.

With an administrative locus in the Office of the Director of the NIH Clinical Center, Ms. Patricia Piringer has coordinated the B2B program since its inception in 1999.

The Deputy Director for Intramural Research, NIH, and the Director, NIH Clinical Center (CC) issue a Call for Proposals jointly and annually. Investigators in all NIH Institutes and Centers (ICs) are eligible to compete for a number of awards (determined by available funds) of up to $100,000 per year for two years. About four months are allowed for proposal preparation, approval by Scientific Directors of each IC involved, and submission to the Clinical Center Director. A review committee reviews all proposals and makes a selection in about one month. Successful applicants are then notified.

The B2B program has become popular in the intramural program and carries the prestige of competitive selection as well as the financial research support. In FY 2007, for example, a Call for Proposals was issued in August 2006, 43 proposals were received by the deadline in November, and 19 awards were announced in December. Recipients are obliged to submit annual progress reports.

The Call for Proposals, August 9, 2006, is Appendix A of this report.

Previous tabular progress report

In 2004, the progress reports of the first 64 B2B projects were compiled into a tabular summary of investigators and accomplishments. It was then decided to experiment with the program format by allowing extramural NIH grant awardees to be included as collaborating investigators. Information provided in that report is included and updated in this report.

Projects per year

In the first eight years of the B2B program, 100 projects have been supported. Table 1 displays the number and cumulative number of supported projects per year. All but two of the projects supported in 2005 and 2006 included extramural collaborators.

Table 1. Number of Bench-to-Bedside projects supported

Year	New Projects	Cumulative Projects
1999	8	8
2000	9	17
2001	9	26
2002	6	32
2003	13	45
2004	19	64
2005	17	81
2006	19	100

Limited Objectives of this Review

The objective of this review is to extend the compilation of accomplishments first created in 2004, and to solicit and summarize the views of the supported principal investigators and of some Office Directors who generously provide funds or matching funds. Special interest is paid to the projects with intramural and extramural collaborators. This is not an evaluation of the impact of the process or program with comparison to other non-B2B research projects or research-support mechanisms.

Methods

Voluntary on-line data collection

With the assistance of NIH Center for Information Technology's Division of Enterprise and Custom Applications, a two-part Web-based data-collection instrument was crafted. Three hundred twenty-four (324) selected investigators received e-mail invitations from the CC Director to provide information. There were two or more investigators invited from each of 100 projects. Each was provided with a unique login code. Investigators involved in more than one B2B project received a code for each project. Upon login, each investigator was shown the title of the project for verification. The data collection web site was active for one month; a reminder was e-mailed after two weeks.

Part 1 – B2B project accomplishments from multiple co-investigators; previous information returned for completion

All solicited investigators from a given project could view and collaboratively prepare their answers to the lists of accomplishments sought in Part 1. Information from the accomplishments table compiled in 2004 was entered before the first invitation was sent to minimize the effort required to respond. Previous information could be edited on-line.

Part 2 – Personal views by single investigators; more questions for projects with extramural participants

Information received from investigators in Part 2 was not viewable by collaborators. An extended set of questions was posed to investigators involved in intramural/extramural collaborations. These questions were not pertinent to projects with only NIH employees. Each topic allowed for fixed- and unformatted responses.

A copy of the on-line solicitation is available from the Director of the B2B Program.

Responses and rates

One hundred three (103) responses were received to the 324 solicitations, a 32 percent rate of response. The responses came from 85 different investigators, 12 of whom provided information about two or more (one for as many as five) B2B projects. The questionnaire yielded returns from investigators on 67 different projects (67 percent). Combined with the information that was already available from the 2004 report, there are now accomplishments listed for 91 (91 percent) of the 100 B2B projects, although some of it is probably incomplete. The numbers of investigators, their affiliations and degrees

in this report are not based on the solicitation, but on a database compiled from B2B project applications, the NIH Enterprise Directory (NED), and some direct contacts. There is an undercount of investigators by about 23, because 7 projects only listed ICs and extramural institutions of Associate Investigators without providing names. Participation statistics are based on known investigators and co-investigators.

Telephone interviews with supporting Office Directors

Conversations were held with four of the five Directors of the administrative units that are providing financial underwriting of B2B projects in support of their own missions. The five units are the Office of Aids Research, the Office of Rare Diseases, the National Center on Minority Health and Health Disparities, the Office of Research on Women's Health, and the National Center for Research Resources.

Findings

Participation

Institutes and Centers and Extramural Institutions

Twenty administrative units of the NIH had employees participating in the B2B program as named investigators, including 17 ICs, the Clinical Center, the Office of Research Services, and the Office of the Director. There are also 27 extramural institutions whose staff collaborated in the B2B projects. Table 2 presents the numbers of project investigators from each NIH IC or other unit. The total, 374, includes 281 individuals, some of whom are participating in more than one project.

Table 2. Number of B2B project investigators from each participating IC or other unit

NCI	99
CC	53
NHLBI	51
NIAID	39
NINDS	31
NICHD	24
NHGRI	19
NIDDK	14
NIDCR	11
NEI	7
NIEHS	6
NIMH	6
NIAMS	4
NIDCD	3
NIDA	2
CIT	1
NIAAA	1
NINR	1
OD	1
ORS	1
TOTAL	374

Typically there is collaboration, not only between clinician and bench researchers, but also between investigators from more than one IC. Only 19 projects had investigators from a sole IC. Sixty-two had 2 ICs collaborating; 17 had 3 ICs collaborating and two projects had investigators from four different ICs.

The following extramural institutions have staff investigators who collaborated on B2B projects (number of projects also shown):

Center for Biologics Evaluation and Research, FDA
Children's National Medical Center
Dartmouth Medical School
Fred Hutchinson Cancer Research Center (2)
Georgetown University (2)
Harvard University
Johns Hopkins School of Medicine (2)
Karmanos Cancer Institute and Wayne State University
M. D. Anderson Cancer Center (2)
Makerere University, Mulago Hospital, Uganda (2)
Mayo College of Medicine
Medical College of Virginia
MedImmune, Inc.
Memorial Sloan-Kettering Cancer Center
Naval National Medical Center
Ontario Cancer Institute and University of Toronto
Oregon State University
San Francisco General Hospital/UCSF (2)
St. Michaels' Medical Center, NJ
The Kennedy Krieger Institute
University of Illinois at Chicago
University of Maryland (3)
University of Pennsylvania (3)
University of Southern Calif.
University of Wisconsin
Walter Reed Medical Research Center (2)
Washington Hospital Center

Twenty-two B2B projects had one or more extramural collaborators.

Investigators

Individuals vs. project investigators

There are 316 known individuals working on the 100 B2B projects, and 66 of them are or have been involved working on more than one project. One investigator has collaborated on six projects. Three investigators work on five projects each, two work on four projects each, 10 work on three projects each, and 51 have worked on 2 projects each.

The number of investigators listed per project varies from two to 11, with the median between three and four. As noted above, a few projects did not list the entire team on their applications, and some changes may have occurred after the award was made.

In the following analyses, unless otherwise noted, investigators are counted with each project, so some individuals will be counted or tabulated more than once.

Degrees

A wide variety of clinical and research degrees are held by B2B investigators. Clinical degrees include MD, DMD, DDS, VMD, DO, RN, MMed and MBchB. Research degrees include PhD, DSc and MPH. For a few, Bachelors and Masters of Science is the highest degree. The cadre of investigators held these degrees and other degrees, such as JD and MBA in a variety of combinations. For use in analysis, the degrees have been grouped into four categories: clinical, research, clinical/research and other, as displayed in Table 3:

Table 3. Distribution of Degrees held by B2B Project Investigators	
Clinical (e.g. MD)	246
Clinical and Research (e.g., MD-PhD)	59
Research (e.g., PhD)	100
Other (MS, BS)	6

Role vs. Degree

Investigators were asked to indicate the role they played on each project, whether as a bench scientist or clinician investigator (or both or other), and they were asked to elaborate with comments if they desired.

The team role played by investigators who participated in multiple projects sometimes varied from project to project.

On a larger scale, there is no strict correspondence between degree held and role played, as one might expect. Table 4 shows the correspondence for the 103 investigators who indicated their self-described role.

Table 4. Investigator role played and degrees held by 103 B2B participants				
	Role played in B2B Project			
Degree Group	Clinician investigator	Both, not principally one or other	Bench scientist	Other
Clinical (e.g. MD)	23	13	17	2
Research and Clinical (e.g., MD-PhD)	6	8	5	2
Research (e.g., PhD)	11	5	8	2
Other (MS, BS)	1	0	0	0

A sample of volunteered comments demonstrates the versatility of investigators who fill both roles, sometimes not by design:

- "…very involved both with vector development and with the actual conduct of a subsequent clinical trial."
- "…primarily performing the preclinical studies on DMAG [(17-dimethylaminoethylamino-17-demethoxygeldanamycin)] and bortezomib activity in vitro and in vivo animal studies, but we are referring patients to an NCI-sponsored study of DMAG to obtain preliminary evidence for clinical activity, and are following these patients with HNSCC [(head and neck squamous cell carcinoma)]."
- "I worked as both basic scientist driving the translation research and the clinical scientist who was going to oversee the clinical trial. My collaborator whose lab was supposed to provide the necessary clinical support did not meet the expectations of the B2B proposal, and therefore [I] was required to search elsewhere for clinical support."
- " I performed both laboratory research as well as patient care as much as practicable in conducting my protocol."

Importance of B2B Project Support

Over-two thirds of responding project investigators indicated that, in their projects, "collaboration between bench and clinical scientists was enhanced by the B2B project'" and that "it would not have been initiated without B2B funds." Nearly 40 percent reported that the program's "peer review and endorsement" to be helpful.

The unstructured responses were nearly all positive endorsements of the B2B program. While one commented that their project might have been done anyway, and one never received their funds, all of the other comments noted that the B2B provided "essential seed money" to begin their project. The endorsement of peer review was noted, and in one case, the outside endorsement demonstrated "to the Scientific Director [that] the research performed in the laboratory was of some value." The program received credit from several respondents for starting the collaborations for this project and other projects. "The funding mechanism was instrumental in promoting intramural/extramural collaboration." One investigator reported that the application preparation and initiation of research led to intense collaboration, even though the hypothesis of the work turned out to be incorrect.

Was B2B project successful?

Asked to rate the success of their B2B *projects*, 54 percent indicated "highly successful", and another 38 percent "successful" or moderately successful". Only eight percent said "slightly successful" or "not at all successful." Some new project investigators noted that it is still too early for them to judge their own success.

Success of new collaborations

Respondents were equally positive about the success of their new *collaborations*: Fifty-nine percent rated then "highly successful", and 33 percent either "moderately successful or "successful." Eight percent said "slightly successful or "not at all successful."

Were major milestones achieved?

By the time of the request for information, three-quarters of the project investigators said they achieved major milestones. Some elaborated on these, and some gave reasons for delays. Among the milestones reported were identifying clinical biomarkers and demonstrating cytotoxic activity, identifying metabolites that show particular effects in diseased patients, determining one mechanism underlying autoimmunity of a particular syndrome, completing large-scale sequencing, developing treatment strategies and protocols, getting IRB approval for protocols, getting IND required for the clinical trial (noted as a cause of delay), recruiting first patients, enrolling 300th patient (in six months!), starting clinical trials, completing a clinical trial, filing for patents, preparing manuscripts, publishing articles, commercializing a new assay, expanding the project into additional studies and clinical trials.

A few of the earlier projects now boast having had an impact, e.g., demonstrating an effective treatment for precocious puberty, and changing a departmental strategy for donor recruitment.

One project reported the ironic milestone of becoming convinced that their drug resistance approach was not practical or very useful.

One project boasted a new imaging protocol that can be shared across centers, but added that validation of the utility of the protocol will require more funds and a longitudinal study.

Another investigator noted that all work-to-date on missense changes in the clinically important genes [for this study] has been confined to European-American women, but this project is providing data for African-American women on the potential functional impact of missense changes.

An extramural investigator on a new project reported: "Novel animal neuro-imaging procedures and protocols were developed by the laboratory of Dr. Elliot Stein at NIDA IRB. My lab [at the University of Pennsylvania] additionally modified the instrumentation and surgical procedures we use to carry out intravenous cocaine self-administration sessions so that the animals can be placed in the neuro-imaging equipment. We have also developed procedures that are new for our laboratory and that are required to complete the proposed experiments. For example, we have established odorant discrimination in rats. Animals are trained to associate one odor with availability of drug and another with the non-availability of the drug. We developed this procedure because we have proposed to characterize the neuronal response to drug-paired cues in the imaging studies and odors are the only cues that we can feasibly present to animals during the imaging…. We are now running our first set of animals through the proposed research protocols."

Intermediate Accomplishments

While the long-range goal of the B2B program is patient-oriented research for the diagnosis and therapeutic intervention of medical disorders, there are intermediate achievements that may be observed earlier and more objectively. The investigators themselves reported the tangible accomplishments of the B2B projects. Each co-investigator could view and add or amend the information already provided by other project co-investigators. Some of the data were first initially provided in 2004; reviews and/or new information were provided for 67 projects. Altogether, there is some report of accomplishment for only 87 of the 100 projects, so the tallies provided in this section are necessarily undercounts of the total accomplishments of the entire B2B Program to-date.

Appendix B provides an extensive table of accomplishments reported by each investigator team. With the title and year of each project is a list of their ICs or extramural institutions, and degrees held by all named investigators. Below is a brief tally of the investigators' reports.

Protocols

At least 62 active clinical research protocols were initiated under the B2B program. Others were abandoned, and several, especially those awarded within the past two years, are still at various stages of design or are actively seeking approvals.

Invention reports, Investigational New Drugs, patents and licenses

Seventeen projects have filed at least one Employee Invention Report or patent application. At least 3 patents have been awarded. No respondents commented on INDs.

Publications

At least 121 publications in first-line journals have reported progress and findings from the B2B projects. In addition, many posters, abstracts and oral presentations have been made at numerous conferences, workshops, and the NIH Research Festival. Many articles are still in pre-publication review.

NIH press releases have reported on some of the projects, and a 3-page news article about one B2B project on Williams-Beuren Syndrome appeared in *Science*, "Friendly faces and unusual minds", Volume 131: 802-4, 2005, although no mention was made of the NIH Bench-to-Bedside program.

The journals where B2B project papers have been published are listed in Appendix C. The quality of the work being perfoemed is evident from the successful peer-review and publication in many first-line journals. The full references to published articles, titles of articles in preparation, abstracts, posters, workshop preseentations, etc., are included in Appendix B.

Other self-reported accomplishments

The extensive table in Appendix B lists a wide variety of other accomplishments and explanations of individual barriers that some projects had to face. In a few cases, the projects terminated themselves. In others, the barriers are being surmounted.

Summary of reported intermediate accomplishments

Table 5 provides a tally of the intermediate accomplishments reported by B2B investigators.

Table 5. Protocols, patents, and publications of B2B projects, by year of project awards

Year of project award	1999	2000	2001	2002	2003	2004	2005	2006
B2B projects awarded	8	9	9	6	13	19	17	19
Protocols initiated	8	10	9	3	2	16	10	5
Inventions and patents	5	1	4	1	1	1	2	2
Journal publications	19	20	18	10	29	12	8	5

Funding adequacy and utilization

Supplements

Thirty-four percent of the responding investigators said that the B2B funds were sufficient for their projects; 55 percent acknowledged that these funds were supplemented. The remaining 11 percent described how they augmented their resources in ways other than funding, such as hiring an IRTA fellow or redeploying other scientists in the branch. Some received additional support from the Office of Rare Diseases to sponsor a conference or research roundtable. Some were supplemented with animals and reagents bought with the lab's operating budget. Monkeys cost more than the B2B funds could afford. One project used AIDS program money to recruit patients.

One expensive project pooled B2B funds with several extramural grants and, in addition, a CRADA was pursued, but the B2B funds were instrumental in keeping the progress moving forward.

There were apparently some misunderstandings about the terms of B2B support. One investigator was disappointed to learn that it was not for three years, and he was forced to supplement it.

The amount of supplemental funding per project reported is presented in Table 6 for 48 projects whose investigators provided data. (In the few cases where different-sized supplements were reported, the larger value is tabled.)

Table 6. Supplemental funding for B2B projects	
Size of supplement	Number of projects reporting
<$10,000	3
$10,000 - $25,000	8
$25,000 - $50,000	8
$50,000 - $75,000	6
$75,000 - $100,000	7
>$100,000	16

How B2B funds were used

After removing duplicative answers from multiple investigators responding for the same project, the categories of usage of funds (on 57 projects) and tallies are presented in Table 7.

Table 7. Uses of B2B funds	
Category of use	Number of projects reporting
Laboratory equipment	34
Salaries for research assistants	33
Medical diagnostics	17
Salaries for clinical assistants	10
Travel	10
Medications	3

Research equipment and assistants were the major categorical uses of the B2B Program funds. More details were provided and other uses were described in additional comments. Travel, for example, was used for rare patients and, in one project, for essential travel to Nigeria.

Other expenses covered by B2B funds included:

- Animal purchases and housing
- Reagents and other supplies
- Microarray chips
- Peptide synthesis
- Large-scale preparation of pure vectors
- Contract genotyping
- Statisticians
- Post-doctoral fellows and visiting fellows
- Extramural clinical assistance
- Partial salary for a clinical pediatric fellow

B2B Program Process

Clarity of Call for Proposals

There was near unanimity (98 percent) that the Call for Proposals was clear and that the required leadership approvals and signatures were easily obtained (89 percent). (Extramural collaborators reminded us that they were not the recipients of the Call and did not initiate their projects' applications.)

"Each year the 'Call' becomes clearer," commented one investigator, but he/she also felt that in later years it became necessary to understand how the funds needed to be distributed between the CC and ICs, requiring phone calls to ("always knowledgeable and helpful") Program Director Pat Piringer. Some failed to receive the 'Call' long enough in advance. One opined that the scope of the 'Call' is too narrow.

Obtaining signatures

Obtaining signatures was problematic in a few instances where ICs wanted assurance that the funding was coming from another Office and not from the IC. The Office of Rare Diseases received praise for rescuing some of them. It was reported that the Scientific Directors were not consistently supportive, and that the internal review by intramural research directors' offices took too long. Others reported only enthusiastic and positive support for an easy collection of approvals.

Adequacy of funding

Asked straight out, "Was the funding adequate," three-quarters of the project investigators replied "Yes." In their comments, however, several investigators said that what was provided was essential seed money, a catalyst, and they acknowledged that they knew they would have other sources of funding for the rest of the project. One estimated that the B2B program provided about half of what was needed.

One researcher did not understand the need for prospective budgeting of the indirect costs for the extramural component of his project, and, consequently, the extramural site was forced to proceed without this component, asking a lot of them.

A few noted that the first-year funding came late and work was accelerated accordingly. For this reason, another respondent favors extending the B2B grant to three years, which would then be, really, two and a half years. One suggested that a mechanism for expansion and extension would be useful. Said another, "I believe that enhanced funding of this program could encourage more innovative research and enhance collaborative science."

General Comments on the B2B Program

More than half of the investigators contacted used the opportunity to comment on the Bench-to Bedside Program, per se. Most, but not all, were positive testimonials. "The program allows the development of studies that would otherwise be difficult to fund." "Fantastic program." "Very important program [that] gave us the initial funding to generate key proof of concept data and led to follow-up funding from other Government institutions." "This is a great program and should be continued." "It's a wonderful opportunity to development collaborative research that should be highly praised." "Outstanding program that stimulates inter-institutional discussions and collaborations on cutting-edge research projects of high risk." "Fosters collaboration and collegiality." Some linked the objective peer review with a growing prestige of the program.

Some problems and suggestions about the process of the program surfaced. The uneven support of the ICs and the Scientific Directors (SDs) was a common observation, and there was a plea for better support. "Most ICs hate these awards, think they are Clinical Center and investigator 'double dipping' and that these funds should not be given outside the usual IC/Board of Scientific Counselor process. I don't know who is right; I'm glad I got an award, but if I were an SD, I might feel the same way my SD feels about the program." One felt constrained to study rare diseases because support was coming from ORD while no funding was coming from his IC. More ICs should demonstrate their "buy-in." This was a source of "disappointment" and "confusion" to others, as well.

A suggestion that came from several people was for roll-over funding, particular since the first year was somewhat abridged, and it is difficult to "ramp up" to spend the first-year funds.

Two commented that the name of the program is misleading, that it might equally be Bedside-to-Bench or simply Bench-Bedside to promote good translational science. One opined the current name denigrates and impairs the clinical components. Another wants the program expanded to support work that is "pre-clinical (not basic) and clearly translational."

A side-benefit of the proposal and peer-review process, one said, accrued to their trainee who will go elsewhere and can now say he/she wrote and was awarded a grant.

"The Bench-to-Bedside initiative is a very valuable and great program. Many investigators like myself have ideas that emerge from their experiments that they would like to implement in human patients to treat or diagnose diseases. The B2B is a program that allows us to create an infrastructure and assemble a team to make that translational effort possible. It is both constructive and catalytic. The basic-clinical collaboration is also transforming, my group is now much more focused on doing research that is both interesting and useful. Exploring mechanisms is only one level. Taking the knowledge gained and shaping it into a new treatment or diagnostic tool provides an entire new level of engagement and excitement to our biomedical research efforts and will have practical benefit for patient care."

"As a former intramural investigator at the NIH and now an extramural one, my view is that this type of program is very timely and important. NIH definitely has advantages in translational research and there is good science going on outside the campus. Problem is that for many investigators the hurdles to facilitate true translational research are too high on the outside. Thus this program really brings together strengths in ways that will definitely benefit the public. Also … this type of program also serves as a catalyst to getting corporate involvement. The corporate entities can see that the science has been appropriately vetted and that a clear pathway to clinical implementation is on hand through this type of partnership."

Effects of Intramural/Extramural Collaborations

Nineteen B2B projects were awarded in 2006, and all but two of them involved extramural investigators selected by their intramural collaborators. Several additional questions were posed only to investigators on the 2006 projects, and twenty-one investigators (12 intramural and 9 extramural) provided the following information.

New collaborations resulted from B2B

Eighty-nine percent indicated that new collaborations between intramural and extramural investigators were established as a result of their project.

The variety of extramural institutions is shown in the section on "Participation", above. Some were international: "Dr. Aliyu was able to build a research relationship with his counter partners in Nigeria." "We had previously collaborated with investigators at CSF but not at Makerere University [in Uganda]."

Some commented that the relationship was mainly for patient referral. Others commented on "many new ideas [that] have been exchanged and new projects initiated."

Others commented on the science that was enabled through collaboration, interactions of vitamins, imaging, and clinical samples that are now available.

Few fellows exchanged

Only 10 percent answered that fellows were exchanged between intramural and extramural labs.

Visits between NIH and extramural labs

About two-thirds said intramural and extramural investigators visited each other's labs and clinics. Reported visits were monthly, quarterly, semi-annually and annually. Some visits were international.

New sabbaticals not stimulated

Only ten percent reported sabbaticals were either initiated or extended as a result of the B2B project. Some were not aware that it was an option.

No exchanges of patients

There were no reports of NIH patients going to an extramural site and few reports of extramural patients being referred to an NIH intramural research group. However, extramural patient samples were sent to NIH for study, and NIH investigators evaluated cardiac and metabolic performance of the Li Fraumeni patients that were being followed extramurally.

Little stimulation of staff recruitment

Eleven percent reported recruitment resulted from the B2B program. One intramural investigator reportedly left NIH for a higher salary at the extramural site. One post-bac was recruited to work full-time on an NCI B2B project.

Few medical students participated

Only eight percent reported medical student participation. One investigator noted that epidemiology students and NIH post-docs did participate. Another reported a part-time effort from one Clinical Research Training Program student.

Stimulation of new extramural grants

Nearly ninety percent indicated that their projects did or probably would lead to new extramural grant applications. One elaborated: "My [extramural] laboratory plans to write an R01 application in 2008. Data collected in the context of the bench-to-bedside project will be used as the preliminary data for that application. The plan is to use the R01 funds to continue the novel work that Dr. Stein and I have initiated."

Critical nature of intramural/ extramural partnership

Ninety-five percent of responding investigators from the latest cohort (2006 B2B projects) indicated the intramural/extramural partnership was critical to the success of their projects. They offered several reasons:

- "It allows our intramural program to expand a pilot clinical trial from one site to three sites, accelerating the clinical accrual and completion of the trial. The consequent multi-site nature of the trial will enhance the eventual credibility of the trial results."
- "Most of the clinical samples collected so far (over 20 total) have been sent to us from the extramural site."
- "Clinical trial is being carried out in Nigeria. Without the partnership of the Nigerian investigators this would not have been possible."
- "The extramural partnership with St. Christopher's allows Dr. Hsu to work here at the NIH on the animal studies that will help move this project into the clinical arena, where Dr Hsu will be a co-investigator."
- "[This is t]he heart of the whole project: an excellent use of funds."
- "The infrastructure, clinical program, and patient recruitment were entirely dependent on the extramural partnership. However, they did not have the laboratory expertise or resources to undertake the laboratory aspects of this study."

- "The needed population was held by extramural scientists."
- "The project could not be accomplished without the extramural scientific and reagent development, and the NIH Clinical Center will be essential for any subsequent clinical trial."
- "The vitamin E study requires the administration of an intravenous preparation of deuterium-labeled vitamin E. This procedure is not possible to carry out anywhere except at the NIH."
- "The relationship is absolutely critical. There is no one here at Penn that is currently capable of conducting the small-animal imaging components of the experiments. Dr. Stein is also uniquely qualified to contribute intellectually to the project given his various expertise and research interests."

While it would be interesting to make comparisons between the initial, intramural-only B2B projects and the intramural/extramural B2B projects in terms of their intermediate and long-term impacts, such a comparison will have to wait. The intramural/extramural collaborations are all too new to have measurable outcomes.

Views of supporting Office Directors

Five NIH components have provided major support to enhance the B2B program and their own missions. The five are the Office of AIDS Research (OAR), the Office of Rare Diseases (ORD), the National Center on Minority Health and Health Disparities (NCMHD), the Office of Research on Women's Health (ORWH), and the National Center for Research Resources (NCRR). Each has been involved for from two to five years.

The directors of each of these Offices and Center were contacted, and four were interviewed by telephone to ascertain their level of satisfaction with the B2B program and to solicit possible suggestions for change.

There was general satisfaction and some enthusiasm for the opportunity to leverage the use of their funds by sharing costs and interest with the ICs. Of these organizations, only NCRR has the legislative authority or capability to solicit, review, and award extramural grants. But all have strong faith in the effectiveness of the peer review component of the B2B Program.

Through 2007, ORWH has supported two projects, NCMHD supported eight projects, NCRR supported 13, OAR supported 24, and ORD has provided support for 38 projects. They have different levels of need for feedback from the projects they support, but all welcome feedback and the public acknowledgement that they are co-sponsors. Generally a final report would suffice rather than progress reports.

The Office of Rare Diseases lists all of the B2B grants they have made on their website. They are happy when they get brief updates from individual programs, and they frequently supplement the funds to the investigators to host a conference on their project and the specific rare disease it addresses. ORD also advertises B2B application deadlines on the website.

The directors were generally keen on the new intramural-extramural aspect of the B2B program and hope this will continue, especially in support of high-risk studies. Promising outcomes might then be supported as Phase 2 studies by industry.

The current levels of funding serves the program's purposes well, some said. It is akin to an R01 grant to derive preliminary data. The basic scientist – clinician collaboration is a good learning experience. They generally hope the program will grow, perhaps adding some projects that are well focused on specific diseases.

All of the directors interviewed anticipate continuing their participation in the future.

Conclusions

The Bench-to-Bedside program is a continuing success. The record of accomplishments is tangible and growing. That some individual projects have not been successful indicates that risks are being taken. Collaboration between individuals with bench science and clinical skills has been stimulated and has led to new protocols. Collaboration between intramural and extramural investigators stimulated enthusiastic expectations of synergistic accomplishments. Continuing support from sponsoring offices looks promising. The level of funds awarded is not typically found to support the entire project, but does support the seeds of translational ideas and initial growth; supplemental funds and subsequent grant support is frequently sought. An increase in the size of each award, unchanged since 1999, may be worthy of consideration. From the principal investigators, it can be inferred that the support from Scientific Directors of various Institutes and Centers is not uniform and may be an appropriate subject for discussion.

Appendices

Appendix A: Bench to Bedside Program Call for Proposals, August 9, 2006

Appendix B: One hundred projects: investigators, protocols, patents, publications, and other accomplishments

Appendix C: Journals publishing Bench to Bedside reports

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

August 9, 2006

TO: NIH Intramural Investigators

FROM: Deputy Director for Intramural Research
Director, NIH Clinical Center

SUBJECT: FY 2007 Bench-to-Bedside Awards

We are pleased to announce the call for proposals for the FY 2007 bench-to-bedside program. The process is similar to the FY 2006 pilot bench-to-bedside program which incorporated new categories of projects and opportunities for extramural collaborations with intramural investigators. With contributions last year from the Office of AIDS Research (OAR), the Office of Rare Diseases (ORD), the Office of Research on Women's Health (ORWH), the National Center on Minority Health and Health Disparities (NCMHD), and the National Center for Research Resources (NCRR) and matching IC funds on several projects, over $4M was awarded to intramural and extramural PIs.

Based upon this success, we have secured ~$3M to support these awards from our same contributors as last year and ICs will match funds in 3 categories. We encourage intramural investigators to identify extramural researchers as partners. Thus, if the clinical investigator is from the intramural program, the basic science investigator could be from extramural NIH (or vice versa). The extramural partner must have a current NIH grant related closely to the general subject of the bench-to-bedside proposal. Projects with intramural and extramural partners will receive priority. For FY 2007, proposals once again may be submitted within the following five categories.

(1) Rare Diseases: The ORD will co-fund with institutes up to nine projects for two years. These projects must focus on an area of science/research directly related to a rare disease. An orphan or rare disease is generally considered to have a prevalence of less than 200,000 affected individuals in the United States. Certain diseases with more than 200,000 affected individuals are included but subpopulations of these conditions may be less than the prevalence standard for a rare disease. A comprehensive list of rare diseases, updated regularly, is available at http://ord.aspensys.com/asp/diseases/diseases.asp.

(2) AIDS: The OAR will fund five exemplary AIDS-related projects for two years.

(3) Minority Health & Health Disparities: The NCMHD will co-fund with institutes up to five projects that improve outreach, recruitment, and retention of minorities, women, and persons with disabilities. These projects must focus on an area of science/research that promotes minority health and supports the NIH effort to reduce and ultimately eliminate health disparities.

(4) Women's Health: The ORWH will provide funds to support one project for two years that focuses on efforts to improve the health of women through biomedical and behavioral research on the roles of sex and gender in health and disease.

(5) General: As in the past, additional meritorious projects will be awarded in the 'general' category to be funded by the sponsoring institutes. Extramural funds for the general category will be provided by the NCRR.

To summarize, up to 22 projects will receive a maximum of $100,000/year. Support will be for two years. Investigators in all institutes/centers are eligible. Investigators must adhere to the deadlines and follow the instructions listed in Attachment 1. The timeline assures that Scientific and Clinical Directors have sufficient opportunity to review proposals. Information about the FY 2007 bench-to-bedside initiative is available electronically at http://www.cc.nih.gov/ccc/btb/awards.shtml.

A review group appointed by the Deputy Director for Intramural Research and the Director, Clinical Center will review and rank the proposals. The review group will include both intramural and extramural basic and clinical scientists representing multiple institutes and centers and will include expertise in rare diseases, AIDS, women's health and minority research. Criteria used by the review group are described in Attachment 1. Please note that preference will be given to those applications that address these criteria.

Principal investigators for each project must submit original proposals to the Scientific Directors and Clinical Directors of **all** institutes involved in the project by **October 23, 2006**. For each proposal submitted, an original copy of the budget sheet (Attachment 2) **must** be signed by Scientific and Clinical Directors. The appropriate category for each proposal should be clearly distinguished. On the budget sheet, extramural partners must identify an NIH grant which will need to be active during the period of this project and directly related to the subject matter of the proposal.

Proposals **with required signatures** are due in Dr. Gallin's office (CRC 6-2551) by **Monday, November 13, 2006**. Please note that it is the responsibility of the principal investigators to verify that all Scientific and Clinical Directors involved in each project receive proposals in a timely manner for review and that signed originals of each proposal are delivered to CRC 6-2551 by the November 13th deadline. Principal investigators for projects selected will be notified in mid-December 2006.

For projects selected for awards, extramural funds will be directed as an administrative supplement to the grant and, if indicated, the amounts of funds to extramural investigators may be increased to cover indirect costs. Direct costs at participating institutions cannot exceed $50,000/year. All funds for extramural partners will come from the contributors described above.

Principal investigators for all awarded projects will be required to submit annual progress reports on the project's status.

Please feel free to contact us if you have any questions about the bench-to-bedside program.

Michael M. Gottesman, M.D.

John I. Gallin, M.D.

Attachments

cc: Institute Directors
Scientific Directors
Clinical Directors
Jack Whitescarver, Ph.D., Director Office of AIDS Research
Stephen C. Groft, Pharm.D, Director Office of Rare Diseases
Vivian W. Pinn, M.D., Director Office of Research on Women's Health
John Ruffin, Ph.D., Director, National Center on Minority Health and Health Disparities
Barbara Alving, M.D., Acting Director, National Center for Research Resources
Norka Ruiz Bravo, Ph.D., Deputy Director for Extramural Research

Attachment 1

DEADLINES FOR SUBMISSION/TIMELINE

Monday, October 23, 2006	Proposals due to Scientific/Clinical Directors for signature
Monday, Nov. 13, 2006	Proposals **MUST** be received in Dr. Gallin's office (CRC 6-2551) **with all necessary signatures**
Week of Nov. 20, 2006	Selection of proposals by review team
Week of Dec. 15, 2006	Principal Investigator(s) notified of decision

INSTRUCTIONS FOR FY 2007 BENCH-TO-BEDSIDE PROPOSALS

Each proposal should:

- include an abstract of the project
- identify one principal clinical or translational investigator and one principal basic scientist
- demonstrate evidence that the proposal was particularly stimulated by the availability of this special funding mechanism
- include budget details per Attachment 2
- not exceed five pages in length. Note that proposals >5 pages will not be considered; this limit does not include abstract or references)
- satisfy the following criteria:
  - inter-institute collaborations are preferred (i.e., proposals should involve investigators from more than one IC)
  - collaborations between intramural and extramural investigators will receive priority review
  - quality of science should be high
  - promise to evolve into an active clinical protocol should be clearly articulated
  - the plan for use of patients (not just tissue specimens) in the bedside component should be defined
  - the potential to result in understanding an important disease process or lead to new therapeutic intervention should be explained
  - proposals should have bench and bedside components clearly related in a translational sense – the components should complement each other – one should lead logically to the next, and both components should be strongly developed
  - the work should be a truly new initiative, not a funding request for a 'work in progress'

Attachment 2

PROPOSED BUDGET FOR BENCH-TO-BEDSIDE AWARDS

PROJECT TITLE: _____

_____

EXTRAMURAL GRANT # (if applicable): _____

PROJECT CATEGORY:	Funding Source	Check category(ies)
Rare Diseases	(50% ORD; 50% ICs)	
AIDS	(100% OAR)	
Women's Health	(100% ORWH)	
Minority Health & Health Disparities	(50% NCMHD; 50% ICs)	
General	(ICs; NCRR Extramural)	

Include **full name(s)/ credentials/ address/ phone** *(attach 2nd page if necessary)*

	Intramural	Extramural
Principal Investigator(s)	**(1)** **(2)**	**(1)** **(2)**
Associate Investigator(s)	**(1)** **(2)** **(3)**	**(1)** **(2)** **(3)**

All costs, intramural and extramural, should be projected for each institute/institution to receive funds. Extramural PIs can receive no direct costs >$50K/year. Estimates of indirect costs for extramural sites should be included.

Costs	Intramural				Extramural			
	IC:_____ Year 1	Year 2	IC:_____ Year 1	Year 2	Institution:_____ Year 1	Year 2	Institution:_____ Year 1	Year 2
Personnel								
Supplies								
Contract Costs								
Equipment								
Indirect Costs *(extramural only)*								
TOTAL COSTS								

SIGNATURES

Signature of SD and CD are required for every project requesting intramural funds. IC funds will cover all/partial intramural costs for projects in the general, rare diseases, and minority health categories.

_____ _____ _____ _____

Scientific Director, _____ Date Clinical Director, _____ Date
IC IC

_____ _____ _____ _____

Scientific Director, _____ Date Clinical Director, _____ Date
IC IC

_____ _____ _____ _____

Scientific Director, _____ Date Clinical Director, _____ Date
IC IC

Appendix B: Publications associated with Bench to Bedside projects

Appendix B: One hundred B2B projects: investigators, protocols, patents, publications

B2B#1	**"Pretargeted Therapy of Epithelial Cancers with Radiolabeled Monoclonal Antibody B3"**
1999	

Investigators

Pastan, Ira	MD	NCI
Carrasquillo, Jorge	MD	CC

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Synthesized 10 different peptides…unfortunately none formed stable hemodimers.

Decided to terminate project" (12/2001**) Project Completed 2001**

B2B#2	"Gene Therapy for X-Linked Severe Combined Immunodeficiency"
1999	

Investigators

Puck, Jennifer	MD	NHGRI
Malech, Harry	MD	NIAID

Protocols

02-I-0057 "Ex vivo retroviral transfer for treatment of X-linked severe combined immunodeficiency" ONGOING 02-I-0057.

Patents and Licenses

Clinical grade vector supernatant has been prepared and tested using funds from this award.

Publications

Avilés Mendoza GJ, Seidel NE, Otsu M, Anderson SM, Simon-Stoos K, Herrera A, Hoogstraten-Miller S, Malech HL, Candotti F, Puck JM, Bodine DM. Comparison of five retrovirus vectors containing the human IL-2 receptor gamma chain gene for their ability to restore T and B lymphocytes in the X-linked severe combined immunodeficiency mouse model. Molecular Therapy 3:565-573, 2001.

Tsai EJ, Malech HL, Kirby MR, Hsu AP, Seidel NE, Porada CD, Zanjani ED, Bodine DM, Puck JM: Retroviral transduction of IL2RG into CD34(+) cells from X-linked severe combined immunodeficiency patients permits human T- and B-cell development in sheep chimeras. Blood 100:72-79, 2002.

Hay B, Davis J, Hsu A, Tsai E, Malech H, Puck J. Evaluation of post-bone marrow transplant patients with XSCID in preparation for gene therapy. NHGRI Retreat abstract selected for oral presentation, Oct., 2001. (ms in preparation for a peer-reviewed journal)

Malech HL. Use of serum-free medium with fibronectin fragment enhanced transduction in a system of gas permeable plastic containers to achieve high levels of retrovirus transduction at clinical scale. Stem Cells 18:155-156, 2000

Chinen, J, Puck, J., Davis, J., Linton, GF, Whiting-Theobald, N, Woltz, PC, Buckley, RH, Malech HL: Ex vivo gene therapy of a preadolescent with X-linked severe combine immunodeficiency, Blood 104:120a, 2004

Puck JM, Malech HL. Gene therapy for immune disorders: good news tempered by bad news. J Allergy Clin Immunol. 2006 117:865-9.

Ting-De Ravin SS, Kennedy DR, Naumann N, Kennedy JS, Choi U, Hartnett BJ, Linton GF, Whiting-Theobald NL, Moore PF, Vernau W, Malech HL, Felsburg PJ. Correction of canine X-linked severe combined immunodeficiency by in vivo retroviral gene therapy.
Blood. 2006 107:3091-7.

Chinen J, Davis J, De Ravin SS, Hay BN, Hsu AP, Linton GF, Naumann N, Nomicos EY, Silvin C, Ulrick J, Whiting-Theobald NL, Malech HL, Puck JM. Gene therapy improves immune function in pre-adolescents with X-linked severe combined immunodeficiency. Blood. 2007 Mar 19; [Epub ahead of print]

Other Accomplishments or Comments

NIH CC heavily utilized – 7 XSCID pts here on multiple occasions for evaluation of immune status and to determine eligibility criteria for trial; also, 21 family members here for genetic counseling and mutation testing for XSCID. CC use to increase as trial gets underway

Major source of difficulty and delay in initiating XSCID gene therapy clinical trial is large amount of required regulatory paperwork and documentation

This project directly resulted in the initiation of a clinical gene therapy protocol that is ongoing and treating patients with X-linked severe combined immune deficiency with gene therapy. This protocol is ongoing and two patients have been successfully treated under this protocol and resulted in the preliminary abstract report above.

Project completed 2006

B2B#3	"Vasculogenesis Using Progenitor Cells"
1999	

Investigators

Quyyumi, A. A.	MD	NHLBI
Finkel, Toren	MD, PhD	NHLBI

Protocols

01-H-0119, "Endothelial Progenitor Cells and Risk Factors for Coronary Artery Disease"

Patents and Licenses

No data available

Publications

Endothelial Progenitor Cells as Putative Targets for Angiostatin"; H. Ito, I.I. Rovira, M.L. Bloom, K. Takeda, V.J. Ferrans, A.A. Quyyumi, T. Finkel. Cancer Research 59, 5875-5877, 12/1/99

Hill, J., Zalos, G., et al. "Circulating Endothelial Progenitor Cells as Novel Biological Determinants of Vascular Function and Risk," NEJM; 348: 593-600; 2003**In this NEJM article, the authors write in the concluding acknowledgments "This work was funded by the NIH Bench to Bedside Award Program"

Other Accomplishments or Comments

With some funds able to hire British cardiologist, Dr. Jonathan Hill

Research selected as finalist in Young Investigator Award at the AHA

Project completed 2003

B2B#4	**"Evaluation of Therapeutic Reduction of Raised Elastase Levels by Reducing Neutrophil Numbers or by Direct Anti-Elastase Treatment on the Acceleration of the Rate of Healing"**
1999	

Investigators

Wahl, Sharon	PhD	NIDCR
Wysocki, A.	PhD	NINR
Ashcroft, Gillian Sarah	MD, PhD	NIDCR
Dionne , Raymond	DDS, PhD	NIDCR

Protocols

00-D-0116 "Effects of topical antinflammatory Agents on Cutaneous Wound Healing"

Patents and Licenses

No data available

Publications

Ashcroft, G.S., Lei, K.J., Jin, W.W., Longnecker, G., Kulkarni, A.B., Greenwell-Wild, T., Hale-Donze, H., McGrady, G., Song, X.Y. and Wahl, S.M., 2000. Secretory Leukocyte Protease Inhibitor (SLPI) mediates non-redundant functions necessary for normal wound healing. Nature Med. 6:1147.

Other Accomplishments or Comments

Developed an ultrasound technique in collaboration with Dr. B. Sonies to facilitate quantitation of the healing process in such clinical trials. As reagents for these trials are approved, acquired and formulated for human use, it is anticipated that trials will commence.

Project Completed 2004

B2B#5	"Gene Therapy for Chronic Cancer and Arthritic Pain"
1999	

Investigators

Iadarola, Michael	PhD	NIDCR
Dionne, Raymond	DDS, PhD	NIDCR
Klippel, J.	MD	NIAMS

Protocols

No human protocols were generated as a result of this project. Essentially, the project was about 20 years ahead of its time in terms of the approach and the state-of-the-art for in vivo viral gene transfer methodology and viral vector development. We have not abandoned it entirely, however, further pursuit of this approach was superceded by the second BtoB project for pain control that was more tractable, practical and has generated a human clinical protocol.

Patents and Licenses

Iadarola MJ, Caudle RM, Finegold AA and Mannes AJ: Methods for treating Chronic Pain. U.S. Patent # 6,596 269. This patent concerns our gene therapy \"paracrine paradigm\" for pain control.

Publications

Finegold AA, Mannes AJ and Iadarola MJ: A paracrine paradigm for in vivo gene therapy in the central nervous system: treatment of chronic pain. Human Gene Therapy 10:1251-1257, 1999.

Zheng C, Iadarola MJ, Baum BJ and O\'Connell BC: Genomic integration and long term expression by a modified adenoviral vector. Nature Biotechnology 18:176-180, 2000.

Finegold AA, Perez F and Iadarola MJ: Antisense knock-down of NMDA receptors by gene transfer to motor neurons in vivo. Molec Brain Res 90:17-25, 2001.

Other Accomplishments or Comments

This BtoB was a pioneering effort in the use of in vivo gene transfer for the control of chronic pain problems. The BtoB funds allowed us to generate proof of concept studies. We developed a new approach to that we called the paracrine paradigm in which we trnsduced cells of the pia mater (a non-neuronal meningeal cells that line the surface of the spinal cord) and engineered them to secrete active beta-endophin (an opioid neuropeptide). This system worked and produced beta-endorpin and functionally measurable analgesia. The paracrine paradigm has since been emulated by other laboratories and with other viral vectors all with the idea of controling chronic pain.

We also targeted neuronal gene expression by transfer of an antisense cassette to motorneurons. We targeted the N-methyl-d-aspartate receptor which binds the excitatory amino acid transmitter glutamate by expression of a short (60 bp) antisense cassette to the translation start site. In vivo injection of the virus supressed receptor expression in the transduced motor neurons. It may be possible to use such an approach to treat degenerative motoneuron diseases like ALS or spinal muscular atrophy.

One of the problems we encountered in the course of these experiments was difficutly in making the expression of the therapeutic gene last longer and express stronger. We tried many of the tricks that were current, but could not improve substantially over our original vector. At the time, we would have been the first to perform a clinical trial of in vivo gene therapy for pain control and, therefore, definitely wanted a vector system that was gauranteed to be safe and higly effective and long lasting. This goal still has not been achieved but new technologies are now available that can be evaluated.

Another problem occurred that was completely out of our control, but did impact on our drive to clinical trial, which was the death of a patient at University of Pennsylvania in an adenoviral gene therapy trial. This tragic event had the effect of halting our progress with adenovirus and forced a switch to other vectors (lentivirus and AAV). We evaluated both but at the time, they were either very new and unproven or very inefficient and slow to express. Our goal was to treat pain not to turn the lab into a vector evaluation facility, and, at this point, we began a new round of experiments using a bioengineered protein therapeutic agent and a small molecules. These approaches resulted in the second BtoB.

Project completed 2001

B2B#6	"Development of Novel Therapies for Sickle Cell Disease"
1999	

Investigators

Schechter, Alan	MD	NIDDK
Keefer, Larry	PhD	NCI
Ognibene, Frederick	MD	CC
Woude, G. Vande	PhD	NCI
Masur, Henry	MD	CC

Protocols

00-H-0031 Vascular Effects of Endothelium-Derived vs Hemoglobin-Transported Nitric Oxide in Healthy Subjects

01-DK-0088 Determining the Prevalence and Prognosis of Secondary Pulmonary Hypertension in Adult Patients with Sickle Cell Anemia

01-H-0140 Nitric Oxide Inhalation Therapy for Myocardial Ischemia in Patients with Coronary Artery Disease

Patents and Licenses

Nitric oxide inhalation for dilating blood vessels: Invention report filed

Publications

Gladwin, M., Schechter, AN, Shelhamer, JH, Ognibene, F. The acute chest syndrome in sickle cell disease: Role of nitric oxide in its pathophysiology and treatment. Am. J. Resp. Crit. Care Med. 159: 1368-1376, 1999.

In addition to these listed, 50 to 100 publications from 1999 to the present resulting from this project

Noguchi, C.T., Gladwin, M., Diwan, B., Merciris, P., Smith, R., Yu. X., Buzard, G., Fitzhugh, A., Keefer, L.K., Schechter, A.N., Mohandas, N. Pathophysiology of a sickle cell trait mouse model: human alpha(beta)(S) transgenes with one mouse beta-globin allele. Blood Cells Mol. Dis. 27:971-7, 2001.

Diwan, B.A., Gladwin, M.T., Noguchi, C.T., Ward, J.M., Fitzhugh, A.L., Buzard, G.S. Renal pathology in hemizygous sickle cell mice. Toxicol. Pathol. 30:254-252, 2002

Other Accomplishments or Comments

Note: All papers from late 99 re: this project and studies using the mouse model for sickle cell disease to 2002 are considered to have been catalyzed by B2B program

Project completed.

B2B#7	"Production of Clinical Grade ITX to Perform Clinical Trials for Treatment of Muscle Spasm Disorders (e.g., Torticollis and Blepharospasm) at NIH"
1999	

Investigators

Youle, Richard	PhD	NINDS
Hallett, Mark	MD	NINDS

Protocols

No data available

Patents and Licenses

US 6,780,413 B2 (August 24, 2004) Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders. Inventors: J. Hott, R. Youle, M. Hallett and M. Dalakas

Publications

(1) Hott, JS, Dalakas, MC, Sung, C, Hallett, M and Youle RJ: A skeletal muscle-specific immunotoxin for the treatment of focal muscle spasm. Neurology 50: 485-491, 1998.

(2) Christiansen , SP, Sandnas, A, Prill, R and Youle, RJ and McLoon, LK. Acute Effects of the Skeletal Muscle-Specific Immunotoxin, Ricin-Mab 35, on Extraocular Muscles of Rabbits. Investigative Opthamology 41: 3402-3409, 2000.

(3) Christiansen, SP, Peterson, D., To, T., Youle, RJ, and McLoon, LK. Long-Term Effects of Ricin-mAb 35 on Extraocular Muscles of Rabbits: Potential Treatment for Strabismus. Investigative Opthamology and Visual Science, 2002 Mar;43(3):679-85.

Other Accomplishments or Comments

Unable to produce ITX on contract due to costs, so produced ITX for shipment to Allergan and if found suitably active, Allergan may be prepared to prepare clinical grade ITX for NIH clinical trials.

Re: research: continued animal investigations of ITX for treatment of muscle spasm disorders…in past year, found long-term effects of ITX in a rabbit model of strabismus lasting up to 3 months – this offers significant encouragement of utility of this approach.

The project really never went anywhere. We were hoping to find a company to produce the drug for human use and do the toxicology. This has proven impossible. No money was ever used.

Project completed 2000.

B2B#8	**"Study of the Effect of the Humanized Monoclonal Antibody Against the Interleukin-2 Receptor alpha Subunit (IL-Ra; ZenapaxR) on Inflammatory Activity in the Central Nervous System in MS in a Baseline-to-Treatment, Cross-Over, MRI-Controlled Single-Center Phase I/II Trial"**
1999	

Investigators

Martin, Roland	MD	NINDS
McFarland, Henry	MD	NINDS
Waldmann, Thomas	MD	NCI

Protocols

99-N-0169 "Effect of the Humanized Monoclonal Antibody Against the Interleukin-2 Receptor alpha Subunit (IL-Ra; ZenapaxR) on Inflammatory Activity in the Central Nervous System in MS in a Baseline-to-Treatment, Cross-Over, MRI-Controlled Single-Center Phase I/II Trial"

01-N-0089 "Safety, tolerability and effects of Rolipram on inflammatory activity in the CNS in MS. A phase II, open label crossover trial using MRI as an outcome measure

Patents and Licenses

Employee invention report filed; asked Office of Tech Transfer whether use of Zenapax alone or in combo w/interferon in interferon-failing patients can be licensed by NIH

Publications

No data available

Other Accomplishments or Comments

Demanding regulatory issues, though protocol progressing well. (12/2001)

The use of phosphodiesterase type IV inhibitor in MS is an exciting endeavor, made possible through bench-to-bedside mechanism.

B2B#9	**"Phase 1 Study of 5-aza-2'dexycytidine in lung cancer: Tumor response and analysis of altered gene expression and chromatin structure following DNA demethylation in vivo"**
2000	

Investigators

Kaye, Frederic	MD	NCI
Schrump, David	MD	NCI
Wolffe, A.P.	PhD	NICHD

Protocols

99-C-0129, "Phase I Study of Decitabine Mediated Induction of Tumor Antigen and Tumor Suppression Gene Expression in Patients with Unresectable Lung or Esophageal Cancer or Malignant Pleural Mesothelioma"

Patents and Licenses

No data available

Publications

Presented at recent CTEP-sponsored State of the Science meeting on non-small cell lung cancer (5/2000)

Other Accomplishments or Comments

Goals for project include testing the feasibility of obtaining in vivo biopsy samples for biological assays in patients with advanced lung cancer. This will be an important platform for future studies in lung cancer with biological endpoints.

B2B#10	**"Treatment of neuronal ceroid lipofuscinosis patients with phospho-cysteamine"**
2000	

Investigators

Mukherjee, Anil	MD, PhD	NICHD
Caruso, Rafael	MD	NEI
Levin, Sondra	MD	NICHD
Zhang, Zhongjian	MD, PhD	NICHD
DeB. Butler, Jean	PhD	NICHD

Protocols

"Pilot Study of Cystagon (Cysteamine bitartrate) as a Potential Therapy for Infantile Neuronal Ceroid Lipofuscinosis" - clinical protocol approved

Patents and Licenses

No data available

Publications

(1) Zhang, Z., Butler, J. DeB., Levin, S.W., Wisniewski, K.E., Brooks, S.S. and Mukherjee, A.B. (2001) Nature Medicine 7: 478-484.

(2) Caruso, R.C., Quezado, Z., Levin, S.W., Fischbeck, K.H., Gropman, A.L., Hofmann, S., Patronas, N., Wisniewski, K., Zhang, Z. and Mukherjee, A.B. (2004)

(3) "Serial Electrophysiological Measurements of Visual Function in Infantile Neuronal Lipofuscinosis." Invest. Ophthalmol. Vis. Sci. 45: E-Abstract 5141

Other Accomplishments or Comments

Completed lab experiments in order to establish which of several compounds with nucleophilic properties would be most suitable for clinical application.

These studies will continue until 20 patients are admitted and studied. So far, we have admitted 8 patients to this protocol and continue to recruit more patients until 20 patients are treated. A n interim report describing our experience at this juncture is being prepared for publication.

B2B#11	"Tumor Specific Replicating Vaccinia Virus Expressing Cytosine Deaminase for Therapy of Metastatic Colorectal Cancer"
2000	

Investigators

Bartlett, David L.	MD	NCI
Moss, Bernard	MD, PhD	NIAID
Alexander, H. Richard	MD	NCI
Libutti, Steven	MD	NCI
Chang, Charles	MD	CC
Chen, Clara Chi	MD	CC

Protocols

Phase 1 trial of intratumoral injections of vaccine expressing GmCSF has been written

Patents and Licenses

Through a contract with Novavax, producing 2 vectors in clinical grade for a clinical trial

Patent application submitted

Publications

Cancer Research 61, 8751-8757; Dec. 15, 2001

Human Gene Therapy 17, 31-45; Jan 2006

Cancer Research 65, 9991-999; Nov. 2005.

Human Gene Therapy 16, 435-444; April 2005

Cancer Gene Therapy 9, 1001-1012; Dec. 2002.

Other Accomplishments or Comments

Plan in next year to push ahead w/clinical trials using each of vectors produced in clinical grade (2002 update)

B2B#12	**"Anti-Tumor Immunotherapy: Linking the mouse to the human experience through the Danger Model"**
2000	

Investigators

Matzinger, Polly	PhD	NIAID
Marincola, Francesco	MD	CC

Protocols

NCI-00-C-0182 "Immunization of patients with metastatic cancer using the MAGE-12 epitope associated with HLA-Cw*0702" Protocol completed

"Randomized Comparison of Peptide Immunization in Patients at High Risk for Recurrence of Nasopharyngeal (in process) . Unfortunately, this protocol was not completed due to lack of sufficient funding to hire a research nurse co-ordinator. The protocol was terminated without any accrual of patients

Patents and Licenses

No data available

Publications

1)Perez-Diez A, Spiess PJ, Restifo NP, Matzinger P and Marincola FM. Intensity of the vaccine-elicited immune response determines tumor clearance. J Immunol 168: 338-347, 2002

2)Monsurro, V, Nielsen M-B, Perez-Diez A, Dudley ME, Wang E, Rosenberg SA and Marincola FM. Kinetics of T cell receptor utilization in response to repeater epitope-specific immunization. J Immunol 166: 5817-5825, 2001.

3)Bettinotti Maria P., Panelli Monica C, Ruppe E, Mocellin S, Phan G, White DE, Rosenberg SA and Marincola FM. Clinical and immunological evaluation of patients with metastatic melanoma undergoing immunization with the HLA-Cw*0702 associated epitope MAGE-12:170-178. Int J Cancer, 105: 210-216, 2003.

Other Accomplishments or Comments

Study performed in animals showed intensity of immune responses to immunization is dependent on # of immunizations and type of immunogen. Results showed that intensity of immune response is directly proportional to its anti-tumor effects.. In humans, frequency of vaccine-specific T cells was in direct correlation with the # of vaccinations received by pt and at least 12-16 immunizations were necessary. subsequent to a seminar in Spain, in which Dr. Matzinger reported the results of the study, Bendandi and his group decided to try the protocol in a study of human lymphoma treatment. They found that it was successful and published a report in the JNCI vol 98:pg 1292 \"Clinical Benefit Associated with Vaccination in Patients with Follicular Lymphoma"

Project completed 2006.

B2B#13	**"Effect of the aromatase inhibitor letrozole on estrogen levels and fibrous dysplasia of bone in patients with the McCune-Albright syndrome"**
2000	

Investigators

Feuillan, Penelope	MD	NHGRI
Robey, Pamela	PhD	NIDCR

Protocols

00-D-0183 "Effects of Aromatase Inhibitor Letrozole on Pubertal Progression and Indices of Bone Turnover in Girls with Precocious Puberty and McCune-Albright Syndrome (MAS)

Letrozole has been effective in slowing puberty in MAS girls. Patients continue to be seen, but for the most part, just as follow-up. Two new subjects enrolled in 2006-7 year.

Patents and Licenses

No data available

Publications

Abstract submitted to society of Pediatric Research in 2003 (unable to attend meeting)

Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome; a pilot study, J. Clin. Endo. Metab., in press

Other Accomplishments or Comments

Patient accrual to continue. Current total accrual is 19 subjects; 5 are receiving treatment

B2B#14	"Genotypic & Phenotypic Dissection of the Smith-Magenis syndrome: An Interdisciplinary Study of Physical, Cognitive and Neurobehavioral abnormalities in SMS"
2000	

Investigators

Smith, Ann C.	DSc (Hon)	NHGRI
Friedman, Thomas	PhD	NIDCD
Blancato, J.	PhD	Georgetown University
Gropman, Andrea	MD	NHGRI
Wolters, Pamela	PhD	NCI

Protocols

01-HG-0109 "Natural History Study of the Clinical and Molecular Manifestations of Smith-Magenis Syndrome (SMS)"

reviewed by NHGRI IRB for continuing renewal (year6) and approved Feb, 2007. Total enrollment since inception of the protocol in 2001 is 346 subjects (120 confirmed/suspected SMS; 156 parents;42 unaffected siblings). This is a longitudinal study, so follow-up is ongoing.

NHGRI IRB approved 2/2007 (new protocol): A Phase 1 Treatment of the Circadian Sleep Disturbance in Smith-Magenis Syndrome. (Protocol Services HOLD, pending IND filing)

Patents and Licenses

No data available

Publications

Smith, ACM, Gropman, AL, et al. (2002) "Hypercholesterolemia in Children with Smith-Magenis Syndrome (SMS): (17) (p.11.2)." Genetics in Medicine, 4 (30).

Smith ACM, Leonard AK, Gropman A & D. Krasnewich (2004): Growth Assessment of Smith-Magenis Syndrome. Poster 700, Amer. Soc. Hum. Genet, Toronto, Oct. 2004.

Hammond P, Hutton T, Allanson J, Buxton B, Campbell L, Karmilof-Smith A, Murphy K, Patton M, Pober B, Smith A and M Tassabehji (2004): 3D dense surface models identify the most discriminated facial features in dysmorphic syndromes. Poster 775, Amer. Soc. Hum. Genet, Toronto, Oct. 2004.

Brewer C, Zalewski C, Solomon B, and ACM Smith: Audiologic Phenotype in persons with SMS. Presented at American Academy of Audio logy, April, 2004.

Hildenbrand H, Furst G, and ACM Smith (2004) Sensory Processing Issues in SMS. Presented at Occupational Therapy Association meetings, Alaska, May, 2004 (manuscript in progress).

Hildenbrand H, Furst G, and ACM Smith (2004) Patterns of Sensory Processing in Children with Smith-Magenis syndrome (SMS). NIH Research Festival, 2004.

Smith ACM & Duncan W. Chapter 13: Smith-Magenis Syndrome - A Developmental Disorder with Circadian Dysfunction. in Genetics of Developmental Disabilities. MG Butler and FJ Meaney (Eds), Taylor and Francis, New York, NY, 2005.

Smith ACM and A Gropman. "Smith-Magenis Syndrome" in Management of Genetic Syndromes, 2nd Edition, Cassidy and Allanson (Eds), Wiley-Liss, New York, 2004.

Vlangos, CN, Blancato J, Wilson, M, Smith ACM, Elsea S. (2005): Diagnostic FISH probes for del(17)(p11.2p11.2) associated with Smith-Magenis syndrome should contain the RAI1 gene. Amer J Med Genet 132A: 278-282.

Introne W, Jurinka A, Krasnewich D, Candotti F, Smith ACM (2005): Immunologic Abnormalities in Smith-Magenis syndrome (del 17p11.2). Poster 605, presented American Society of Human Genetics, Salt Lake City, UT, Oct. 2005.

Smith ACM, Allanson JE, Elsea SH, Finucane BM, Haas-Givler B, Gropman A, Johnson KP, Lupski JP, Magenis E, Potocki L, Solomon B: Smith-Magenis syndrome (Updated August,11, 2006) in GeneReviews, at GeneTests-GeneClinics, Medical Genetics Information Resource, [database online] Copyright, University of Washington, Seattle. Available at http://www.geneclinics.org

Gropman AL, Duncan WC, Smith AC. (2006): Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2). Pediatr Neurol. 2006 May;34(5):337-50. PMID: 16647992 (TOP 10 papers downloaded on the web in 2006.)

Martin SC, Wolters PL, Smith AC. Adaptive and Maladaptive Behavior in Children with Smith-Magenis Syndrome. J Autism Dev Disord. 2006 Mar 29; [Epub ahead of print] PMID: 16570214

Smith AC, Magenis RE, Elsea SH. Overview of Smith-Magenis syndrome. J Assoc Genet Technol. 2005;31(4):163-7. PMID: 16354942 [PubMed]

Tomona N, Smith AC, Guadagnini JP, Hart TC. (2006) Craniofacial and dental phenotype of Smith-Magenis syndrome. Am J Med Genet A. 2006 Sep 25; [Epub ahead of print]

Morse RS1, Bernert RA1, Introne W1, Smith ACM (2006): Family Functioning & Coping in Smith-Magenis Syndrome (SMS): (poster), Amer Soc Hum Genetics (New Orleans Oct, 2006)

Smith ACM, Pletcher BA, Spilka J, Blancato J, Meck J (2006): First Report of Two Siblings with SMS due to Maternal Mosaicism. ACM Smith1,2, BA Pletcher3, J Spilka2, J Blancato2, J. Meck2 (poster). Amer Soc Hum Genetics, New Orleans, Oct, 2006.

Edwards H, Gottlieb, E, Ciccone, C, Parkes J, Huizing M, and Smith ACM (2006): Genetic Analysis of 17p11.2 deletion in patients with Smith-Magenis syndrome (poster), NHGRI Scientific Retreat, Gettysburg, PA.

Gropman AL, Elsea S, Duncan WC and Smith ACM. New Developments in Smith-Magenis Syndrome (SMS) (del 17p11.2)- Invited Review, Current Problems in Neurology, Submitted & accepted for publication, 2007.

Bentley, J. E., Morse, R., Zalewski, C., Smith, A.C.M, Brewer, C. B: Hyperacusis in Patients with Smith Magenis Syndrome. American Academy of Audiology (April 2007); accepted for presentation.

Elsea SH, Truong H, Blanchard CL, Pletcher BA, Spilka J, Meck JM Blancato JK and Smith ACM (2007): Deletion and duplication syndromes due to parental Mosaicism: Implications for genetic counseling in genomic disorders. (Poster) Amer College Med Genetics, Nashville, TN, April 15, 2007.

NIH SMS Research Team: What is New in SMS Research? (Flyer distributed in Australia at Camp Breakaway (July 2006) and to families seen at NIH.

Solomon B, LH Gerber and Smith ACM (2005): A research update of the oral motor, swallowing, speech and voice functions in Smith-Magenis syndrome children. Poster at International Speech/Language meeting in Brazil. April, 2005

Solomon B and Smith ACM (2005): Smith-Magenis syndrome: Speech Language Issues in the Early Childhood Years. American Speech and Hearing Association conference, Nov., 2005

Hammond P, Hutton TJ, Allanson JE, Buxton B, Campbell LE, Clayton-Smith J, Donnai D, Karmiloff-Smith A, Metcalfe K, Murphy KC, PattonM , Pober B, Prescott K, Scambler P, Shaw A, Smith ACM, Stevens AF ,Temple IK ,Hennekam R, and Tassabehji M. (2005) Discriminating Three-Dimensional Facial Morphology. Am J Hum Genet 77:999-1010.

Edelman EA, Girirajan S, Finucane B2, Pragna Patel P, James R. Lupski JR, Smith ACM, Sarah H. Elsea SH: Smith-Magenis syndrome: Further exploration of genotype, phenotype, and gender relationships. Clinical Genetics (in press), 3/2007.

Miller S, Gradstein L, Tsilou E, Rubin B, Kaiser M, Fitz-Gibbon E, Krasnewich D, and ACM Smith. Ocular Abnormalities in Smith-Magenis syndrome. NIH Research Festival, 2005; 2005 NHGRI Scientific Retreat (poster awardee).

Duncan WC, Morse RS, Krasnewich D, Smith ACM (2005): Late Evening Settling & Early Morning

Sleep Maintenance Differentiate the Sleep Patterns of Adolescents & Younger Children with Smith-Magenis Syndrome (SMS). Poster 580, presented American Society Human Genetics, Oct. 29, 2005, Salt Lake City, UT.

Shirley Dechaine, with forward and epilogue by ACM Smith and RE Magenis: All About Me! One Family\'s Experiences with SMS Mountain Creek Publications, 2005.

Other Accomplishments or Comments

Following establishment of natural history protocol to study SMS, the SMS Research Unit was established in Medical Genetics Branch of NHGRI. Patient referrals to the study, a research roundtable for intramural and extramural investigators, novel neuro assessment tools and international collaborations were implemented as a result of B2B funds.**

Final funds were used for 3 SMS Research team members to go to Australia as invited speakers on SMS; also conducted field research clinic there in January 03.

SMS Research Team members B. Solomon (CC-RMD), W. Duncan (NIMH) and PI ACM Smith (NHGRI) returned to Camp Breakaway, San Remo, NSW Australia in July 2007 to conduct 2nd SMS Clinic (13 f/up visits and 6 new families).

In collaboration with PRISMS (Parents & Researchers Interested in SMS), the advocacy support group for SMS, the PI (ACM Smith;NHGRI) and NIH SMS Research Team convened the 3rd and 4th SMS Research Roundtables in May 2005 and May 2007 (scheduled), respectfully.

B2B#15	"Inhibition of Angiogenesis in Severe Early Rheumatoid Arthritis"
2000	

Investigators

El-Gabalawy, Hani	MD	NIAMS
Eckelman, William	PhD	CC
Carrasquillo, Jorge	MD	CC
Balaban, Robert	MD	NHLBI
Koenig, Scott	PhD	MedImmune, Inc.

Protocols

00-AR-0061 H(2)(15)O Positron Emission Tomography (PET) in the Assessment of Synovial Vascularity and Blood Flow in Rheumatoid Arthritis Patients

01-AR-0151 H215O Positron Emission Tomography (PET) in the Assessment of Synovial Blood Flow in Rheumatoid Arthritis Patients

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Series of patients completed but it was not technically feasible to separate and quantify the blood flow to the synovium on imaging..

Project completed

B2B#16	"Selective depletion of donor lymphocytes causing graft-versus-host disease to improve outcome of allogeneic stem cell transplantation"
2000	

Investigators

Barrett, Austin	MD	NHLBI
Read, Elizabeth	MD	CC

Protocols

01-H-0162 "Ex vivo selective depletion of alloreactive donor T lymphocytes utilizing RFT5-SMPT-dgA, a specific anti-interleukin-2 receptor immunotoxin: reducing graft-versus-host disease risk associated with HLA-matched, nonmyeloblative, peripheral blood stem cell (PBSC) transplantation for hematologic malignancies in older adults"

Patents and Licenses

No data available

Publications

Solomon SR, Tran T, Carter CS et al. Optimized clinical-scale culture conditions for ex vivo selective depletion of host-reactive donor lymphocytes: a strategy for GvHD prophylaxis in allogeneic PBSC transplantation. Cytotherapy. 2002;4: 395-406.

Oral presentations:

Solomon, S., A. John Barrett, et al. "Optimized Clinical Scale Culture Conditions for Ex Vivo Selective Depletion of Alloreactive Donor Lymphocytes;" ISHAGE, 6/15/2001

Solomon, S., A. John Barrett, et al. "T Cell Receptor Vb-specific superantigen responses used as a model to optimize selective depletion of graft-versus-host disease (GVHD)-reacting T Cells with an immunotoxin targeting the IL-2 Receptor;" ASH, 12/11/2001

In preparation:

Scott R. Solomon, Laura Wisch, Bipin Savani, Aldemar Montero, Richard Childs, Carol Boss, Nancy Hensel, John Schindler, Victor Ghetie, Ellen S. Vitetta, Susan F. Leitman, Thao Tran, Charles Carter, Elizabeth J. Read, and A. John Barrett Selective depletion of alloreacting donor lymphocytes – a novel method to reduce the severity of graft-versus-host disease in older individuals following matched sibling donor stem cell transplantation

Other Accomplishments or Comments

In 2002 we achieved the project goal covering pre-clinical work through translational research to a clinical trial.

At bedside, obtained FDA approval for IND allowing testing of anti-CD25 immunotoxin approach to selective T cell depletion in clinical setting.

We have developed more effective ways to deplete activated donor T cells, firstly using CD25 coated magnetic beads in collaboration with Miltenyi Inc. and secondly using a photodepletion system as a CRADA with CelMed of Montreal. The magnetic bead system is currently undergoing pre-clinical validation.

A second clinical trial is now planned to start in 2005 using the magnetic bead depletion approach. The trial will test SD in HLA identical transplants for leukemia and will test whether GVHD is reduced firstly in the presence of cyclosporine immunosuppression and subsequently in the absence of all immunosuppression. If successful it is planned to extend the SD technique to HLA identical unrelated donor transplants and to mismatched family donor transplants.

16 patients, median age 65 years (range 51-73) with advanced hematologic malignancies were entered into the clinical; trial of selective depletion (SD). Cyclosporine was used as the only additional GVHD prophylaxis. SD allografts contained a median CD34 dose of 4.5x106/kg (3.5-7.3) and a CD3 dose of

1.0x108/kg (0.2-1.5). 15 patients achieved sustained engraftment. The helper T lymphocyte precursor (HTLp) frequency assay demonstrated successful depletion of host-reactive donor T cells (mean 5-fold depletion) in 9/11 cases tested, with conservation of 3rd party responses. Actuarial rates of grade III-IV acute GVHD were significantly lower than those seen in a historical control group of patients receiving cyclosporine alone for GVHD prophylaxis (12±8% vs. 41±14%, p=0.08). Of note, patients who developed visceral (gut ± liver) GVHD showed ineffective allodepletion by HTLPf assay.

Gladwin, M., Schechter, AN, Shelhamer, JH, Ognibene, F. The acute chest syndrome in sickle cell disease: Role of nitric oxide in its pathophysiology and treatment. Am. J. Resp. Crit. Care Med. 159: 1368-1376, 1999.

B2B#17	"Studies of CD40 Ligand Trimer as an Adjuvant for HIV-1 Vaccines"
2000	

Investigators

Franchini, Genoveffa	MD	NCI
Jain, Ashish	MD	NIAID
Strober, Warren	MD	NIAID
Kovacs, Joseph	MD	CC
Seder, Robert	MD	NIAID

Protocols

No data available

Patents and Licenses

No data available

Publications

2 publications in Journal of Virology

Other Accomplishments or Comments

Scope of original work changed due to inability to reach CRADA agreements-Study designed to assess immunogenicity of NYVAC-SIV-gag-pol-env administered by IM, intranasal, or intrarectal route in macaques. Study is 1st of its kind in nonhuman primates. Project completed

B2B#18	**"Magnetic Resonance Elastography – A Clinical Technique in the Management of Malignant Acute Hemispheric Stroke with Implications for Patient Intervention by Hemicraniectomy and Duroplasty"**
2001	

Investigators

Moore, David F.	MD, PhD	NINDS
Dimitriadis, Emilios	PhD	OD
Brady, Roscoe	MD	NINDS
Warach, Steven	MD, PhD	NINDS
Talagala, Sardha	PhD	NINDS
Koretsky, Alan	PhD	NINDS

Protocols

02-N-0123 "In vivo Brain Elasticity Measurement by Magnetic Resonance Elastography in Healthy Volunteers"

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Project began 8/2001; protocol measures in vivo brain elasticity; potential benefit in predicting potential adverse clinical outcomes in brain herniation states following head trauma and acute stroke.

B2B#19	**"A Phase I/II Pilot Study to Evaluate the Induction of Immune Tolerance in Patients with Sight Threatening Autoimmune Uveitis Treated with Zenapax and Rapamycin"**
2001	

Investigators

Ragheb, Jack	MD, PhD	NEI
Waldmann, Thomas	MD	NCI
Nussenblatt, Robert	MD	NEI

Protocols

04-EI-0115

Patents and Licenses

EIR-Use of anti-CD25 antibodies for the specific prevention of undesirable humoral responses in humans

Based on preliminary results to date, I expect to submit another EIR based on this B2B

Publications

Abrogation of Potent Humoral Vaccine Responses in Patients on Long-Term anti-CD25 Therapy (under review)

Direct Inhibition of CD40L Expression Can Contribute to the Clinical Efficacy of Daclizumab Independently of its Effects on Cell Division and Th1/Th2 Cytokine Production. Blood In press.

A Novel Cell-Cell Contact Dependent Requirement for Human CD40 Ligand Expression. Submitted.

Other Accomplishments or Comments

IC funding for this project began in Oct, 02. Clinical trial to begin 2003 or 2004

B2B#20	"Use of IL-10 to Improve the Therapeutic Window of Cisplatin"
2001	

Investigators

Star, Robert	MD	NIDDK
Bartlett, David L.	MD	NCI
Alexander, H. Richard	MD	NCI

Protocols

No data available

Patents and Licenses

No data available

Publications

Jiangping Deng, Yukimasa Kohda, Hsi Chiao, Yuqin Wang, Xuxhen Hu, Stephen M. Hewitt, Takehiko Miyaji, Paul McLeroy, Bobby Nibhanupudy, Shujun Li, and Robert A. Star. 2001 IL-10 inhibits ischemic and cisplatin-induced acute renal injury. Kidney International 60: 2118-2128.

Other Accomplishments or Comments

Despite getting the publicity, the project never received money – hence, we were unable to do critical parts of project.

Project completed

B2B#21	"Targeted Delivery of Nitric Oxide by Hemoglobin to Improve Regional Blood Flow in Sickle Cell Disease""
2001	

Investigators

Ognibene, Frederick	MD	CC
Cannon, Richard	MD	NHLBI
Gladwin, Mark	MD	NHLBI

Protocols

01-CC-0078 Targeted delivery of nitric oxide by hemoglobin to improve regional blood flow in sickle cell disease

01-H-0223 Inhaled Nitric Oxide and Transfusion Therapy for Patients with Sickle Cell Anemia and Secondary Pulmonary Hypertension

Patents and Licenses

No data available

Publications

1) Gladwin MT, Sachdev V, Castro O, Minter K, Schechter AN, Nichols JS, Cole W, Smatlak PK, Rodgers GP, and Ognibene FP. A prospective clinical study of the prevalence and etiology of secondary pulmonary hypertension in sickle cell anemia. Submitted to the American Thoracic Society Meeting 2002.

2) Jison ML, Shelhamer JH, Ognibene FP, Pease-Fye M, Logun C, Cintron P, Gerstenberger E, Nichols JS, Danner RL, and Gladwin MT. Activated mononuclear cell gene expression in patients with sickle cell anemia. Submitted to the American Thoracic Society Meeting 2002.

3) Gladwin MT, Schechter AN, Ognibene FP, and Cannon III RO. Reduced nitric oxide bioavailability in men with sickle cell disease. Manuscript in preparation.

4) Ognibene FP, Gladwin MT, Cannon RO, Schechter AN. The role of intravascular hemoglobin and nitric oxide species in blood flow regulation in humans. Manuscript in preparation.

5) Jison ML, Ognibene FP, Castro O, Coles WA, Nichols JS, Hunter LA, Sachdev V, and Gladwin MT. Secondary Pulmonary Hypertension in Sickle Cell Disease: Prevalence, Severity, Mortality and Vasodilator Responsiveness. Presented at the American Thoracic Society meeting in Seattle, WA May 16 – 21, 2003.

6) Gladwin MT, Sachdev V, Jison M, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder W, Schechter AN, Rodgers GP, Castro O, and Ognibene FP. Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease. NEJM, 2004; 350:886-895.

Other Accomplishments or Comments

Award allowed co-investigators to evaluate therapeutic efficacy of inhaled NO in sickle cell disease. Two clinical trials were executed in evaluating the effects of nitric oxide inhalation on regional blood flow, mononuclear cell gene expression, and as a therapy for pulmonary hypertension.

B2B#22	"Combination Anti-Viral and Immunomodulatory Therapy for Chronic Hepatitis B"
2001	

Investigators

Ghany, Marc	MD	NIDDK
Rehermann, Barbara	MD	NIDDK
Alter, Harvey	MD	CC

Protocols

01-DK-0246 "Combination of Lamivudine and Adefovir Dipivoxil for treatment of Chronic Hepatitis B"

Patents and Licenses

No data available

Publications

Mizukoshi E, Sidney J, Livingston B, Ghany M, Hoofnagle J, Sette A, Rehermann B. Cellular immune responses to the hepatitis B virus polymerase. J. Immunol, 173: 5863-5871, 2004

P. Vandepapelière, B. Rehermann, M. Koutsoukos, P. Moris , N. Garçon, M. Wettendorff , G. Leroux-Roels. Potent enhancement of cellular and humoral immune responses against recombinant hepatitis B antigens using AS02A adjuvant in healthy adults. Vaccine, 23: 2591-2601, 2005

Other Accomplishments or Comments

No data available

B2B#23	"Mutation of human growth hormone (hGH sorting motifs to facilitate gene therapeutics applications with salivary glands in adult hGH-deficient patients"
2001	

Investigators

Baum, Bruce	DMD, PhD	NIDCR
Loh, Yoke Peng	PhD	NICHD
Nieman, Lynnette	MD	NICHD

Protocols

While no clinical protocols have yet been initiated, the general goal of this B2B project has entered large animal studies in miniature pigs (ASP #06-358) and macaques (ASP #H0098).

Patents and Licenses

No data available

Publications

Commentary on using salivary glands for treating endocrine disorders and other systemic single protein deficiencies appeared in Gene Therapy, 11: 1425-26, 2004: "Salivary glands and gene therapy: the mouth waters" by R. Zufferey and P. Aebischer

"Partial re-direction of transgenic human growth hormone secretion from rat salivary glands" by Jianghua Wang 1§, Niamh X. Cawley2§ Antonis Voutetakis1, Yazmin M. Rodriguez2, Corinne M. Goldsmith1, Lynnette, K. Nieman3, A.T.M. Shamsul Hoque4, Stuart J. Frank5, Chris. R. Snell 6, *Y. Peng Loh2, and *Bruce. J. Baum 1Gene Therapy and Therapeutics Branch, NIDCR; 2Laboratory of Developmental Neurobiology, NICHD, 3Pediatric and Reproductive Endocrinology Branch, NICHD,; 4Division of Hematology, Office of Blood Research and Review, CBER, FDA,; 5Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, University of Alabama at Birmingham, Birmingham, AL; 6Medivir U.K. Ltd., Cambridge, CB1 9PT, U.K

1Baum BJ, 1Voutetakis A, 1Wang J (2004). Salivary glands: novel target sites for gene therapeutics. Trends Mol Med 10: 585-590. 1Gene Therapy and Therapeutics Branch, NIDCR

1Voutetakis A, 1Kok MR, 1Zheng C, 1Bossis I, 1Wang J, 1Cotrim AP, 1Marracino N, 1Goldsmith CM, 1Chiorini JA, 2Loh YP, 3Nieman LK, and 1Baum BJ (2004). Reengineered salivary glands are stable endogenous bioreactors for systemic gene therapeutics. Proc Natl Acad Sci USA 101: 3053-3058. 1Gene Therapy and Therapeutics Branch, NIDCR; 2Laboratory of Developmental Neurobiology, NICHD,; 3Pediatric and Reproductive Endocrinology Branch, NICHD

1Voutetakis, A., 1Zheng, C., 1Mineshiba, F., 1Cotrim, A.P., 1Goldsmith, C.M., 1Schmidt, M., 1Afione, S., 1Roescher, N., 2Metzger, M., 3Eckhaus, M.A., 1Chiorini, J.A., 2Dunbar, C.E., 2Donahue, R.E., and 1Baum,, B.J.. AAV2-mediated gene transfer to the parotid glands of non-human primates. Hum. Gene Ther. 18:142-150. 1 Gene Therapy and Therapeutics Branch, NIDCR, 2 Hematology Branch, NHLBI, and 3 Division of Veterinary Resources, NIH

Other Accomplishments or Comments

General project has continued as a quite active collaboration addressing the original hypothesis, as well as in related directions

Future Directions: We have initiated a project aimed at using salivary gland gene transfer to help manage diabetes mellitus. Proinsulin is the precursor of both insulin chains (A and B). After synthesis, proinsulin is physiologically sorted to the regulated secretory pathway and retained in dense core granules due to interactions with its sorting receptor, carboxypeptidase E (CPE). The proinsulin is then proteolytically cleaved, converted into insulin and peptide C, stored and subsequently released into the bloodstream upon stimulation. Wild type proinsulin has ~1% of the activity of insulin and can be found in the bloodstream at low levels (~20% that of insulin). Proinsulin sorting results from a structural signal based on four amino acids (EB13, LB17, LA16, and EA17; Dhanvantari et al., Mol Endocrinol, 2003). A number of patients with high proinsulin levels in the bloodstream have been identified. The abnormally

high proinsulin levels result from autosomal dominant point mutations in the insulin gene that alter its' binding to CPE with consequent deficient entry into the regulated secretory pathway (Dhanvantari et al, ibid). Two mutations (B10 and A65) result in proinsulin and partially processed proinsulin molecules that are secreted via the constitutive pathway into the bloodstream. We have hypothesized that transfer of these mutant proinsulin genes to salivary glands will result in considerable proinsulin secretion into the bloodstream with potential therapeutic benefits. We have now constructed recombinant adeno-associated viral vectors encoding either wild type proinsulin, the B10 mutant or the A65 mutant and will soon begin testing of these vectors in vitro and in vivo.

B2B#24	"Genomic Changes in Pre-malignant, Pre-invasive and Invasive Breast Cancer in Women Genetically at High Risk for Breast Cancer"
2001	

Investigators

Giusti, Ruthann M.	MD	NCI
Ried, Thomas	MD	NCI
Chow, Catherine	MD	CC
Filie, Armando	MD	NCI
Greene, Mark	MD	NCI

Protocols

Breast imaging study initiated

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

This Bench-to-Bedside award allowed us to integrate the collection of BDL fluid for cytologic studies including comparative genomic hybridization (CGH) into ongoing imaging study of women from families with identified BRCA1/2 mutations who will be followed prospectively using mammography, breast MRI and BDL over 4 year time period. To date, 12 normal volunteers recruited. (11/01)

B2B#25	"Treatment of Smith-Lemli-Opitz Syndrome with Simvastatin"
2001	

Investigators

Porter, Forbes	MD, PhD	NICHD
Yergey, Alfred	PhD	NICHD
Tierney, Elaine	MD	The Kennedy-Krieger Inst.

Protocols

03-CH-0225 "Investigation of Simvastatin Therapy in Smith-Lemli-Opitz Syndrome"

02-CH-0311 Investigations into inborn errors of cholesterol synthesis and related disorders

Patents and Licenses

No data available

Publications

Wassif, C.A., Krakowiak, P.A., Wright, B.S., Sterner, A.L., Javitt, N., Yergey, A.L., Porter, F.D. (2005) Fractional cholesterol synthesis and simvastatin induction of cholesterol synthesis in Smith-Lemli-Opitz syndrome. Mol Genet Metab. 85: 96-107.

Correa-Cerro, L.S., Wassif, C.A., Kratz, L., Miller, G.F., Munasinghe, J.P., Grinberg, A., Fliesler, S.J., Porter, F.D. (2006) Development and Characterization of a Hypomorphic Smith-Lemli-Opitz Syndrome Mouse Model and Efficacy of Simvastatin Therapy. Hum. Mol. Genet. 15: 839-851.

Wassif, C.A., Yu, J., Cui, J., Porter, F.D., Javitt, N.B. (2003) 27-hydroxylation of 7- and 8-dehydrocholesterol in Smith-Lemli-Opitz syndrome: A novel metabolic pathway. Steroids. 68: 497-502.

Krakowiak, P.A., Wassif, C.A., Kratz, L., Cozma, D., Kovářová, M., Harris, G., Grinberg, A., Yang, Y., Hunter, A.G.W, Tsokos, M., Kelley, R.I., Porter, F.D. (2003) Lathosterolosis: An Inborn Error of Human and Murine Cholesterol Synthesis due to Lathosterol 5-desaturase Deficiency. Hum Mol Genet. 12: 1631-1641.

Other Accomplishments or Comments

In vitro cell culture and in vivo mouse experiments have been completed and published.

The clinical protocol is progressing. Seventeen patients have been recruited. Three patients have completed the two year blinded phase and are on an open-label extension. Baseline data will contribute to two publications over the next year.

An IND has been procurred for the simvastatin preparation. The protocol continues to undergo anual review by both the NICHD IRB and the NICHD DSMC.

B2B#26	"New Treatments for Intractable Pain"
2001	

Investigators

Iadarola, Michael	PhD	NIDCR
Berger, Ann	MD	CC

Protocols

In January of 2004 we had written an initial draft of our clinical protocol and which went through our Institute\'s IRB for a first go-round. Because it was considerably more complex than the standard NIDCR protocol we eventually moved it to the NCI for review by their IRB. This turned out to be beneficial since they were much more attuned to toxicological issues and the Chairman of the pre-review committee (PRMC), was an expert on intrathecal drug administration and we obtained good advice on dose calculations for this body compartment. The protocol has since been reviewed and provisionally approved by the full NCI IRB and is now awaiting the IND approval from the FDA for finalization and initiation of the clinical trial.

Patents and Licenses

FitzGerald DJ and Iadarola MJ: Novel disulfide conjugated cell toxins and methods of making and using them. U.S. Patent # 6,881,718. This patent application covers the Substance-P-Pseudomonas exotoxin compound, associated chemistry and uses that we developed to delete cells via agonist-mediated receptor endocytosis.

Iadarola MJ, Karai L, and Olah Z: Image-guided molecular neurosurgery for pain control. Patent Pending. This patent application covers the use of vanilloid agonists to control pain via intrathecal and intraganglionic administration.

Publications

Mannes AJ, Brown DC, Perkowski SZ, Keller J, Caudle RM, Iadarola MJ, Meng QC: Measurement of resiniferatoxin in cerebrospinal fluid by high-performance liquid chromatography. J Chromatography B 780: 245-247, 2002.

Neubert JK, Kim H-S, Jun JH, Karai L, Iadarola MJ: Peripherally induced resiniferatoxin analgesia. Pain 104:219-228, 2003.

Karai L, Brown DC, Mannes AJ, Connelly ST, Brown J, Gandal M, Wellisch OM, Neubert JK, Olah Z and Iadarola MJ: Deletion of TRPV1-expressing primary afferent neurons for pain control. J. Clinical Investigation. 113:1344-1352, 2004 (note: credit in acknowledgement to bench-to-bedside program)

Caudle RM, Karai L, Mena N, Cooper BY, Mannes AJ, Perez FM, Iadarola MJ, Olah Z: Resiniferatoxin induced loss of plasma membrane in vanilloid receptor expressing cells. J. Neurotoxicology 24:895-908, 2003

Tender GC, Walbridge S, Olah Z, Karai L, Iadarola MJ, Oldfield EH, Lonser RR: Selective ablation of nociceptive neurons for elimination of hyperalgesia and neurogenic inflammation.J Neurosurg. 102:522-525, 2005.

Brown DC, Iadarola MJ, Perkowski SZ, Hardem E, Shofer F, Karai L, Olah Z, Mannes AJ: Physiologic and antinociceptive effects of intrathecal resiniferatoxin in a canine bone cancer model. Anesthesiology 103:1052-1059, 2005.

Mannes AJ, Brown DC, Keller JA, Cordes L, Eckenhoff RG, Caudle RM, Iadarola MJ, Meng QC: Measurement of Resiniferatoxin in Serum Samples by High-Performance Liquid Chromatography. J Chromatography B 823:184-188, 2005.

Other Accomplishments or Comments

In 2004, all mechanisms in place for clinical grade production of drug from natural source (a Moroccan cactus, actually a succulent called Euphorbia resinifera); secured a source in Morocco for raw latex from

Euphorbia resinifera. We eventually had to contract with a second company to finalize the purificaton. In 2005-2006, we completed the production of clinical grade material and its QC/QA to meet FDA compliant guidelines.

In 2004 we established a formal collaboration with NIDA to design and conduct the toxicological testing or RTX and to generate the documents needed to apply for an Investigational New Drug license with the FDA. This inter-Institute collaboration was (and still is) an essential element in bringing this new treatment to clinical trial in man.

In mid-2006 we conducted the formal toxicological testing in two species and are finalizing the neurotoxicological evaluations now (early 2007). These elements were a direct result of the NIDA collaboration.

From 2001 to now we have had the benefit of working with the Pharmaceutical Development Service of the NIH Clinical Center\\\'s Pharmacy Department. We addressed many issues related to formulation of the drug product, solubility, stability testing, etc. The PDS helped us to address all of the practical issues of related to making a drug product (as distinct from the chemical itself) that will be administered to humans and will meet FDA guidelines. We continue to work together to simplify the formulation and enhance the stabilty.

B2B#27	"T Cell-Depleting Monoclonal Antibody Campath-1H in Patients with Inclusion Body Myositis: Correlation of Clinical Response with Changes in Endomysial T-Cell Epitopes, Inflammatory Cytokines, and Costimulatory Molecules"
2002	

Investigators

Dalakas, Marinos	MD	NINDS
Martin, Roland	MD	NINDS
Vasconcelos, Olavo	MD	NINDS
Raju, Raghavan	PhD	NINDS
Muraro, Paolo	MD, PhD	NINDS

Protocols

04-N-0133 Effects of a T Cell-Depleting Monoclonal Antibody, Alemtuzumab, in Patients with Inclusion Body Myositis: A Pilot Clinicopathological Study. Principal Investigator: Marinos C. Dalakas, M.D.

Patents and Licenses

No data available

Publications

Raju, R, Vasconcelos OM, Granger RP, Dalakas MC. Expression of Interferon-Gamma inducible chemokines in the muscles of patients with Inclusion Body Myositis. J Neuroimmunol 2003;141:125-131.

Schmidt J, Rakocevic G, Raju R, Dalakas MC. Upregulated Inducible Costimulator and ICOS-Ligand in Inclusion Body Myositis muscle: Significance for CD8+ T cell Cytotoxicity. Brain 2004;127:1182-1190.

Salajegheh M, Rakocevic G, Shatunov A, Raju R, Goldfarb LG, Dalakas MC. Spectratyping of the T cell receptor beta-chain-variable region in the peripheral blood lymphocyte and muscle of patients with sporadic inclusion body myositis: Evidence of local expansion of T cell clones. Ann Neurol 2004;S(8)56:6. Presented at the 129th Annual Meeting of the American Neurological Association. Toronto, Canada. October 2004.

Other Accomplishments or Comments

The "bench side" is going very well. The "bed side" is also going well. A clinical protocol using CAMPATH has begun and two patients have already completed the study.

T cell clones have been established from more than 10 patients' muscle biopsies and their T Cell Receptor profile has been characterized. Combinatorial peptide libraries are being used to test peptides recognized by the T cell clones. Further, costimulatory molecules have been identified. The information obtained will be used as baseline to compare with the changes in the endomysial T cell receptor repertoire and cytokines obtained after therapy.

B2B#28	"Alloreactive natural killer (NK) cell immunotherapy to improve outcome of allogeneic stem cell transplantation"
2002	

Investigators

Barrett, Austin	MD	NHLBI
Read, Elizabeth	MD	CC

Protocols

Since these studies were conceived it has become possible to select NK cells using clinical grade CD56 antibody coupled to magnetic beads (Miltenyi system) which is more straightforward than expanding them in culture. Dr Childs in the Hematology Branch is developing a clinical protocol to magnetically select alloreactive NK cells from a donor apheresis to give to patients with solid tumors.

Patents and Licenses

No data available

Publications

Sconocchia G, Keyvanfar K, El Ouriaghli F, Grube M, Rezvani K, Fujiwara H, McCoy JP, Hensel N, Barrett AJ. Phenotype and function of a CD56+ peripheral blood monocyte. Leukemia. 2005;19:69-76.

Sconocchia G, Fujiwara H, Rezvani K, Keyvanfar K, El Ouriaghli F, Grube M, Melenhorst J, Hensel N, Barrett AJ. G-CSF-mobilized CD34+ cells cultured in interleukin-2 and stem cell factor generate a phenotypically novel monocyte.. J Leukocyte Biol. 2004;76:1214-9.

Giuseppe Sconocchia, Maurizio Provenzano, Katayoun Rezvani, Jongming Li, Jos Melenhorst, Nancy Hensel , and A John Barrett. CD34+ cells cultured in stem cell factor and interleukin-2 generate CD56+ cells with antiproliferative effects on tumor cell lines. J Transl Med. 2005 Apr 14;3(1):15.

In preparation:

Giuseppe Sconocchia, Michelle Lau, *Maurizio Provenzano, Katayoun Rezvani , Hiroshi Fujiwara, Nancy Hensel, Melenhorst J, Li J, **Soldano Ferrone, and A John Barrett. The anti-leukemic effect of NK and NK-T cells in CML involves NKG2D-MICA/B interactions and is not counteracted by killer inhibitory receptors

Other Accomplishments or Comments

The first phase of the study was to investigate methods of expanding NK cells in sufficient quantities for therapeutic use. We explored techniques to differentiate and expand NK cells from their CD34+ stem cell progenitors. Prior studies suggested that NK cells could be generated by culturing CD34 cells with IL-2 and stem cell factor (SCF). We were not able to generate cytotoxic mature NK cells but this work led to three papers which describe in detail the nature and function of CD56+ cells derived from CD34 cells in these growth conditions. (see below). We then explored methods to expand NK cells from peripheral blood. However this approach was not successful. Currently however it does not appear that there are suitable culture techniques available for growing and expanding NK cells in vitro.

A second part of the study was to explore the role for alloreactivity in NK cells based on recent work by Vellardi and clooeagues who demonstrated that Killer Immunoglobulin-like receptor (KIR) disparity between host and donor could lead to powerful NK alloresponses. We set out to study the effect of NK cells on human chronic myelogenous leukemia established in a SCID-NOD mouse model. Unfortunately it was not possible to obtain reproducible proliferation of the human leukemia in the SCID mouse. We therefore studied NK alloreactivity in vitro using NK cells from HLA matched and mismatched donors and patient leukemia as the target. Surprisingly inhibition of leukemic colony formation was equally effective with HLA matched (KIR compatible) or HLA mismatched (KIR incompatible) effectors. Further analysis suggests that NK cells activation signals from the leukemia predominate over the inhibitory effects. An important activation pathway in chronic myelogenous leukemia appears to be the interaction between MIC-A and MIC-B molecules on the leukemia with NKG2D on the NK cell.

Milestones:

This work took us in a different direction than originally projected. Although it was not possible to develop a clinical

scale system for NK cell expansion we made three novel observations; 1) We found a novel subset of monocytes generated in our cultures which has a mature counterpart in circulating blood of normal individuals. 2) Immature NK cells are not cytotoxic but they have a novel antiproliferative action on cell lines. 3) Our studies show that KIR disparity between patient and donor is not a prerequisite for generating antileukemic effects of NK cells. Future Directions: Our observation that even KIR compatible NK cells can have antileukemic activity opens the way for enhancing NK cell autoreactivity. Strategies to increase NK cell antitumor efficacy would include blocking the KIR molecules and enhancing expression of NKG2D activating molecules using demethylating agents.

B2B#29	"Intracellular Calcium Measurement in Adipocytes (ICMA): An Adjunct to the Study of Supplemental Calcium in Overweight Out Patients (SCOOP) Study"
2002	

Investigators

Parikh, Shamik	MD	NICHD
Blank, Paul	PhD	NICHD
Adler-Wailes, Diane	MS	NICHD
Zimmerberg, Joshua	MD, PhD	NICHD

Plus six AIs from NICHD, CC Nutrition, CC Pharmacy, CC Nuclear Medicine

Protocols

Clinical protocol being developed

Patents and Licenses

No data available

Publications

1)Parikh SJ, Edelman M, Semega-Janneh M, Freedman R, Calis KA and Yanovski JA. Relationships between calcitropic hormones and measures of insulin sensitivity in overweight adults. Accepted for the 63rd Annual ADA meeting June 13-17, 2003, New Orleans.

2)Parikh SJ, Edelman M, Denkinger B, Calis KA, Slaughter PC, McHugh T and Yanovski JA. *High prevalence of Vitamin D insufficiency in Obese African American subjects. Accepted for the 85th Annual Meeting of the Endocrine Society, June 18-21; 2003, Philadelphia. *Selected among the 125 most newsworthy abstracts for Endo 2003 out of 2500 abstracts submitted.

3) Parikh SJ, Sebring NG, Denkinger B, Edelman M, Slaughter PC, McHugh T and Yanovski JA. Two new tools for assessing mean daily calcium intakes of adults. Accepted for the 85th Annual Meeting of the Endocrine Society, June 18-21; 2003, Philadelphia

4) Parikh SJ, Yanovski JA. Calcium Intake is Negatively Correlated to Measures of Adiposity in Women but not Men. Abstract submitted for 2003 NAASO meeting

5) Edelman M, Parikh SJ, Denkinger B, Slaughters P, McHugh Terry & Yanovski JA. 1, 25-dihydroxy Vitamin D levels are not elevated in obese subjects. Submitted for 2003 NAASO meeting

Other Accomplishments or Comments

No data available

B2B#30	"Impact on platelet survival of donor/recipient selection based on definitive sequence-based HLA typing"
2002	

Investigators

Leitman, Susan	MD	CC
Marincola, Francesco	MD	CC

Protocols

Considering starting a prospective clinical protocol using HLA matchmaker (based on sequence based typing information) for the selection of platelet donors to test in a randomized fashion whether molecularly matched platelets donation can prevent the development of refractoriness to transfusion in long-term recipients

The study was published in 2006 in Blood. In this study we observed that HLA matching of platelet using HLAMatchmaker improved the outcome of platelet transfusion. We are presently utilizing this strategy for the identification of potential donors particularly in allo-immunized patients. Thus, the study brought to an improvement in our standard practice. The study is presently continuing to assess the value of high resolution in the context of HLAMatchmaker. However, limited funding is slowing the process since we had to stop HLA typing by sequencing of the new platelet donors due to insufficient personnel in the HLA service lab to support research initiatives.

Patents and Licenses

No data available

Publications

Planning submission of two abstracts to the Annual meeting of the American Society of Histocompatibility and Immunogenetics (one regarding the sequencing results and the second a preliminary report on the correlation between molecular mismatches and clinical outcome. Upon completion of the analysis a full manuscript will be submitted (possibly in the next few months)

The study yielded the following major publication:
"HLAMatchmaker-driven analysis of responses to HLA-typed platelet transfusions in alloimmunized thrombocytopenic patients." Blood. 2006 Feb 15;107(4):1680-7

Other Accomplishments or Comments

Ongoing. In the first phase completed the sequence based typing for HLA-A and B of approximately 900 platelet donors and for HLA-A, B and C for approximately 75 platelet recipients; have contacted and started a collaboration with Dr. Rene Duquesnoy at the transplant unit in the Univ. of Pitt. to implement HLA matchmaker as a program to quantify the relationship between molecular mismatches and platelet transfusion outcome; in addition, working with MIS to get organize clinical information relevant to the analysis of individual patients.

B2B#31	"Characterization of High Risk Breast Duct Epithelium by Cytology Breast Duct Endoscopy, and cDNA Gene Expression Profile"
2002	

Investigators

Danforth, David	MD	NCI
Steeg, Patricia	PhD	NCI
Zujewski, Jo Anne	MD	NCI
Giusti, Ruthann	MD	NCI
Abati, Andrea	MD	NCI
Simon, Richard	DSc	NCI
Ried, Thomas	MD	NCI

Protocols

02-C-0077 "Characterization of High Risk Breast Duct Epithelium by Cytology, Breast Duct endoscopy, and cDNA Gene Expression Profile."

Patents and Licenses

No data available

Publications

Danforth DN Jr., Zujewski J, Abati A, Filie A, Prindiville , Palmieri D, Simon R, Reid T, Steeg P. Combined Breast Ductal Lavage and Ductal Endoscopy for the Evaluation of the High Risk Breast: A Feasibility Study. Jour Surg Oncol, 94(7):555-564, 2006.

Other Accomplishments or Comments

We have studied 25 subjects and correlated ductal epithelial cytology with ductal architecture on endoscopy, shown that ducts can be easily accessed for repeat evaluation, shown that epithelial cytologic atypia evaluated on repeat followup ductal lavage and endoscopy may be a transient phenotype in the high risk breast, and significantly enhanced collection of cellular specimens for cytologic and molecular studies with the use of targeted intraductal sampling using endoscopic coil and brush sampling devices. Plan: Continue accrual to reach complete cohort of premenopausal and postmenopausal women, characterize gene expression profile of high risk breast epithelial cells, and define model for the study of the high risk breast.

B2B#32	"Potential involvement of a brain-specific isoform of the winged helix transcription factor RFX4 in human congenital hydrocephalus"
2002	

Investigators

Blackshear, Perry	MD	NIEHS
Zeldin, Darryl	MD	NIEHS

Protocols

Resequencing has been completed on the promoter and protein coding region for 120 affected subjects. Genotyping assays have been developed for the 22 discovered snps in the protein coding region, and have been applied to 300 control subjects. Genotyping methods are being developed for 28 additional promoter snps, and will be applied to the controls.

Genotyping has been completed and extensive data analysis is ongoing

Patents and Licenses

Title: A novel RFX4 transcript for use in the diagnosis and prevention of familial congenital hydrocephalus.
Co-inventors: P.J. Blackshear, D. Stumpo, J. Graves, and D.C. Zeldin (NIEHS)
Status: U.S. Patent Application No. 10/511,362 published as U.S. 2005/0181369 on August 18, 2005

Publications

Blackshear, P.J., Graves, J., Stumpo, D.J., Cobos, I., Rubenstein, J.L., and Zeldin, D.C. Graded Phenotypic Response to Partial and Complete Deficiency of a Brain-Specific Transcript Variant of the Winged Helix Transcription Factor RFX4. Development 130: 4539-4552, 2003

Zhang, D., Stumpo, D.J., Graves, J.P., DeGraff, L.M., Grissom, S.F., Collins, J.B., Li, Leping, Zeldin, D.C. and Blackshear, P.J. Identification of Potential Target Genes for RFX4_v3, a Transcription Factor Critical for Brain Development. Journal of Neurochemistry 98: 860-875, 2006.

Zhang, D., Zeldin, D.C. and Blackshear, P.J. Regulatory Factor X4 Variant 3 (RFX4_v3): A Transcription Factor Involved in Brain Development and Disease. Journal of Neuroscience Research In Press, 2007.

Zhang, D., Harry, J.G., Blackshear, P.J. and Zeldin, D.C. GPS2 Interacts with RFX4_v3 and Functions as a Transcriptional Co-Activator. Journal of Biological Chemistry Submitted for Publication.

Other Accomplishments or Comments

Project completed 2005.

B2B#33	"Investigation of Brain and Behavioral Effects of Specific Gene Deleted in 'Williams Syndrome Critical Area' of Chromosome 7q11.23 in Patients and Knockout Mice"
2003	

Investigators

Berman, Karen	MD	NIMH
Crawley, Anthony	PhD	NIMH
Koretsky, Alan	PhD	NINDS

Protocols

No data available

Patents and Licenses

No data available

Publications

Meyer-Lindenberg A, Kohn P, Mervis CB, Kippenhan JS, Olsen RK, Morris CA, and Berman KF: Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. Neuron, 43:623-631, 2004. see accompanying commentary entitled "Fulfilling the Promise of the Cognitive Neurosciences" (NIH PRESS RELEASE: http://www.nih.gov/news/pr/sep2004/nimh-01.htm)

Meyer-Lindenberg A, Mervis CB and Berman KF: Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behavior. Nature Reviews Neuroscience, 7:38-393, 2006

Meyer-Lindenberg A, Hariri A, Munuz KE, Mervis CB, Mattay VS, Morris CA, Berman KF: Neural correlates of genetically abnormal social cognition in Williams syndrome. Nature Neuroscience, 8:991-993, 2005. (NIH PRESS RELEASE: http://www.nih.gov/news/pr/jul2005/nimh-10.htm)

Kippenhan JS, Olsen RK, Mervis CB, Morris CA, Kohn PD, Meyer-Lindenberg A, Berman KF: Genetic contributions to human gyrification: Sulcal morphometry in Williams syndrome. Journal of Neuroscience, 25:7840-7846, 2005.

Meyer-Lindenberg A, Mervis CB, Sarpal D, Koch P, Steele S, Kohn P, Marenco S, Morris CA, Das S, Kippenhan JS, Mattay VS, Weinberger DR and Berman KF: Functional, structural and metabolic abnormalities of the hippocampal function in Williams syndrome. Journal of Clinical Investigation 115:1888-1895, 2005

Other Accomplishments or Comments

We have made important insights into gene mechanisms of brain dysfunction leading to cognitive impairment, and none of this would have been possible without the support of the BTB program

2005: NIH DIRECTOR'S AWARD FROM DR. ZERHOUNI TO DR. BERMAN FOR WORK RELATED TO THIS B2B.

3-page write-up of this work in Science magazine: Friendly faces and unusual minds, Science 131: 802-4, 2005. http://www.sciencemag.org/cgi/reprint/310/5749/802.pd

B2B#34	"Sialic Acid Replacement in Patients with Hereditary Inclusion Body Myopathy (HIBM) Caused by Mutations in the GNE (Sialuria) Gene"
2003	

Investigators

Dalakas, Marinos C.	MD	NINDS
Huizing, Marjan	PhD	NHGRI
Krasnewich, Donna	MD, PhD	NHGRI
Vasconcelos, Olavo	MD	NINDS

Protocols

"Intravenous Immunoglobulin (IV-Ig) use in Hereditary Inclusion Body Myopathy"; in preparation.

Principal Investigators: Dr. William A. Gahl and Dr. Marinos C. Dalakas

Patents and Licenses

No data available

Publications

1. Huizing M, Rakocevic G, Sparks SE, Mamali I, Shatunov A, Goldfarb L, Krasnewich D, Gahl WA, Dalakas MC. Hypoglycosylation of alpha-dystroglycan in patients with hereditary IBM due to GNE mutations. Molecular Genetics and Metablism 2004; 81: 196-202.

2. Sparks SE, Ciccone C, Lalor M, Orvisky E, Sanchez C, Gottlieb E, Klootwijk E, Savelkoul P, Dalakas M, Krasnewich D, Gahl WA, Huizing M. Use of a cell-free system to determine UDP-N-acetylglucosamine 2-epimerase and N-acetylmanno-samine kinase activities in human Hereditary Inclusion Body Myopathy. Glycobiology. 2005 Nov;15(11):1102-10. Epub 2005 Jun 29.

Published abstracts:

1. Sparks S, Lalor M, Orvisky E, Huizing M, Krasnewich D, Sun MS, Dalakas M, Gahl W. UDP-GlcNAc 2-epimerase activity in hereditary inclusion body myopathy. American Journal of Human Genetics 2003; 73: 1626.

2. Huizing M, Rakocevic G, Sparks S, Gahl W, Dalakas M, Krasnewich D. Incomplete glycosylation of alpha-dystroglycan in hereditary inclusion body myopathy. Glycobiology 2003; 13: 293.

3. Sparks SE, Lalor M, Orvisky E, Huizing M, Krasnewich D, Sun MS, Dalakas M, Gahl WA. Hereditary inclusion body myopathy; Epimerase activity, GNE mutations and treatment strategies. Glycobiology 2003; 13: 57.

4. Sun MS, Huizing M, Sparks S, Krasnewich D, Schwartzberg PL, Settara C, Gahl WA. Generation of a conditional knock-in mouse model with deficiency of UDP-N- acetylglucosamine 2 epimerase/N-acetylmannosamine kinase to mimic hereditary inclusion body myopathy. Molecular Genetics and Metablism 2004; 81: 180-181.

5. Sparks SE, Lalor M, Orvisky E, Huizing M, Krasnewich D, Sun MS, Dalakas M, Gahl WA. Hereditary inclusion body myopathy due to mutations in GNE: epimerase activity and treatment strategies. Molecular Genetics and Metablism 2004: 81: 179-180.

6. Huizing M, Sparks S, Savelkoul P, Gottlieb E, Ciccone C, Sun MS, Darvish D, Naiem S, Rakocevic G, Dalakas M, Krasnewich D, Gahl W. Evaluation of the underlying defects causing the muscle destruction in hereditary inclusion body myopathy. Glycobiology 2004; 14: 394.

7. Sparks SE, Ciccone C, Lalor M, Orvisky E, Krasnewich D, Sun MS, Gahl WA, Huizing M. In vitro and fibroblast culture measurements of UDP-GlcNAc 2-epimerase/ManNAc kinase activity in hereditary inclusion body myopathy. Glycobiology 2004; 14: 422.

Other Accomplishments or Comments

The "Bench side " of this proposal has made good progress:

In muscle biopsies of patients with HIBM we identified hypoglycosylation of alpha-dystroglycan (ref 1) similar to that reported in other muscular dystrophies. Through a collaboration we have obtained a knock-in mouse model

mimicking an Iranian-Jewish missense founder mutation in the kinase domain of GNE. Homozygous mice are now being characterized, after which potential treatments will be tested (ManNAc, free sialic acid, IV-Ig).

We have developed a vector construct for creating a knock-in mouse model mimicking a Japanese missense founder mutation in the epimerase domain of GNE. We are in the process of screening mouse embryonic stem cells for successful homologous recombination.

We have developed enzyme assays to measure the individual epimerase and kinase activities of the bifunctional GNE enzyme, and the effects of mutations on these activities. We showed, for the first time, that a cell-free transcription translation system can be used to measure GNE enzyme activities (ref 2).We found that additional epimerases and kinases can compensate for dysfunctional GNE enzyme activity in patient's fibroblasts. This new finding is pertinent for treatment strategies and is currently under further study.

Whole Genome Microarray studies have been performed on muscle and fibroblast RNA of patients; the data are currently under investigation. These data can lead to new insights into the muscle pathology of HIBM.

The "Bed side" of this proposal has also thrived: New HIBM patients have been recruited to NIH and their fibroblasts are being studied; new GNE mutations identified. Patients have been informed of the upcoming clinical protocol and possible participation has been discussed.

A clinical protocol is in preparation for intravenous immunoglobulin (IV-Ig) treatment to provide patients a source of sialic acid is in preparation (Dr. W.A. Gahl and Dr. M.C. Dalakas). Further development of other proposed clinical protocols for free sialic acid administration and ManNAc treatment are dependent on the outcome of the IV-Ig protocol. In the mean time, free sialic acid and ManNAc dose and toxicity studies will be performed on the HIBM mouse models.

B2B#35	"MRI Detection of the Migration of Feridex -PPL Labeled Cells into the CNS in Multiple Sclerosis Patients"
2003	

Investigators

Frank, Joseph	MD	CC
McFarland, Henry	MD	NINDS
Martin, Roland	MD	NINDS
Arabi Ali, Syed	PhD	CC
Leitman, Susan	MD	CC
Read, Elizabeth	MD	CC

Protocols

No data available

Patents and Licenses

No data available

Publications

Frank, J.A., Miller, B.R., Arbab, A.S., Zywicke, H.A., Jordan, E.K., Lewis, B.K., Bryant Jr., L.H., Bulte, J.W.M., Clinically applicable labeling of mammalian cells and stem cells by combining (FDA)-approved super paramagnetic iron oxides and commonly available transfection agents. Radiology 2003;228:480-487.

Arbab, A.S., Bashaw, L.A., Miller, B.R., Jordan, E.K., Lewis, B.K., Kalish, H.R., Frank, J.A., Characterization of Biophysical and Metabolic Properties of Cells Labeled with Super paramagnetic Iron Oxide Nanoparticles (Ferumoxides) and Transfection Agent (Poly-L-lysine) for Cellular MR imaging. Radiology 2003;229:838-846.

Anderson, S.A., Shukaliak-Quandt, J., Jordan, E.K., Arbab, A.S., Martin, R., McFarland, H.F., Frank, J.A., Trafficking of Magnetically Labeled Encephalitogenic T-cells in the EAE mouse model by Cellular Magnetic Resonance Imaging. Annals of Neurology 2004;55:654-659.

Bulte, JWM, Arbab, AS, Douglas, T, Frank, JA. Preparation of magnetically labeled cells for cell tracking by magnetic resonance imaging. Methods in Enzymology 2004;386:275-299.

Arbab, A.S., Jordan, E.K., Bashaw, L.A., Yocum, G.T., Lewis, B.K., Frank, J.A. In vivo Targeting iron oxide labeled human mesenchymal stem cell by magnetic field gradients: Detection by MRI in rat model. Human Gene Therapy 2004;15:351-360.

Arbab, A.S., Yocum, G.T., Bashaw, L.A., Kalish H., Ashari, P., Jordan, E.K., Frank, J.A., Comparison of Transfection Agents in Forming Complexes with Ferumoxides, Cell Labeling Efficiency and Cellular Viability. Molecular Imaging 2004;3:24-33.

Arbab, AS, Yocum, GT, Kalish, H, Jordan, EK, Khakoo, A, Anderson, SA, Read, EJ, Frank, JA, Magnetic Cell Labeling with Protamine Sulfate complexed to Ferumoxides for Cellular MRI. Blood 2004;104:1217-1223.

Anderson, SA, Glod, J, Arbab, AS, Noel, M, Fine, HA, Frank, JA., Non-invasive MR imaging of magnetically labeled stem cells to directly identify neovasculature in a glioma model. Blood 2005;105:420-5.

Yocum GT, Bashaw L, Ashari P, Jordan EK, Frank JA, Arbab, AS, The Effect of Ferumoxides-Poly-L-Lysine Labeled Human Stem Cells on Hematological and Biochemical Measures Following Infusion Into the Nude Rat. Radiology In Press

Arbab, AS, Yocum,GT, Anderson, SA, Kalish, H, Read, EJ, Frank JA. Ferumoxides-Protamine Sulfate labeling does not alter differentiation of mysenchymal stem cells. Blood 2004;104:3412-3.

Arbab, AS, Pandit, SD, Anderson, SA, Yocum, GT, Bur, M, Frenkel V, Read, EJ, Frank, JA, Magnetically Labeled Endothelial Progenitor Cells trafficking to Tumor Angiogenesis by MRI and Confocal Microscopy. Stem Cells 2006:24:671-78.

Arbab AS, Yocum GT, Rad, AM, Khakoo AY, Read EJ, Frank JA. Labeling of Cells with Ferumoxides-Protamine Sulfate Complexes does not Inhibit Functional or Differential capacity of Hematopoietic or Mesenchymal Stem

Cells. NMR in Biomedicine 2005;18:383-9.

Arbab, SA, Wilson, LB, Ashari, P Jordan, EK, Lewis, BK, Frank, JA, A model of lysosomal metabolism of dextran coated superparamagnetic iron oxide (SPIO) nanoparticles: Implications for Cellular Magnetic Resonance Imaging. NMR in Biomedicine 2005;18:383-389

Other Accomplishments or Comments

This project is still ongoing and has resulted in the development of new labeling techniques using two FDA approved agents Ferumoxides and protamine sulfate. We have demonstrated the ability to monitor the temporal spatial migration of labeled stem cells and other cells in vivo in experimental models by MRI. We are actively working with FDA to obtain the required preclinical data demonstrating safety and the ability to detect the labeled cells in disease models for inclusion in INDs for submission along with IRB protocol for clinical trials. Protocols and evaluation of automated scale-up procedures for labeling Hematopoietic stem cells, T-cells, Monocytes, and Granulocytes with Ferumoxides Protamine Sulfate complexes in GMP Facility Cell Processing Section, Division of Transfusion Medicine have been develop and used to label cells. Demonstrated that Ferumoxides-Protamine Sulfate labeling approach using two FDA approved agents has no short or long-term toxicity, changes in function, differentiation capacity, phenotype when compared to unlabeled cells Including, Macrophages, Monocytes, Naïve T-cells, Antigen Sensitized T-cells, Mesenchymal Stem Cells or Hematopoietic Stem Cells.

Demonstrated that Ferumoxides-Protamine Sulfate labeled CD 34 AC 133 endothelial progenitor cells will incorporate into ongoing vasculogenesis in experimental tumor model.

Initiated pre-clinical requested FDA studies evaluating the safety and ability to detect Ferumoxides-Protamine Sulfate labeled CD 34 + cells incorporation into ongoing vasculogenesis in a mouse glioma model by MRI. Data is required for submission of IND to FDA of labeling cells with Ferumoxides-Protamine sulfate for clinical trial.

Plan: Submit Master file to FDA on the labeling of Monocytes, T-cells, CD 34 cells, Mesenchymal Stem Cells, Granulocytes with Ferumoxides- Protamine Sulfate

Submit IND to FDA on using Ferumoxides-Protamine Sulfate labeled CD 34 cells in patients with primary or recurrent brain tumors in collaboration with Dr. Howard Fine (NCI/NINDS) to determine if these cells can be detected migrating and incorporating into tumor neovasculature. Plan to obtain pre-clinical data using Ferumoxides-Protamine Sulfate labeled lymphocytes, NK cells and specific T-cell populations in experimental models used to file disease specific IND and IRB protocols in patients with MS or malignancy.

B2B#36	"Dendritic cell vaccination to augment graft-versus-leukemia after allogeneic stem cell transplantation for acute lymphoblastic leukemia (ALL)"
2003	

Investigators

Wayne, Alan	MD	NCI
Mackall, Crystal	MD	NCI
Barrett, Austin	MD	NHLBI
Bishop, Michael	MD	NCI
Fry, Terry	MD	NCI
Gress, Ronald	MD	NCI
Grubbe, Matthias	MD	NHLBI
Kurlander, Roger	MD	CC

Protocols

Clinical trial written;
FDA (for IND) and IRB review in process

Patents and Licenses

No data available

Publications

Rezvani K, et al: Transfer of defined T cell clones with graft-versus-leukemia (GVL) activity from donor to recipient by stem cell transplantation: identification, quantification and characterization. Submitted

Rezvani K, et al: T cell responses against four HLA-A*0201 epitopes of WT1 in healthy donors and patients with leukemia. Submitted

The above 2 papers were also presented in poster format at the 2004 annual meeting of the American Society of Hematology

Dendritic cell product process and characteristics presented (oral and abstract) at NCI/FDA tumor vaccine workshop in 2/07.

Other Accomplishments or Comments

Pre-clinical studies completed in AI laboratories: Mackall & Fry (NCI), Barrett (NHLBI), Kurlander (CC), DTM Cell Processing Section (CC)

Clinical grade peptides for clinical trial synthesized and purchased.

Clinical trial written and submitted as above

Unavailability of CD40 Ligand for generating mature DCs required that an entirely new dendritic cell maturation process be developed. CD40L could not be used due to technology transfer barriers between private industry (Amgen) and the NIH. We therefore needed to acquire new clinical grade reagents and develop and entirely new process for dendritic cell maturation. We are now using \"clinical grade LPS\" plus IFN gamma and believe that the dendritic cells generated may actually be superior to CD40L generated DCs as evidenced by higher IL-12 production and improved motility. This new process has now been validated and scaled up. The IND is currently being completed and will be submitted to the FDA for review within 1 month. The development of this new assay required close collaboration with CC DTM Dept. of Cell Processing which underwent great transition during the last two years.

Project completed 2006.

B2B#37	"Evaluation of HMG-CoA reductase inhibitors in pulmonary sarcoidosis"
2003	

Investigators

Park, Matthew	MD, PhD	NHLBI
Manganiello, Vincent	MD, PhD	NHLBI
Farber, Joshua	MD	NIAID
Fontana, Joseph	MD	NHLBI

Protocols

No data available

Patents and Licenses

No data available

Publications

An abstract/summary of these results is attached, some of which were presented in a poster session at the 2004 American Thoracic Society Meeting (Am J Resp Crit Care Med, 169: A61, 2004).

Other Accomplishments or Comments

Basic Research :In collaboration with Dr. J. Farber's lab (NIAID), we examined immunomodulatory effects of statins on cultured human peripheral monocyte-derived dendritic cells, cord blood T-lymphocytes, and alveolar macrophages from patients with Pulmonary Sarcoidosis (PS). Our results indicated that statins decreased expression of co-stimulatory and activation molecules on dendritic cells, and suppressed T-cell differentiation and chemokine production in alveolar macrophages. Thus statins may have beneficial anti-inflammatory effects in patients with sarcoidosis. Clinical Studies: Dr. Fontana will be PI of a clinical protocol, a randomized, double-blinded, placebo-controlled clinical trial, studying effects of atorvastatin in patients with stage II and III PS

B2B#38	"Clonal Insertion Site Analysis in Rhesus Macaques & NIH Patients Transplanted with Retrovirally-Transduced Hematopoietic Progenitor & Stem Cells: Implications for Leukemogenesis"
2003	

Investigators

Dunbar, Cynthia	MD	NHLBI
Candotti, Fabio	MD	NHLBI
Malech, Harry	MD	NIAID
Baxevanis, Andreas D	PhD	NHGRI
Donahue, Robert	VMD	NHLBI

Protocols

No new human protocols but have analyzed samples from patients already enrolled in ADA and CGD gene therapy trials at the NIH

Patents and Licenses

No data available

Publications

Hematti, P. et al, Distinct genomic integration of MLV and SIV vectors in primate hematopoietic stem and progenitor cells. PLoS Biology. 2004 Dec;2(12):e423. Epub 2004 Nov 23.

Laukkanen, M.O. et al, Low dose total body irradiation causes clonal fluctuation of primate hematopoietic stem and progenitor cells. Blood, 2005 Feb 1;105(3):1010-5. Epub 2004 Sep 21.

Kiem, H.P. et al, Long-term clinical and molecular followup of large animals receiving retrovirally-transduced stem and progenitor cells: no progression to clonal hematopoiesis or leukemia. Molecular Therapy 9:389-395, 2004

Brenner S, Ryser MF, Choi U, Whiting-Theobald N, Kuhlisch E, Linton G, Kang E, Lehmann R, Rosen-Wolff A, Rudikoff AG, Farese AM, Macvittie TJ, Roesler J, Horwitz ME, Malech HL. Polyclonal long-term MFGS-gp91phox marking in rhesus macaques after nonmyeloablative transplantation with transduced autologous peripheral blood progenitor cells. Mol Ther. 2006 14:202-11.

Other Accomplishments or Comments

The samples that the FDA has required for long-term followup on all gene therapy trials have been analyzed and this has allowed continuation of the ADA trial.

The non-human primate data has been of great interest to the FDA and the gene therapy community and is changing the focus of vector development to lentiviral as compared to MLV retroviral vectors.

Project completed 2005

B2B#39	"Use of 5 Fluorouracil (5FU) in Combination with Antiretroviral Drugs as a Salvage Strategy to Overcome Drug Resistance in Heavily Treated HIV-Infected Pediatric Patients"
2003	

Investigators

Wood, Lauren	MD	NCI
Womack, Chad	PhD	NIAID

Protocols

Protocol development has been deferred given the NCI's administrative decision in December 2004 to close the pediatric HIV clinical research program.

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Multiple clinical isolates from pediatric patients with a range of HIV-1 RNA levels and rounds of HAART treatment experience have been obtained. Multiple attempts to isolate virus from purified subcompartments was yielded viral isolates from only 1 patient (an adult) despite utilization of 2 different protocols. Dr. Chad Womack left the NIAID, VRC as of 01/14/05. The BTB work is continuing under the supervision of Drs. Barney Graham and Mario Roederer. New viral isolation protocols have been established utilizing antiCD3 coated plates in addition to combination cytokine cocktails utilizing IL2, IL4, IL6, TNF-a and IL10 in hopes of stimulating virus production. We simultaneously are in the process of refining and quantitating the lower level of sensitivity of a nested PCR assay to characterize provirus in cell subpopulations in the event that the new methodologies fail to consistently yield detectable virs.

B2B#40	"Imaging Probe for the In Vivo Assessment of HIV-1 Dynamics"
2003	

Investigators

DiMascio, Michele	PhD	NIAID
Pandit, Sunil	PhD	NHLBI
Li, King	MD	CC
Imamichi, Tomozumi	PhD	NCI
Lane, Henry	MD	NIAID

Protocols

Studies on in vivo labelling of lymphocytes in controls, patients with HIV infection and patients with HIV infection receiving IL-2.

Patents and Licenses

No data available

Publications

Kovacs JA, Lempicki RA, Sidorov IA, Adelsberger JW, Herpin B, Metcalf JA, Sereti I, Polis M, Davey RT, Tavel J, Falloon J, Stevens R, Lambert L, Dewar R, Schwartzentruber D, Anver MR, Baseler MW, Masur H, Dimitrov D, Lane HC. Identification of dynamically distinct subpopulations of T lymphocytes that are differentially affected by HIV. J Exp Med. 194:12, 1731-1741, 2001.

Kovacs JA, Lempicki RA, Sidorov IA, Adelsberger JW, Sereti I, Sachau W, Kelly G, Metcalf JA, Davey RT Jr, Falloon J, Polis MA, Tavel J, Stevens R, Lambert L, Hosack DA, Bosche M, Issaq HJ, Fox SD, Leitman S, Baseler MW, Masur H, Di Mascio M, Dimitrov DS, Lane HC. Induction of prolonged survival of CD4+ T lymphocytes by intermittent IL-2 therapy in HIV-infected patients. J Clin Invest. 115:2139-2148, 2005.

Other Accomplishments or Comments

In vitro experiments completed. The project is moving to in vivo experiments in SHIV-infected Rhesus Macaques.

We have modified two HIV-1 fusion blockers, T-20 and T-1249, by adding a chelator (DTPA) during the synthesis of the compounds. In vitro assays have shown preservation of the inhibitory activity of viral replication for the modified T-1249 chelated to cold Indium, but reduced inhibitory activity for the modified T-20. Thus, the modified T-1249 appears to be a potential new radiotracer that is suitable for in vivo imaging studies in SHIV infected Rhesus Macaques

Future Directions: We are proceeding with the quantitative processing of the images to test whether these images show evidence of anatomic loci with specific uptake of the radiotracer-

B2B#41	"Therapeutic Targeting of a Virally Regulated Host Cell Molecule in HIV Infection"
2003	

Investigators

Wahl, Sharon	PhD	NIDCR
Masur, Henry	MD	CC
Sporn, Michael B.	MD	Dartmouth Medical School
Vazquez-Maldonado, Nancy	PhD	NIDCR

Protocols

Pending drug development

Patents and Licenses

No data available

Publications

Journal of Virology, in press

Other Accomplishments or Comments

Future: Continued analysis of signaling pathways engaged by HIV in macrophages; generation of sufficient CDDO for clinical trials

B2B#42	"Role of Recombination in HIV-1 Drug Resistance in vitro and in vivo"
2003	

Investigators

Maldarelli, Frank	MD, PhD	NCI
Palmer, Sarah	PhD	NCI
Hu, Wei Shau	PhD	NCI
Coffin, John	PhD	NCI
Polis, Michael	MD	NIAID
Mican, Joann	MD	NIAID

Protocols

A study of the effects of recombination is in development. We are considering investigating whether recombination contributes to the spread of archived mutations in HIV-1 infected patients in the context of a salvage regimen:

- Enrolling patients with a history of drug resistance to a particular class of antiretroviral, who do not have current evidence of resistance by commercial genotyping

- Restarting the previous drug class, which should have activity against the current virus and combined with new drugs that have activity against the original archived virus.

- Measure the effect of this new salvage regimen on HIV-1 viral RNA level, and the composition of the rebound virus

Patents and Licenses

No data available

Publications

Several abstracts have been presented or accepted for presentation at national and international meetings that have investigated the presence of recombination in HIV-1 infected individuals:

- 12th International Workshop on HIV Dynamics and Evolution 2005

- Conference on Retroviruses and Opportunistic Infections 2005

- XIII International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications 2004

Other Accomplishments or Comments

Clinical: 1. Ongoing analysis of samples obtained through other existing protocols. 2. Development of clinical protocol to study the role of recombination in spread of drug resistance mutations

Laboratory: We are developing the laboratory technique to detect the presence of recombinant molecules in infected cells

Milestones:

Analysis of clinical samples has suggested that HIV-1 recombination is frequent in HIV-1 infected individuals (ms in preparation, presented in abstract form).

Recombination rates in vivo were estimated at 0.5-8 recombination events per genome per cycle. The implication is that the proportion of dually infected cells in infected individuals may exceed 20%. These data have been presented at national and international meetings, and more data are being accumulated for the manuscript.

Future Directions:

- We have recently identified an individual in the Washington D.C. area with a relatively unusual HIV-1, denoted HIV-1 group O. We are interested in determining whether HIV-1 group O can recombine with other subtypes, especially subtype B, the predominant HIV subtype in the US. Subtype O is intrinsically resistant to certain antiretrovirals, and as such, this virus represents a particularly difficult virus to treat. If the group O virus recombines

with subtype B, then it will represent the introduction of a new resistance challenge.

- Similarly, we are investigating the presence of recombination between HIV-1 and HIV-2, as HIV-2 is also intrinsically resistant to certain antiretrovirals. HIV-2 is present in few patients in US but represents a significant proportion of infections in certain geographic areas of Africa, including areas where antiretroviral therapy is currently being introduced. Recombination between HIV-1 and HIV-2 has the potential to compromise the newly introduced therapy and therefore represent a significant public health issue in these resource poor areas.

B2B#43	"Treatment of Drug Resistant and Persistent HIV-1 Infection with the Designed Proteins 5-Helix and 5-Helix-PE"
2003	

Investigators

Hamer, Dean	PhD	NCI
Kovacs, Joseph	MD	CC

Protocols

On hold pending animal efficacy test results.

Patents and Licenses

No data available

Publications

Manuscript in preparation on macaque phase I testing.

Other Accomplishments or Comments

In vitro experiments have been completed and show that 5-helix and 5-helix-PE are highly active against a wide spectrum of HIV isolates. Initial in vivo experiments in HIV-infected SCID mice failed to demonstrate inhibition of HIV replication; these measurements are being repeated with more potent reagents. Phase I testing in macaques generated an acceptable safety profile; efficacy testing is in progress.

B2B#44	"HIV-1 Infections During Vaccine Trials: Identifying New Peptides for the Differential Diagnosis of HIV-1 Infection in the Face of Vaccine-Generated Antibodies"
2003	

Investigators

Golding, Hana	PhD	CBER,FDA
Graham, Barney	MD, PhD	NIAID

Protocols

A new HIV Diagnostic was developed based on the initial data generated in the B2B funds.
This assay was termed HIV SELECTEST. It is currently perform at very high levels of sensitivity and specificty wirh early seroconversion sera from individuals infected with very diverse HIV clades. The further develpment of this assay was heavily supported by the National Hearts Blood and Lung Institute in the FY 2004-2007. Most importantly, the NHBLI is posting an RFP for assay manufacturing, valdation, and licensure for the next 5 years. It is expected that the HIV SELECTEST will be available for the upcoming \\\\\\\"proof-of-concept\\\\\\\" Phase IIB HIV vaccine trials, including the one in which the VRC vaccine will be tested in multiple sites in North and South America and in several sites in Africa. The HIV SELECTEST was already included in several INDs sumitted to the FDA.

88. S. Khurana, J. Needham, S. Park, B. Mathieson, M.P. Busch, G. Nemo, P. Nyambi, S. Zolla-Pazner, S. Laal, J. Mulenga, E. Chomba, E. Hunter, S. Allen, J. McIntyre, I. Hewlett, S. Lee, S. Tang, E. Cowan, C. Beyrer, M. Alfred, X.G. Yu, A. Tounkara, O. Koita, A. Kamali, N. Nguyen, B.S. Graham, D. Todd, P. Mueynyi, O. Azala, E. Sanders, N. Ketter, P. Fast, and H. Golding. 2006. Novel approach for differential diagnosis of HIV infections in the face of vaccine generated antibodies: Utility for detection of diverse HIV-1 sybtypes. J. Acquired Immunodeficiency 43 (No. 3): 304-312

Patents and Licenses

PCT/US2005/031287
Title: COMPOSITION AND METHODS FOR THE DETECTION OF HIV-1/HIV-2 INFECTION

Publications

1. S. Khurana, J. Needham, B. Mathieson, I. Rodriguez-Chavez, A.T. Catanzaro, R.T. Bailer, J. Kim, V. Polonis, D.A. Cooper, J. Guerin, M.L. Peterson, M. Gurwitz, N.Nguyen, B.S. Graham, H. Golding and the HIV Vaccine Trial Network. 2006. A novel assay for diagnosis of HIV infections in the presence of antibodies induced by candidate HIV preventive vaccines. J. Virol. 80:2092-2099

2. S. Khurana, J. Needham, S. Park, B. Mathieson, M.P. Busch, G. Nemo, P. Nyambi, S. Zolla-Pazner, S. Laal, J. Mulenga, E. Chomba, E. Hunter, S. Allen, J. McIntyre, I. Hewlett, S. Lee, S. Tang, E. Cowan, C. Beyrer, M. Alfred, X.G. Yu, A. Tounkara, O. Koita, A. Kamali, N. Nguyen, B.S. Graham, D. Todd, P. Mueynyi, O. Azala, E. Sanders, N. Ketter, P. Fast, and H. Golding. 2006. Novel approach for differential diagnosis of HIV infections in the face of vaccine generated antibodies: Utility for detection of diverse HIV-1 sybtypes. J. Acquired Immunodeficiency 43 (No. 3): 304-312

Other Accomplishments or Comments

The goals of our project was to identify new HIV-1 epitopes which fulfill the following criteria: a) do not contain protective antibody or cytotoxic T cell epitopes; b) are not included or can be easily removed from current and future HIV-1 vaccine candidates; c) broadly reactive with early serum samples from individuals infected with HIV virus strains from all clades. EIA based on these new epitopes should give negative results with sera from vaccine recipients and positive results with infected individuals.

In order to identify new serologic epitopes that conform to the above criteria, we constructed a gene-fragment phage display library expressing fragments spanning the entire HIV-1 genome. After limited DNase I digestion of HIV-1 DNA (NL4-3 clone), 50-300 bp long fragments were cloned at the N-termini of the coat protein of phage display vectors. Therefore, every possible HIV-1 encoded peptide in any of the reading frames is present in the phage library. The library was subjected to panning on immobilized serum antibodies from HIV-1-infected individuals. Phages that bound to the immobilized antibodies were retained, while non-binders were washed-off. DNA sequencing of the captured phages, allowed mapping of the selected peptides to known HIV proteins. Of the initial

11 phagotopes identified, we focused on two sequences, located in gag-p6 and in the cytoplasmic tail of gp41, which to our knowledge, do not contain protective epitopes and are not included in most current HIV vaccines. With support from the NIH Bench-to-Bedside grant (FY03-04), we have developed ELISA assay based on the two peptides we have identified. To date, we tested more than two hundreds negative samples as well as several well-characterized panels of seroconverstors from Boston Biomedica. So far our assay performed well compared with results obtained with the Abbot HIV1/2 seroconversion kit. We have also tested mixed clades panels from around the world (including 100 specimens from Cameroon), and obtained data supporting the utilization of our assay in detecting antibodies in clades A, B, C, D, E, F infections. Currently, our assay performs at >97% specificity and sensitivity levels. Testing of second-generation consensus peptides and further assay optimization are ongoing. It will be essential for this assay to achieve >99% specificity and >98% sensitivity.

Importantly we already screened samples from Phase II trial of prophylactic HIV vaccines conducted by DOD. Around 80% of vaccine gave false positive results in a commercial HIV-1 detection kits. All scored negative in our new EIA assay. This comprises a strong proof-of-concept of our assay.

Our goal for the next two years:

1) Further improvements to peptides used in our assay and optimization of the EIA conditions in order to achieve >99% sensitivity and specificity.

2) Screening of blinded samples of early seroconvertors from the US, Australia, and Africa.

3) Screening of blinded samples of chronically infected individuals from multiple countries.

This project was also supported by the FDA Office of Women Health. A special effort was made to demonstrate the the new HIV Diagnostic assay is equally sensitive in men and women.
Our next goal is to convert the assay to a Rapid Test platform that will be very useful for Point-of-Care low cost testing.

B2B#45	"Effect on Immune Responses and Sustainability of Viral Suppression in HIV-Infected Children of a Therapeutic Vaccination Strategy with a Multiclade HIV-1 DNA Plasmid Vaccine Prime and a Recombinant Adenovector Boost"
2003	

Investigators

Zeichner, Steven	MD, PhD	NIAID
Koup, Richard	MD	NIAID
Worrell, Carol	MD	NICHD

Protocols

"A Phase I/II Clinical Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Therapeutic Vaccination Strategy Utilizing a Multiclade HIV-1 DNA Plasmid Vaccine Prime (VRC-HIV DNA009-00-VP) and a Recombinant Adenovector Boost (VRC-HIV ADV010-00-VP) in HIV-1-infected Children" This protocol was written and approved at the Branch level and by the NCI protocol review and monitoring committee. The protocol has not gone forward to the IRB because of production problems with the vaccine and insufficient safety data so far from the preceding adult trial.

Patents and Licenses

No data available

Publications

None yet

Other Accomplishments or Comments

Lab work is underway. Protocol development, initial characterization of the immune response to the potential vaccine antigens and adenovirus in patients who would be candidates for the protocol, development of highly sensitive assays to detect genotypic differences and sequence evolution in the virus of viral genes encoding antigens targeted by the vaccines.

Future Directions: We hope to finish work on some of the in vitro preliminary studies soon. However, the NCI has decided to close the intramural pediatric clinical HIV program, so it is unlikely that, even once the vaccine and adult data become available, there would be a protocol at the clinical that would open. We may try to pursue doing a pediatric therapeutic vaccine trial through other venues.

B2B#46	**"Neural substrates underlying motor control of a newly implanted hand transplant"**
2004	

Investigators

Cendales, Linda C.	MD	NIAMS
Cohen, Leonardo	MD	NINDS

Protocols

NIAMS: "Hand Transplantation for the reconstruction of below the elbow amputations". IRB approved with stipulations November 30, 2004

NINDS: Protocol was completed and ready to start. However, the NIAMS interrupted the clinical priviliges of my co-investigator and stopped support for the project

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

NINDS : Fellows have been recruited and successfully completed training and completion of various projects very successfully

B2B#47	**"Development of Non-invasive treatment for uterine leiomyoma (fibroids)"**
2004	

Investigators

Davis, Barbara	VMD, PhD	NIEHS
Segars, James	MD	NICHD
Stratton, Pamela	MD	NICHD
Plus other AIs from CC, NCI, NICHD		

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Many efforts by Dr. Segars, PI to access funds to no avail. Participating ICs on this project: NIEHS, NICHD, NCI and CC. PI trying to proceed with the proposal without funds, albeit slowly, as the funds were actually needed to do the research.

B2B#48	"Infrared and Near Infrared Image Guided Minimally Invasive Assessment of Renal Perfusion during Donor Nephrectomies and Partial Nephrectomies"
2004	

Investigators

Elster, Eric	MD	NIDDK
Kirk, Allan	MD	NIDDK
Pinto, Peter	MD	NCI

Protocols

05-DK-0043 Guided Minimally Invasive Live Donor Kidney Donation for Kidney Transplantation. Protocol submitted October 2004 and approved December 2004

99-DK-010 Preliminary data obtained under existing protocol (Live Donor Renal Donation for Allotransplantation and encouraging. enrollment to proceed with approved protocol

Patents and Licenses

3rd generation laparoscopic IR attachment in development with Vipera, Inc.

Laparoscopic Infrared camera to be delivered January 2005.

Publications

No data available

Other Accomplishments or Comments

In addition, large animal studies of cadaveric organs have demonstrated the ability of IR imaging to quantify perfusion as well as guide interventions. Further collaborations utilizing this novel imaging technology in development.

B2B#49	"Novel Approach for treatment of squamous cell malignancies with 17-AAG and bortezomib"
2004	

Investigators

Gius, David	MD, PhD	NCI
VanWaes, Carter	MD, PhD	NIDCD
Neckers, Leonard	PhD	NCI

Protocols

There is an ongoing phase I NCI protocol initiated by another investigator with 17 DMAG for which patients with HNSCC are eligible and we have thus far entered one patient with HNSCC who had stable lung metastatic disease for 8 months before progression on treatment. A collaborative study with DMAG and radiation therapy for patients with HNSCC is in development based on preclinical studies under this B2B proposal.

Patents and Licenses

No data available

Publications

Ricker, J.L, Nottingham, L.N., Yang, X.P., Lee, T.L., Chen, Z., Neckers, L., Gius, D., and Van Waes, C. Sensitivity to Proteasome Inhibitor Bortezomib and Heat Shock Protein 90 Inhibitor 17-DMAG Correlates with Nuclear Factor KappaB Activation and Heat Shock Protein 90 Expression in Head and Neck Squamous Cell Carcinomas with Varying Sensitivities to Standard Chemotherapy Agents. (Submitted), 2007.

Van Waes, C., Chang, A., Lebowitz, P.F., Harkins, C., Chen, Z., Elsayed, Y., Sunwoo, J.B., Headlee, D., Rudy, S.F., Adams, J., Morris, J., Mitchell, J.B., Camphausen, K., Gius, D., Sausville, E.A., Conley, B. Clinical and Biologic Effects of Concomitant Therapy With Proteasome Inhibitor Bortezomib and Re-irradiation in Patients with Recurrent Head and Neck Squamous Cell Carcinoma. Int. J. Rad. Oncol. Biol. Phys. 63:1400-1412, 2005.

Bisht, K., Bradbury, C.M., Mattson, D., Kaushal, A., Sowers, A., Markovina, S., Ortiz, K., Sieck, L.K., Isaacs, J.S., Brechbiel, M.W., Mitchell, J.B., Neckers, L.M., and Gius, D. Increased Radiosensitization in Cervical Tumor Cells Geldanamycin and 17-Allylamino-17-Demethoxygeldanamycin Potentiates the Radiation Response of Cervical Tumor Cells In Vitro and In Vivo. Cancer Research 63:8984-8995, 2003.

Other Accomplishments or Comments

The long-term objective of this work is to determine if HSP90 and the proteasome are clinically viable molecular targets to improve the cytotoxicity of therapeutic ionizing radiation (IR). We believe that this work will, through a combination of in vitro and in vivo experiments, identify molecular markers/targets, as well as ideal timing and dosing, of the geldanamycin derivative 17-AAG and/or proteasome inhibitor bortezomib as an adjuvant to IR alone.Funding for this project was not approved until the fall and in this time we have hired a fellow to begin the proposed experiments. Specific aims:.

- Determine the ideal timing and dosage for 17-AAG and bortezomib administration and IR treatment, using our previously established 17-AAG (twice weekly) and IR (fractionated) in vivo model system.

We began in vitro experiments using clonogenic cell survival experiments to begin to address the proposed experiments as outlined in aim one.

-Determine if the molecular markers identified in our in vitro model systems correlate with in vivo tumor cell response using a twice weekly administration of 17-AAG, bortezomib, and fractionated irradiation model system.

The model system to begin these experiments was validated and initial experiments (must be repeated) Determine if markers identified in vitro are also seen in vivo.

The work proposed in aims 3 to 5 have not yet been initiated but the planning is done and we will begin these experiments in the near future.

Project completed 2007.

B2B#50	"Therapeutic application of intravascular nitrite for sickle cell disease"
2004	

Investigators

Gladwin, Mark	MD	NHLBI
Cannon, Richard	MD	NHLBI

Also AIs from CC, NIDDK, NHLBI

Protocols

05-H-0016 The Therapeutic Application of Intravascular Nitrite for Sickle Cell Disease: Enrollment opened 1/1/05 and closed on 8/4/06.

Patents and Licenses

A provisional patent application has been submitted: Use of nitrite salts for the treatment of cardiovascular conditions. M.Gladwin, A.Schechter, C.Hunter, R. Pluta, E. Oldfield, R. O. Cannon IIII, D.Kim-Shapiro, D.Leffer, R. Patel, G.Power.

Publications

Sodium nitrite increases regional blood flow in patients with sickle cell disease. A. Kyle Mack MD, Roberto Machado MD, Lori Hunter RN, Vicki McGowan BS, Mark T. Gladwin MD, Gregory J. Kato, MD (Abstract submitted to 28th Annual Meeting of the National Sickle Cell Disease Program)

Manuscript in development

Other Accomplishments or Comments

Forearm blood flow studies have been completed on fourteen patients to date. These patients have been infused with SNP, L-NMMA and Nitrite at the three designated doses, and there have been no significant side effects. The average increase in forearm blood flow over baseline with the SNP doses of 0.8mg/min, 1.6mg/min, and 3.2mg/min were +27%, +12%, and +32% respectively. The average drop in forearm blood flow after the L-NMMA infusions of 4mmol/min and 8mmol/min were -17% and -20% respectively. As hypothesized the forearm blood flow did increase after each successive dose of nitrite. The average increase in forearm flow after the 0.4mM, 4mM and 40mM infusions was +8%, +25%, and +77% respectively. The post nitrite SNP forearm blood flow responses were as predicted, greater than the pre-nitrite forearm flows. There was no statistically significant difference in the pre-nitrite SNP forearm blood flow response and the post-nitrite SNP forearm blood flow response in our patients in out 14 patients with sickle cell disease who participated in the study.

Data Analysis Plan: We are seeking to determine the potential therapeutic effect of intra-arterial nitrite infusion to restore nitric oxide dependent regional blood flow in patients with sickle cell disease (SS). Forearm blood flow measured at baseline will be compared to the paired forearm blood flow after 40 μM nitrite infusion in each patient (paired student's t-test). A significant result will be indicated by an increase in forearm blood flow following nitrite infusion vs. baseline values, with $p<0.05$.

We will also perform the following secondary analysis:

(1) Paired measurements of % change in forearm blood flow following L-NMMA and SNP infusion, before vs. after nitrite infusion (comparisons by repeated measures ANOVA).
(2) The effect of nitrite infusions on venous nitrite levels, plasma NO consumption and sickle cell related biomarkers (comparisons by paired Student's t-test).

Project completed 2006.

B2B#51	"Intermediate phenotype and genetic mechanisms for psychosis and cognitive disturbance in 22q11.2-hemideletion syndrome"
2004	

Investigators

Meyer-Lindenberg, Andreas	MD, PhD	NIMH
Goldman, David	MD	NIAAA
Weinberger, Daniel	MD	NIMH
Berman, Karen	MD	NIMH

Protocols

05-H-0016 The Therapeutic Application of Intravascular Nitrite for Sickle Cell Disease: Enrollment opened 1/1/05 and closed on 8/4/06.

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

The protocol has been approved this week so subject accrual for this study is expected to begin soon.

B2B#52	**"Molecular profiling of response to proteasome inhibition by bortezomib (PS341) in a clinical trial of mantle cell lymphoma"**
2004	

Investigators

Wiestner, Adrian	MD, PhD	NHLBI
Wilson, Wyndham	MD, PhD	NCI
Staudt, Louis	MD, PhD	NCI
Dunleavy, Kieron	MD	NCI

Protocols

NCI Protocol 05-C-0170. Principal investigator: Wyndham H. Wilson. Randomized phase II study of dose-adjusted EPOCH-Rituximab-Bortezomib induction followed by bortezomib maintenance versus observation in untreated Mantle Cell Lymphoma with microarray profiling and proteomics. This trial has acrued about 15 patients to date and is ongoing.

Patents and Licenses

No data available

Publications

Edgar G. Rizzatti, Helena Mora-Jensen, Raymond Lai, Masanori Daibata, Therese White, Kieron Dunleavy, Wyndham Wilson, Adrian Wiestner. Bortezomib Induces an Antioxidant and ER-Stress Response Gene Expression Signature in Mantle Cell Lymphoma: Implications for Response Prediction and Optimized Chemotherapy Regimens. Blood 108, Suppl. 1, 830a. Oral Presentation at the 48th American Society of Hematology Meeting, Orlando, FL 2006.

Other Accomplishments or Comments

No data available

B2B#53	"A Phase I/II pilot study to evaluate the treatment of intraocular lymphoma with BL22 immunotoxin"
2004	

Investigators

Nussenblatt, Robert	MD	NEI
Pastan, Ira	MD	NCI
Chao Chan, Chi Chao	MD	NEI
Kreitman, Robert	MD	NCI
Fine, Howard	MD	NCI

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

I. We have established a murine ocular B lymphoma model for the first time using a human B lymphoma cell line. SCID mice were injected with Burkitt's lymphoma cell line CA46 intravitreously. After 3-5 weeks, animals were sacrificed and eyes were examined by histopathology and immunohistochemistry. We showed that the Burkitt's B cell lymphoma could establish colonization and invasion to the retina. Titration and kinetic studies demonstrated that intravitreous injection of as low as 3000-6000 cells/eye could establish ocular lymphoma and SCID mice developed full disease as early as 3 weeks after intravitreous injection. Histopathology suggested that the newly established murine lymphoma model could mimic human ocular lymphoma in many aspects in that the tumor cells could invade into retina, subretinal region as well as inside the central nervous system such as brain. This murine ocular lymphoma model will be useful for 1) to test potential clinical therapies, e.g., HA22 and 2) to understand molecular mechanisms of ocular lymphoma.

II. Immunohistochemistry further confirmed that the lymphoma cells did express abundant surface CD22 receptor. This data support the potential application of HA22, an anti-CD22 antibody conjugated with an exotoxin from pseudomonas. We have so far accomplished a series studies regarding the cytotoxicity of HA22 to the murine eyes upon delivery intravitreously. Initial study suggested that HA22 could be a potent cytotoxin for murine retina. Further titration studies were able to define the cytotoxic range of HA22 to murine retina was from below 1000 ng/eye. This data will be used for therapeutic studies when we use HA22 to treat ocular lymphoma.

We have begun preliminary discussions within the group concerning the clinical study.

B2B#54	"Immunotherapy for Myelodysplastic Syndrome"
2004	

Investigators

Barrett, Austin	MD	NHLBI
Douek, Daniel	MD, PhD	NIAID
Rosenberg, Steven	MD, PhD	NCI

Plus AIs from NHLBI, VRC, NIAID

Protocols

Protocol to be submitted 01/05 to the NHLBI IRB: Lymphoablation, autologous lymphocyte infusion, and WT1 and PR1 peptide vaccination for patients with myeloid malignancies

Patents and Licenses

No data available

Publications

Submitted: Transfer of defined T cell clones with graft-versus-leukemia (GVL) activity from donor to recipient by stem cell transplantation: identification, quantification and characterization. *Katayoun Rezvani, †David A. Price, †Jason M. Brenchley, *Yasemin Kilical, ‡Emma Gostick, ‡Andrew K. Sewell, *Giuseppe Sconocchia, #Roger Kurlander, †Daniel C. Douek, *A. John Barrett (Submitted to PNAS) *Stem Cell Allotransplantation Section, Hematology Branch, National Heart Lung Blood Institute, National Institutes of Health, Bethesda, MD; †Human Immunology Section, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD; ‡Nuffield Department of Medicine, Oxford University, United Kingdom; #Department of Laboratory Medicine, Clinical Center, NIH, Bethesda, MD.

T cell responses against four HLA-A*0201 epitopes of WT1 in healthy donors & patients with leukemia. *Katayoun Rezvani, †Jason M. Brenchley,†David A. Price, *Yasemin Kilical, Matthias Grube,, *Giuseppe Sconocchia, Frank El-Ouriaghi, Hiroshi Fujiwara Jongming Li, ‡Emma Gostick Nancy Hensel, †Daniel C. Douek, *A. John Barrett (manuscript in preparation). , *A. John Barrett (Submitted to PNAS) *Stem Cell Allotransplantation Section, Hematology Branch, NHLBI, NIH, Bethesda, MD; †Human Immunology Section, Vaccine Research Center, NIAID, NIH, Bethesda,MD;Nuffield Department of Medicine, Oxford University, United Kingdom; Clin Cancer Res. 2005 Dec 15;11(24 Pt 1):8799-807

The above 2 manuscripts were also selected as poster presentation at the 2004 annual meeting of the American Society of Hematology

Other Accomplishments or Comments

Pre-clinical data obtained from this project has opened the path to developing vaccination protocols for patients with myelodysplastic syndrome and myeloid leukemias (acute myeloid and chronic myeloid leukemias) in a variety of clinical settings including:

- in the autolgous setting

- following allogeneic transplantation, with or without donor lymphocyte infusions

- and in combination with drugs such as tyrosine kinase inhibitors (Imatinib).

B2B#55	"A Phase I Treatment Trial of the Circadian Sleep Disturbance in Smith-Magenis Syndrome (SMS)"
2004	

Investigators

Smith, Ann C.	DSc (Hon)	NHGRI
Grimes, George	BS	CC
Krasnewich, Donna	MD, PhD	NHGRI
Gradstein, Libe	MD	NEI
Duncan, Wallace	PhD	NIMH
Gropman, Andrea	MD	NHGRI

Protocols

Planned Phase 1 Treatment trial protocol – draft is written with submission to NHGRI planned in late Spring/May, 2005;

Delayed submission of new protocol, Phase 1 Treatment of Circadian Sleep Disturbance in Smith-Magenis Syndrome\" until Nov, 2006, with review and approval Feb. 2007. This delay was required to permit the manufacture of delayed time-release melatonin (dTR-MEL) tablet to specifications required by the CC-PDS (Grimes). The protocol was reviewed by the NHGRI IRB and approved but is on \"hold\" by protocol services until the IND is filed with FDA. We expect to submit the IND in April 2007.

The new protocol, \\\"A Phase 1 Treatment of the Circadian Sleep Disturbance of Smith-Magenis syndrome was submitted to NHGRI IRB for initial review and approved with stipulations on 10/19/06. Responses to IRB stipulations were handled in Nov-Dec, 2006 (appointment of medical monitor) except for submission if IND application to FDA. This is planned for April, 2007.

Patents and Licenses

No data available

Publications

Duncan WC, Morse R, Krasnewich D, and ACM Smith (2004): Body Temperature and Sleep Disturbance in Smith-Magenis Syndrome (SMS), Poster 814, Amer. Soc. Hum. Genet, Toronto, Oct. 2004.

Smith ACM and Duncan WC: "Smith-Magenis Syndrome: A Developmental Disorder with Circadian Dysfunction" in Genetics of Developmental Disabilities, Butler and Meany (Eds), Taylor & Francis Group, New York, NY, 2005.

April 28, 2005, the SMS Research Unit, NHGRI will convene the 3rd SMS Research Roundtable Symposium that includes a half day session, "The Biologic Basis of Sleep in SMS", led by AI Wallace Duncan, PhD (NIMH) that includes a discussion of treatment approaches and results of pilot studies in France and the U.S. The Research Roundtable is co-sponsored by NIH (NHGRI with Office of Rare Diseases) and PRISMS, the parent support group for SMS, and will precede PRISMS' 4th SMS International Educational Conference, "Building Bridges of Hope" that follows in OH.

Duncan WC, Morse RS, Krasnewich D, Smith ACM (2005): Late Evening Settling & Early Morning Sleep Maintenance Differentiate the Sleep Patterns of Adolescents & Younger Children with Smith-Magenis Syndrome (SMS). Poster 580, presented American Society Human Genetics, Oct. 29, 2005, Salt Lake City, UT.

Gropman AL, Duncan WC, Smith AC. (2006): Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2). Pediatr Neurol. 2006 May;34(5):337-50. PMID: 16647992 (TOP 10 papers downloaded on the web in 2006.)

Other Accomplishments or Comments

Development of delayed time release (dTR) melatonin tablet required for treatment trial initiated by CC-Pharmacy (G.Grimes, CC-Pharm). IND application will be filed to FDA in April, 2007 as required by NHGRI-IRB.

We have adapted the existing methodology and validation of the RAI-based salivary melatonin assay that will permit collection of smaller sample volumes (<1cc) of saliva in the home setting (Mark Rollag, PhD, AI/ACM Smith, PI)

and are currently validating this methodology, that will be needed for the trial.

Via the SMS Home Assessment of Sleep (HAS) under protocol 01-HG-0109, we collected critical actigraphy data from SMS and pediatric controls (unaffected siblings) to study the rest/activity (surrogate sleep marker) patterns in SMS. This baseline date was critical to formulation of the research study plan for the treatment study. Ongoing HAS data collection continues, especially on sibling controls and newly added comparision group of children with DD/MR-syndrome (Cornelia deLange) that is associated with as-yet unstudied sleep disturbances.

The new protocol, \"A Phase 1 Treatment of the Circadian Sleep Disturbance of Smith-Magenis syndrome\" was submitted to NHGRI IRB for initial review and approved with stipulations on 10/19/06. Responses to IRB stipulations were handled in Nov-Dec, 2006 (appointment of medical monitor) except for submission if IND application to FDA. This is planned for April, 2007.

B2B#56	**"Pre-clinical non-human primate studies of an invo selectable vector intended for use in a planned clinical trial of gene therapy for chronic granulomatous disease"**
2004	

Investigators

Malech, Harry	MD	NIAID
Dunbar, Cynthia	MD	NHLBI
Kang, Elizabeth	MD	NIAID
Choi, Uimook	PhD	NIAID
Larochelle, Andre	MD, PhD	NHLBI

Protocols

A protocol has been approved for the gene therapy treatment of chronic granulomatous disease 07-I-0017 entitled "Autologous Transplantation of Genetically Modified Cells for the Treatment of X-Linked Chronic Granulomatous Disease" is open for enrollment using vector developed under this project. The first patient was successfully treated in November 2006. Additional clinical grade vector was produced for this project as a result of this support and is in testing.

Patents and Licenses

No data available

Publications

Choi U, DeRavin SS, Yamashita K, Whiting-Theobald N, Linton GF, Loktionova NA, Pegg AE, Malech HL Nuclear-localizing O6-benzylguanine-resistant GFP-MGMT fusion protein as a novel in vivo selection marker. Exp Hematol. 2004 32:709-19, 2004.

Brenner S, Ryser MF, Choi U, Whiting-Theobald N, Kuhlisch E, Linton G, Kang E, Lehmann R, Rosen-Wolff A, Rudikoff AG, Farese AM, Macvittie TJ, Roesler J, Horwitz ME, Malech HL. Polyclonal long-term MFGS-gp91phox marking in rhesus macaques after nonmyeloablative transplantation with transduced autologous peripheral blood progenitor cells. Mol Ther. 2006 14:202-11.

Malech HL, Choi U, Brenner S. Progress toward effective gene therapy for chronic granulomatous disease. Jpn J Infect Dis. 2004 57:S27-8.

Other Accomplishments or Comments

Two primates were transplanted with the vector to be tested which was an RD114 pseudotyped MFGS-gp91phox-IRES-MGMT. This resulted in long term marking of these animals with this vector. The in vivo selective regimen was used with these animals and achieved some increase in in vivo marking. This project is ongoing and plans are in progress to try to increase marking and the margin of increase with selection using a lentivirus vector. Mouse studies with the MGMT marking system are also being performed and have been very successful at achieving enhanced marking with in vivo selection. However, for the current ongoing human clinical trial the Amphotropic MFGS-gp91 vector is being used with plans in the future for use of these other described vectors.

Project completed 2006.

B2B#57	"Isolation and Characterization of Circulating Endothelial Cells in Primary Pulmonary Hypertension: Implications for Early Diagnosis and Novel Therapeutic Targets"
2004	

Investigators

Solomon, Michael	MD	CC
Danner, Robert	MD	CC
Munson, Peter	PhD	CIT
McCoy, John	PhD	NHLBI

Protocols

05-CC-0041: Endothelial Cell Dysfunction in Pulmonary Arterial Hypertension: Biomarkers, Mechanisms of Disease and Novel Therapeutic Targets

Patents and Licenses

No data available

Publications

Khan SS, Solomon MA, and McCoy JP. Detection of circulating endothelial cells in blood by flow cytometry: Comparison of healthy controls to patients with systemic disease. American Thoracic Society 2004 International Conference, American Journal of Respiratory and Critical Care Medicine. 169(7): A155, 2004.

Raghavachari N, Khan SS, Elshal M, Barb J, Logun C, Munson PJ, Gladwin MT, McCoy JP, Danner RL, and Solomon MA. Transcript Profiling of Peripheral Blood Circulating Endothelial Cells. AHA Scientific Sessions 2005, Circulation 112: II-219, 2005.

Other Accomplishments or Comments

Extramural collaborations: Inova-Fairfax Pulmonary Hypertension Program (Steven Nathan, MD), and INO Therapeutics Inc (Clinton, NJ).

Intramural Collaborations: NHLBI Flow Cytometry Core Facility (J. Phillip McCoy, Jr., Ph.D.), and Ultra-micro Analytical Immuno-chemistry lab (Terry M Phillips, PhD, DSc).

Departmental Collaborations: CCMD Functional Genomics Core Facility, (Robert Danner, MD), and Proteomics Core Facility (Anthony Suffredini, MD).

2004 - 2006 CEC detection techniques refined and isolation techniques determined; Viable and verifiable CECs isolated from human peripheral blood.

June 2006 - Patient recruitment initiated (n=16, March 2007)

Protocol currently active

B2B#58	**"Evaluation of the anti-IL-2/IL-15R monoclonal antibody Hu MiK--1 in a therapeutic trial in patients with HAM/TSP and a test of hypotheses concerning the role of IL-15 in the maintenance of CD8+ memory T-cells and in the pathogenesis of HAM/TSP"**
2004	

Investigators

Waldmann, Thomas	MD	NCI
Jacobson, Steven	PhD	NINDS
Fleisher, Thomas	MD	CC

Protocols

04-N-0071 Phase I study of HTLV-I associated myelopathy/tropical spastic paraparesis HAM/TSP using humanized Mik-Beta-1 monoclonal antibody directed toward the IL-2/IL-15 R beta subunit (CD122) that blocks IL-15 action. Status: Approved by the IRB, FDA approval pending completion of multidose toxicological analysis.

Patient accrual has been initiated using Hu-Mik-Beta-1 in patients with T-cell LGL--a required prerequisite for the Hu-Mik-Beta-1 in HAM/TSP study.

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

The project is active completing preclinical toxicological studies required for FDA approval of the initiation of a clinical trial of Hu-Mik-Beta-1 in patients with HAM/TSP. Milestones: A series of FDA mandated tests for ex vivo analysis required for the HAM/TSP trials have been established including: (a) test for the detection of human antibodies which recognize the infused Hu-MiK-Beta-1 monoclonal antibody; (b) ELISA method for the detection of humanized Mik-Beta-1 in human serum. These assays were established on the Metabolism Branch, NCI and established as GLP reproducible assays by Covance Laboratory; (c) Furthermore, an FDA mandated toxicological analysis of multiple dose Hu-MiK-Beta-1 administration to 15 cynomolgus monkeys has been initiated.

On completion of the GLP multidose Hu-Mik-Beta-1 toxicological analyses in 15 cynomolgus monkeys we will request permission from the FDA to initiate a study of Hu-Mik-Beta-1 in the therapy of patients with HAM/TSP. Each patient would receive

1 mg/kg. q. 3 weeks for 9 doses. The impact of therapy on ex vivo T-cell proliferation, the number of antigen specific (aa 11-19 of tax) CD8 T-cells in the circulation will be enumerated and the clinical response of the patients to Hu-Mik-Beta-1 therapy will be determined.

B2B#59	"Childhood Cancer and Plexiform Neurofibroma Tissue Microarray for Molecular Target Screening and Clinical Drug Development"
2004	

Investigators

Fox, Elizabeth	MD	NCI
Baird, Kristin	MD	NCI

Plus AIs from NCI, NHGRI, and Pediatric Phase I/Pilot Consortium

Protocols

Tissue Microarray protocol is open at the NIH and at Texas Children's Hospital and is under review at the other sites

Patents and Licenses

No data available

Publications

Drs. Fox and Baird have been invited to present this project in March 2005 in the plenary session at the annual COG spring meeting in Los Angeles, CA.

Other Accomplishments or Comments

The project is in the organizational and tissue collection phase. We plan to have the tissue microarray manufactured in the spring and start staining for molecular drug targets shortly after that.

On 9/15/04 a planning meeting with our extramural collaborators (Texas Children's Cancer Center [Baylor], Children's National Medical Center, Cincinnati Children's Hospital) was hosted here at the NIH. The list of tumors to be included in the microarray was refined, the source of tumors and a scoring system for immunohistochemical staining were discussed and the image procurement and display software was demonstrated. A Tissue Microarray protocol has been written, reviewed and approved by the NCI PRMC and IRB and by the Baylor IRB and is under review at the other participating sites. We are negotiating material transfer agreements to transfer the blocks to the NIH. In collaboration with the Lab of Pathology, we have identified and set up an automated stainer that will be dedicated to the tissue microarray project. The project concept was presented to the Pediatric Phase I/Pilot Consortium by Dr. Fox in November 2004 and was well received. Selection of targets for testing was discussed.

Future: Once antibody screening is performed, this information will be integrated into selecting potential therapeutic agents for phase 1 clinical trials.

As of Jan 1 2007, 150 tissue blocks have been obtained. To increase rate of tissue acquisition another institution (extramural) has been added: Children\'s memorial Medical Center.

B2B#60	**"Molecular profiling and drug discovery for patients with PTEN Hamartomatous Tumor Syndromes (PHTS)"**
2004	

Investigators

Dennis, Phillip	MD, PhD	NCI
Elkahoun, Abdel	PhD	NHGRI
Hewitt, Stephen	MD, PhD	NCI
Choyke, Peter	MD	NCI

Protocols

A treatment protocol to use a rapamycin analogue RAD001 in PHTS patients is under preparation

Patents and Licenses

No data available

Publications

Tsurutani, J., Ye, J., Hewitt, S., and Dennis, P.A. Analysis of the PI3K/Akt pathway in unaffected, benign, and malignant tissues from patients with PTEN Hamartomatous Tumor Syndromes (submitted)

Other Accomplishments or Comments

Project is ongoing. Patients with PHTS have been recruited to NCI under a tissue procurement protocol. Tissues from these patients are now being analyzed. Future: Continue with ongoing analysis of tissues, and submit/obtain protocol approval

B2B#61	"Assessing the safety and immunogenicity of a therapeutic vaccination strategy using a DNA plasmid vaccine prime and a recombinant adenovector boost in HIV infected adults"
2004	

Investigators

Graham, Barney	MD, PhD	NIAID
Koup, Richard	MD	NIAID
Casazza, Joseph	MD, PhD	NIAID
Catanzaro, Andrew	MD	NIAID
Hamer, Dean	PhD	NCI

Protocols

Clinical Protocols Resulting from Project: We plan on submitting VRC 101, the therapeutic vaccine protocol, to the IRB in May 2005, with enrollment beginning in July

Protocol VRC 101 (Version 1.0, dated October 4, 2005) was initially submitted with the BB-IND application on October 12, 2005. A Response to FDA Request for Information, was submitted to the FDA on December 8, 2005 (SN #001) containing lot release information for agents and placebos used in Protocol VRC 101.

Protocol VRC 101 (Version 2.0, dated May 15, 2006) was submitted on June 15, 2006 (SN #003). This amendment included deletion of the treatment interruption in response the announcement that the SMART (Strategies for Management of Anti-Retroviral Therapy) study had discontinued enrollments and treatment interruptions due to safety concerns. The study objectives were amended to relate only to safety and immunogenicity, the duration of follow-up was shortened to 24 weeks after the last vaccination, and the size was reduced to 15 subjects (10 vaccinees and 5 placebo recipients). The first subject was enrolled under Version 2.0 on August 21, 2006; no subjects had been enrolled under the Version 1.0 protocol.

As of March 16, 2007 13/15 subjects are enrolled, and there have been no study related serious adverse events, and no study subjects have been withdrawn. Immunogenicity data will not be available until accrual is complete.

Patents and Licenses

No data available

Publications

none

Other Accomplishments or Comments

Status: Ongoing

Milestones: Phase I trials for the candidate vaccines, VRC-HIVDNA016-00-VP, a DNA plasmid vaccine, and VRC-HIVADV014-00-VP, a recombinant, replication incompetent adenoviral vector vaccine, have been fully enrolled and all vaccination have been given. These vaccines were well tolerated.

Future Direction: We anticipate proceeding as outlined in our initial protocol.

Interim Progress Report:

Bedside portion- Phase I trials for the candidate vaccines for the therapeutic trial, VRC-HIVDNA016-00-VP, a DNA plasmid vaccine, and VRC-HIVADV014-00-VP, a recombinant, replication incompetent adenoviral vector vaccine, have been fully enrolled and all vaccination have been given. The last scheduled visit for patients vaccinated with VRC-HIVDNA016-00-VP is June 9. The last scheduled visit for patients vaccinated with VRC-HIVADV014-00-VP is April 27. These vaccines have been well-tolerated. No subjects have been discontinued from either study because of side-effects and further studies of these vaccines are planned in HIV-uninfected subjects. Bench portion: In preparation for analysis of the immune response induced by vaccination in our therapeutic trial, conditions for 12 color flow cytometric assay for both CD4+ and CD8+ T cells responses have been established and used to analyze the results from VRC trials 004 and 006. VRC004 is a phase I trial in HIV-uninfected volunteers using a DNA plasmid vaccine, VRC-HIVDNA009-00-VP. This vaccine is similar to the plasmid vaccine to be used in VRC 101. VRC006 is a phase I trail in HIV-uninfected volunteers using VRC-HIVADV014-00-VP, the recombinant,

replication incompetent adenoviral vector vaccine to be used in VRC 101. In uninfected controls, vaccination with both the plasmid vaccine and the recombinant adenovirus vaccine resulted in a CD4+ T cell response to vaccine matched peptide epitopes characterized by IFN-g and IL-2 production (Fig. 1). Stimulation of CD8+ T cell with vaccine matched peptide epitopes produced a response principally characterized by production of IFN-g and MIP-1b in patients vaccinated with the plasmid vaccine or the recombinant adenovirus vaccine (Fig. 2). These responses are different than the responses seen in subjects infected with vaccinia or in individuals with subclinical infection with CMV. In both of these infections, in addition to production of IFN-g and IL-2 by CD4+ T cells, significant production of TNF-a is also seen. In CMV infection a CD107+ response, indicative of degranulation, is also seen in CD4+ T cells (Fig. 3). CD8+ T cell responses to both CMV and vaccinia infections were characterized by CD107 positivity and IFN-g, MIP-1b and TNF-a production (Fig. 4). This results show the difference between the initial responses elicited by non-infectious vaccinations, and protective immunity in vaccinia and CMV infection, and indicate the importance of following the evolution of vaccine-induced immune responses when exposed to the actual viral pathogen

In collaboration with Debbie Persaud at Johns Hopkins, Dr. Koup\'s group will assess the impact of the vaccination on the pool of latent virus within resting memory CD4+ T cells.

B2B#62	"Targeting vascular endothelial growth factor-A (VEGF-A) and receptor-2 (VEGFR-2) for the treatment of Primary Effusion Lymphoma"
2004	

Investigators

Tosato, Giovanna	MD	NCI
Yarchoan, Robert	MD	NCI
Farber, Joshua	MD	NIAID
Little, Richard	MD, PhD	NCI
Aoki, Yoshiyasu	MD	NCI

Protocols

This study in part led to the development of clinical protocol 05-C-0205.

Patents and Licenses

No data available

Publications

1. HIV-1 Tat enhances Kaposi sarcoma-associated herpesvirus (KSHV) infectivity Aoki, Y and Tosato G. Blood 104:810, 2004

Murga, M, Fernandez-Capetillo, O, and Tosato, G. Neuropilin-1 regulate attachment in human endothelial cells independently of vascular endothelial growth factor receptor-2. Blood 105:1992-99, 2005

Narazaki, M and Tosato G. Ligand-induced internalization prioritizes usage of common receptor Neuropilin-1 by VEGF165 over Semaphorin3A. Blood 107:3892-3901, 2006

Other Accomplishments or Comments

No data available

B2B#63	"Pediatric NeuroAIDS in the HAART Era: Identification of Disease Markers and Therapeutic Targets"
2004	

Investigators

Hazra, Rohan	MD	NCI
Major, Eugene	PhD	NINDS
Schwartz, Lynnae	MD	NINDS
Worrell, Carol	MD	NICHD

Protocols

A clinical protocol was approved by the NCI IRB in 2005 - 05-C-0150.

Patents and Licenses

No data available

Publications

None to date

Other Accomplishments or Comments

No data available

B2B#64	"Treatment of Primary-Effusion Lymphoma with Combination Virolytic and Cytotoxic Chemotherapy"
2004	

Investigators

Yarchoan, Robert	MD	NCI
Cohen, Jeffrey	MD	NIAID
Little, Richard	MD, PhD	NCI
Davis, David	PhD	NCI
Tosato, Giovanna	MD	NCI

Protocols

We have initiated a protocol (05-C-0203) from this bench-to-bedside award. In addition, the work on this study has helped inform a related protocol in another KSHV-associated tumor, multicentric Castlema\'s disease (04-C00275).

Patents and Licenses

No data available

Publications

None to date. We have presented our work at the AIDS Malignancy Meeting (2006) and the KSHV workshop (2006). We are continuing this work before submitting it for publication. In addition, the project has helped support a paper on the use of AZT and ganciclovir to kill activated PEL cells -- this paper is now submitted for publication.

Other Accomplishments or Comments

The initial laboratory component has been initiated, examining the effect of cytotoxic drugs on KSHV activation. We are clarifying some results before submitting for publication. It has also helped support a related paper on the killing of these activatedcells with AZT and ganciclovir that is submitted for publication.

B2B#65	"Induction of volitional swallowing in chronic dysphagia post stroke: A novel mechanism-based intervention"
2005	

Investigators

Ludlow, Christy	PhD	NINDS
Cohen, Leonardo	MD	NINDS

Protocols

One protocol has beeen approved and is under way

Patents and Licenses

None yet

Publications

None yet

Other Accomplishments or Comments

Initial fMRI scanning has been performed on normal subjects. Some data have been analyzed, and one paper is in preparation. Patient studies are beginning.

B2B#66	"Induction of Mucosal Tolerance to Recombinant Human E-Selectin for the treatment of Myocardial Ischemia-Reperfusion Injury and Symptomatic Coronary Atherosclerosis. A Collaborative NHLBI/NINDS Investigation"
2005	

Investigators

deSilva, Ranil	PhD	NHLBI
Hallenbeck, John	MD	NINDS
Finkel, Toren	MD, PhD	NHLBI

Plus AIs from NHLBI, NINDS

Protocols

ASP # 1260-06 "Induction of mucosal tolerance to recombinant human or mouse E-selectin to reduce plaque rupture events in a mouse model of coronary atherosclerosis and spontaneous myocardial infarction"

Patents and Licenses

Method for preventing strokes by inducing tmolerance to E-selectin - patent pending

Immunological tolerization to E-selectin prevents the brain damage associated with vascular cognitive impairment - patent pending

Publications

No data available

Other Accomplishments or Comments

SR-B1/ApoE dKO mice have fulminant develpopment of atherosclerosis and sudden death at 8 weeks. This created problems with the NINDS animal care and use committee because the sudden death would place most animals in category E. In addition, it would be hard to achieve E-selectin tolerization before the animal dies. We are now collaborating with NHLBI to produce LDLR/ ApoE dKO mice that develop severe atherosclerosis and myocardial ischemia by 7 months. These animals will be tolerized with E-selectin or PBS and followed. In the meantime we are produceing (with Novavax) cGMP recombinant murine and human E-selectin and are proceeding with preclinical toxicology and immunotoxicology studies in a GLP lab as stipulated by the FDA.

B2B#67	"Natural history, biology and treatment of dermal neurofibromas in neurofibromatosis type 1 (NF1)"
2005	

Investigators

Widemann, Brigitte	MD	NCI
Stewart, Douglas	MD	NHGRI

Plus AIs from Numerics, Inc., University of Alabama

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#68	"Testing Treatment of Hutchinson-Gilford Progeria Syndrome with Farnesyl Transferase Inhibitors"
2005	

Investigators

Gordon, Leslie	MD, PhD	NHGRI
Orlic, Donald	PhD	NHLBI
Introne, Wendy	MD	NHGRI
Gahl, William	MD, PhD	NHGRI
Collins, Francis	MD, PhD	NHGRI
Nabel, Elizabeth	MD	NHLBI

Protocols

"Clinical Investigations into Hutchinson-Gilford Progeria Syndrome" was continued by virtue of this B2B grant, and data were collected for consideration of a therapeutic protocol.

A colony of a mouse model of Hutchinson-Gilford Progeria Syndrome (obtained from Dr. Francis Collins) is currently being expanded and treated with native bone marrow stem cells. The mice will be carried for an additional 4 to 8 months at which time they will be asayed for improved cardiovascular functions.

Patents and Licenses

No data available

Publications

Abstracts were presented at the American Society of Human Genetics meeting in 2006, and a manuscript is being prepared describing the natural history clinical data.
:
Cao K, Capell BC, Erdos MR, Djabali K, Collins FS. Related Articles, Links A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells.Proc Natl Acad Sci U S A. 2007 Mar 14; [Epub ahead of print]
PMID: 17360355 [PubMed - as supplied by publisher]

Capell BC, Collins FS. Related Articles, Links Human laminopathies: nuclei gone genetically awry.Nat Rev Genet. 2006 Dec;7(12):940-52. Review.PMID: 17139325 [PubMed - indexed for MEDLINE]

Other Accomplishments or Comments

Brian Capell won an award for his research on this topic in Dr. Collins' lab. The award was for work by a Medical Student and was granted by the American Society of Human Genetics in 2006.

B2B#69	"Analysis of global gene expression patterns and mitochondrial DNA damage in lymphocytes of Friedreich's Ataxia patients undergoing idebenone treatment in Phase II double-blind placebo controlled study"
2005	

Investigators

Van Houten, Bennett	PhD	NIEHS
Fischbeck, Kenneth	MD	NINDS
Haugen, Astrid	BS	NIEHS
DiProspero, Nicholas	MD, PhD	NINDS

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#70	"Adoptive Cell Therapy for Ewing's Sarcoma Using Artificial Antigen Presenting Cells"
2005	

Investigators

Mackall, Crystal	MD	NCI
Read, Elizabeth	MD	CC
Helman, Lee	MD	NCI
Zhang, Hua	PhD	NCI
Snyder, Kristen	MD	NCI

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#71	"Ganaxolone Therapy for Niemann-Pick Type C"
2005	

Investigators

Porter, Forbes	MD, PhD	NICHD
Pavan, William	PhD	NHGRI

Protocols

06-CH-0186 Evaluation of Biochemical Markers and Clinical Investigation of Niemann-Pick Disease, Type C

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

To date we have recruited and evaluated 14 patients with NPC. This patient cohort now probably represents the largest actively followed cohort of NPC patients. We are currently evaluating cross-sectional data from our cohort. Follow-up visits are now occurring, thus some longitudinal data will be available over the next year. Basic science work is ongoing to investigate the mechanism of action of ganaxalone.

B2B#72	"UVA Sensitivity in Smith-Lemli-Opitz Syndrome: Possible Involvement of -olbCholesta -5,7,9(11)-trien-3
2005	

Investigators

Chignell, Colin	PhD	NIEHS
Porter, Forbes	MD, PhD	NICHD

Protocols

02-CH-0311 Investigations into Inborn Errors of Cholesterol Synthesis and Related Disorders-amended

98-CH-0081 Clinical and Basic Investigations into Smith-Lemli-Opitz Syndrome. Amended.

Patents and Licenses

No data available

Publications

Chignell CF, Kukielczak BM, Sik RH, Bilski PJ, HE YY (2006) Ultraviolet A sensitivity in Smith-Lemli-Opitz syndrome: Possible involvement of cholesta-5,7,9(11)-trien-3 beta-ol. Free Radic Biol Med. 41: 339-346.

Other Accomplishments or Comments

Progress has been made in characterizing the effect of abnormal oxysterols in the mouse model of SLOS and correlating this with cholesterol levels in patients samples. This work has been presented at ASHG and ACMG meetings. We expect a publication within the next year.

B2B#73	"Pre-clinical and clinical investigations into the mechanisms and efficacy of extracorporeal photopheresis (ECP) in the abrogation of graft-vs-host disease (GVHD) and facilitation of graft-vs-tumor (GVT) immunity in pediatric patients"
2005	

Investigators

Wayne, Alan	MD	NCI
Fry, Terry	MD	NCI
Bolan, Charles	PhD	CC
Leitman, Susan	MD	CC
Malech, Harry	MD	NIAID
Pavletic, Steven	MD	NCI
Baird, Kristin	MD	NCI

Protocols

A Phase I - Pilot Study of Continuous Flow Extracorporeal Photopheresis in Children with Chronic Graft-Versus-Host Disease (written, awaiting submission)

Patents and Licenses

No data available

Publications

Herby, S, Davis, J, Wayne, A, Fry, T. Dendritic cell vaccination modulated by extracorporeal photopheresis expands antigen-specific T cells following allogeneic transplantation. Biology of Blood and Marrow Transplantation, 13, 292a, 2007.

Herby, S, Milliron, M, Mackall, C, Fry, T. Subclinical GVHD impairs responses to dendritic cell vaccines post allogeneic transplant. Blood 106, 571a, 2005. Selected for podium presentation.

Other Accomplishments or Comments

No data available

B2B#74	"Site-Selective cAMP Analogs for Treatment of Carney Complex"
2005	

Investigators

Cho-Chung, Yoon S.	MD, PhD	NCI
Stratakis, Constantine	MD	NICHD

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#75	"Pathogenesis of and risk factors for autoimmunity in the Wiskott-Aldrich Syndrome"
2005	

Investigators

Candotti, Fabio	MD	NHGRI
Siegel, Richard	MD, PhD	NIAMS
Nikolov, Nikolay	MD	NIDCR

Protocols

No data available

Patents and Licenses

No data available

Publications

Marsilio Adriani1#, Joseph Aoki1#, Reiko Horai1, Angela M. Thornton2, Akihiro Konno1, Martha Kirby1, Stacie M. Anderson1, Richard M. Siegel3, Pamela L. Schwartzberg1* and Fabio Candotti1*Impaired in vitro regulatory T cell function associatedwith Wiskott-Aldrich syndrome. Clinical Immunology, in press

Nikolay P. Nikolov1,5, Masaki Shimizu2, Daniel Bailey5, Joseph Aoki, 3 Ted Strom4, Pamela L. Schwartzberg3, Fabio Candotti2, and Richard M. Siegel5 Systemic Autoimmunity and defective FasL secretion in Wiskott-Aldrich Syndrome Protein deficiency

Other Accomplishments or Comments

No data available

B2B#76	"Development of a Specific Drug treatment for WHIM Syndrome"
2005	

Investigators

McDermott, David	MD	NIAID
Murphy, Philip	MD	NIAID
Malech, Harry	MD	NIAID
Hwang, Sam	MD, PhD	NCI
Kawai, Toshinao	MD	NIAID

Protocols

05-I-0213 Screening and Baseline Assessment of Patients with Abnormalities of Immune Function

Patents and Licenses

No data available

Publications

Kawai T, Choi U, Whiting-Theobald NL, Linton GF, Brenner S, Sechler JM, Murphy PM, Malech HL. Enhanced function with decreased internalization of carboxy-terminus truncated CXCR4 responsible for WHIM syndrome. Exp Hematol. 2005 33:460-8.

Kawai T, Choi U, Cardwell L, DeRavin SS, Naumann N, Whiting-Theobald NL, Linton GF, Moon J, Murphy PM, Malech HL. WHIM syndrome myelokathexis reproduced in the NOD/SCID mouse xenotransplant model engrafted with healthy human stem cells transduced with C-terminus-truncated CXCR4.Blood. 2007 109:78-84.

Other Accomplishments or Comments

No data available

B2B#77	"Role of HIV-1 RNase in Developing Resistance to Nucleoside Analogs"
2005	

Investigators

Pathak, Vinay	PhD	NCI
Maldarelli, Frank	MD, PhD	NCI
Morse, Caryn	MD	CC

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#78	"Endothelial Dysfunction in HIV-associated Pulmonary Hypertension"
2005	

Investigators

Machado, Roberto	MD	NHLBI
Raghavachari, Nalini	PhD	CC
Gladwin, Mark	MD	NHLBI
Barnett, Christopher	MD, MPH	CC
Masur, Henry	MD	CC
Lederman, Robert	MD	NHLBI
McCoy, John	PhD	NHLBI
Solomon, Michael	MD	CC

Protocols

Protocol 06-H-0165 Evaluation of Endothelial and Hemodynamic Function in HIV Associated and a Phase I/II Safety and Efficacy Trial of Sildenafil in HIV Associated Pulmonary HYpertension

Patents and Licenses

No data available

Publications

Abstract to be presented at 2007 American Thoracic Society Meeting

Other Accomplishments or Comments

This protocol began enrolling in July 2006. To date, we have enrolled 16 controls and completed 7 studies.

B2B#79	"Clinical Development of E. coli Nissle 1917 as Host for a Live Anti-HIV Microbicide"
2005	

Investigators

Hamer, Dean	PhD	NCI
Sereti, Irini	MD	NIAID
Adhya, Sankar	PhD	NCI
Henry, Kenneth	PhD	NCI
Mannon, Peter	MD	NIAID

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#80	"Persistent HIV Reservoirs in Infected Patients Receiving Effective Antiviral Therapy for Prolonged Periods of Time: Delineation of the Mechanism and Source of Viral Replication and Execution of a New Therapeutic Strategy"
2005	

Investigators

Chun, Tae Wook	PhD	NIAID
Healey, Letha	MD	CC
Moir, Susan	PhD	NIAID
Kovacs, Joseph	MD	CC
Kottilil, Shyamasundaran	MD, PhD	NIAID

Protocols

Intensification of antiviral therapy in order to achieve maximal suppression of on-going viral replication in patients with undetectable plasma viremia (through University of Toronto, Canada).

Patents and Licenses

No data available

Publications

Persistence of HIV in Gut-Associated Lymphoid Tissue Despite Long-Term Antiretroviral Therapy, Chun et al. Submitted.

Other Accomplishments or Comments

No data available

B2B#81	"Identification of Biomarkers of Mitochondrial-related Drug Toxicities in HIV-infected Patients Receiving Highly Active Anti-retroviral Therapy"
2005	

Investigators

Kovacs, Joseph	MD	CC
Mican, Joann	MD	NIAID
Morse, Caryn	MD	CC
Dalakas, Marinos	MD	NINDS
Voss, Joachim	PhD, RN	CC
Fischer, Steven	MD, PhD	CC
Danner, Robert	MD	CC

Protocols

05-CC-0127: Assessing the Relationship Between Fatigue and Mitochondrial Toxicity in Patients with HIV/AIDS

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

To date this protocol has enrolled 56 patients of a targeted 75 patients. Laboratory assessment of mitochondrial dysfunction is ongoing. A mitochondrial targeted microarray chip has been validated, and the first set of clinical samples have been examined using this chip. In addition, we have developed a multiplex assay targeting mitochondrial and metabolic-related genes, and are beginning to examine clinical samples using this assay. Once the assays have been run for all samples, we will analyze the data looking for relationships between mitochondrial function and fatigue as well as mitochondrial function and use of antiretroviral therapy.

B2B#82	"Role of Cyclin D1 in Myelodysplasia"
2006	

Investigators

Young, Neal	MD	NHLBI
Sloand, Elaine	MD	NHLBI
Kurlander, Roger	MD	CC
Groopman, Jerome J.	MD	Harvard University
Blancato, Jan	PhD	Georgetown University
More, Kenneth	MD	NNMC

Protocols

A Pilot Study of ON 01919.Na in Patients with Myelodysplastic Syndrome (MDS)

Patents and Licenses

No data available

Publications

CD34 cells from patients with trisomy 8 myelodysplastic syndrome (MDS) express early apoptotic markers but avoid programmed cell death by up-regulation of antiapoptotic proteins. Blood. 2007 Mar 15;109(6):2399-405. Epub 2006 Nov 7.

Other Accomplishments or Comments

Other research accomplishments
1) We demonstrated MDS CD34 cells containing the cytogenetic abnormality trisomy 8 over express cyclin D1
2) In vitro studies of a novel investigational product ON 01910.Na, which appears to have specific activity against cyclin D1, show that it eliminates trisomy 8 leukemic cells from culture leaving the normal cells relatively unaffected.
3) Safety studies on this drug have already been accomplished and show little toxicity in humans
4) the clinical trials agreement has been delivered to the company producing the drug, Onconova so that this drug can be tested in patients with MDS who have leukemic cells in their bone marrow. This could potentially represent a new targeted therapy for a disease for which there is little treatment
5) the protocol designed to test this drug in MDS will go to the next IRB for approval

B2B#83	"Exploring the Anti-Tumor Effects of in vitro Expanded Natural Killer (NK) Cells Against Renal Cell Carcinoma Sensitized to NK-TRAIL Cytotoxicity with Bortezomib"
2006	

Investigators

Childs, Richard	MD	NHLBI
Alvarez, Gauri	DO	WRAMC
Lundqvist, Andreas	PhD	NHLBI
Read, Elizabeth	MD	CC
Suffredini, Anthony	MD	CC
Gorak, Edward	DO	WRAMC
Berg, Maria	BS	NHLBI
Srinivasan, Ramaprasad	MD	NCI

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#84	"A New Global Function for a Rare Disease Gene: Clinical Significance of the Regulation of Mitochondrial Respiration by Tumor Suppressor p53 in Li-Fraumeni Syndrome"
2006	

Investigators

Hwang, Paul	MD, PhD	NHLBI
Strong, Lousie	MD	MD Anderson Cancer Center
Arena, Ross	PhD	Medical College of Virginia
Khakoo, Aarif	MD, MBA	MD Anderson Cancer Center
Balaban, Robert	MD	NHLBI
Matoba, Satoaki	PhD	NHLBI
Sack, Michael	MD	NHLBI
Waclawiw, Myron	PhD	NHLBI
Gavrilova, Oksana	PhD	NIDDK

Protocols

Protocol Number 07-H-0030: Metabolic Regulation of Tumor Suppressor p53 in Li-Fraumeni Syndrome

2007-0114 Metabolic regulation by tumor suppressor p53 in Li-Fraumeni syndrome - pending certificate of confidentiality for approval @ MDACC

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Li-Fraumeni Syndrome family members will be referred from approximately 50 p53 germline mutation kindreds that include more than 60 living mutation carriers between the ages of 20 and 60 years currently being followed by Dr. Louise Strong at the MD Anderson Cancer Center under a preexisting clinical protocol.
We are currently awaiting final approval by the MD Anderson IRB and referral of subjects by Dr. Strong.

Candidate LFS patients have been identified for the study. No formal contacts have been made pending MDA protocol approval. All documents have been reviewed and await receipt of the NIH Certificate of confidentiality.

B2B#85	""Therapeutic Approaches for Cancer Stem Cells in Small Cell Neuroendocrine Carcinomas"
2006	

Investigators

Harris, Curtis	MD	Fred Hutchinson Cancer Research Center & Univ. of Washington
Varticovski, Lyuba	MD	NCI
Bates, Susan	MD	NCI
McKay, Ronald	PhD	NINDS
Travis, William	MD	Memorial Sloan-Kettering Cancer Center

Protocols

Clinical Protocol in planning

Patents and Licenses

No data available

Publications

Two manuscripts are in preparation:
1. Varticovski, L., Pine, S., Salcido, C., and Harris, C.C. Identification and characterization of lung cancer stem cells. Manuscript in preparation, 2007
2. Pine, S., Varticovski, L., Salcido, C., and Harris, C.C. Asymmetric division and the WNT pathway in human cancer stem cells. Manuscript in preparation, 2007

Other Accomplishments or Comments

Progress Report 2007

Bench to Bedside Proposal - Rare Diseases Category
Therapeutic approaches for Cancer Stem Cells in Small Cell Neuroendocrine Carcinomas.

Principal Investigators: Curtis Harris, MD, LHC, CCR, NCI
Associate Investigators: Phillip A. Dennis, MD, Navy Oncology, NCI
Susan Bates, MD, CCR, NCI
Lyuba Varticovski, MD, OD and LHC, CCR, NCI
Cynthia Dunbar, MD, NHLBI
Ron McKay, Ph.D., NINDS_
William D. Travis, MD, MSKCC, New York, NY

We have been highly successful in achieving several milestones for
Specific Aim I: Characterize and isolate cancer stem cells from SCC.

1) We selected a highly metastatic pulmonary small cell cancer cell line, H146, for our initial studies to establish protocols suitable for isolation of cancer stem cells. This analysis resulted in identification of SP fraction (side population of Hoechst dye uptake). The following additional antibodies were used for screening other stem cell-related surface markers and characterization of cancer stem cells:
Antibody
PE-CD24
PE-CD29
PE/FITC-CD44
PE-CD45
APC-CD56
PE-CD90
PE-CD117 (c-Kit)
PE/FITC-CD133
PE-ABCG2

PE-CXCR4
PE-EGFR
anti-nestin

2) For in vitro validation of proliferative capacity of cancer stem cells, the putative stem cell population was sorted using FACS and plated by limiting dilution or by single cell plating in 96-well format tissue culture plates. Colonies counted after 2 weeks showed that cells sorted for expression of putative stem cell markers had 2-3 fold higher proliferative capacity in long-term cultures.

3) For in vivo validation of cancer stem cells, cells sorted for expression of putative stem cell markers were implanted subcutaneously with Matrigel into SCID mice and tumor formation was followed over time. Implantation as few as 50 sorted cancer stem cells resulted in tumor formation, while 10-fold higher number of non-stem cells was required to form tumors in this mouse models.

4) One of critical issues for characterization of human samples was to obtain cancer cells from malignant pleural effusions. Largely due to a long-standing collaboration of LHC with the U of Maryland and recently established collaboration with Dr. J. Willey Professor, Department of Medicine, U. Toledo, Ohio, we were able to collect over 20 pleural effusions for analysis. We have characterized 6 of these pleural effusions from different cancer types based on the expression of drug resistance phenotype and several cell surface markers mentioned above. This work is in progress. Isolation and in vivo validation of cancer stem cells will be performed as outlined above for the H146 cell line.

5) A fundamental characteristic of cancer stem cells is the capacity for self-renewal. Based on analysis of dual label using CFCE and BRDU dyes, we determined that a small population of cancer cells retain BRDU. These cells are likely to represent a population with self-renewing capacity. We also established a protocol for visualization of asymmetric division of cancer cells using confocal microscopy.

Summary: This proposal has been highly successful in achieving most of the goals proposed in Specific Aim 1 and establishing a working platform for isolation of cancer stem cells from pulmonary neuroendocrine tumors within the first year of funding. These studies are novel and all protocols and procedures used for achieving the milestones are novel and were validated. There are two manuscripts describing cancer stem cell isolation and characterization that are a direct result of funding provided by Bed-to-Bedside award.

B2B#86	"High Density Genotyping in Diffuse Large B-cell Lymphoma (DLBCL) and Follicular Lymphoma – Translating Etiologic Clues into Prognostic Relevance Within the NCI-SEER NHL Case Control Study"
2006	

Investigators

Wang, Sophia	PhD	NCI
Chanock, Stephen	MD	NCI
Hartge, Patricia	DSc	NCI
Severson, Richard K.	PhD	Karmanos Cancer Institute and Wayne State University
Cerhan, James	MD, PhD	Mayo College of Medicine
Staudt, Louis	MD, PhD	NCI
Rothman, Nathaniel	MD, MPH	NCI
Morton, Lindsay	PhD	NCI
Wacholder, Sholom	PhD	NCI
Cozen, Wendy	DO, MPH	Univ. of Southern Calif.
Davis, Scott	PhD	NCI

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#87	"Novel Suicide Gene-Modified Donor Th2 Cells for GVHD Prevention"
2006	

Investigators

Fowler, Daniel	MD	NCI
Medin, Jeffrey	PhD	Ontario Cancer Institute and Univ. of Toronto
Read, Elizabeth	MD	CC
Lavie, Aron	PhD	University of Illinois at Chicago

Protocols

No data available

Patents and Licenses

Dr. Medin, the extramural investigator on this bench-to-bedside award, has filed a patent for the TMPK/AZT suicide gene strategy. Dr. Fowler is listed as a secondary inventor on this patent application.

Publications

"Engineered human TmpK/AZT as a novel enzyme/prodrug axis for suicide gene therapy"; this manuscript has been published in the journal, Molecular Therapy (March 20, 2007; e-pub). Bench-to-Bedside recipients Dr. Fowler and Medin are co-author and senior author, respectively. The manuscript details the development of the TMPK/AZT suicide gene strategy that forms the basis for this bench-to-bedside proposal.

Other Accomplishments or Comments

Drs. Medin and Fowler have held talks with a corporate sponsor who is interested in developing this suicide gene strategy for clinical trials. Talks are underway with the NCI Technology Transfer Section and this company to initiate a CRADA. The purpose of this CRADA is to extend our current results with the TMPK/AZT suicide gene strategy. Planned experiments include evaluated gene-modified human T cells in a xenogeneic model of GVHD. Such data will be instrumental in terms of providing further rationale for the planned clinical trial.

Update: Progress on the CRADA has been made; full sign-off should be soon if not already done. In addition, a small research contract between this company and Dr. Medin\'s Institution has also been generated to facilitate QC testing of clinical-grade vector for the planned trial.

B2B#88	"A Nutrigenomics Intervention for the Study of the Role of Dietary Sitosterol on Lipid, Glucose and Energy Metabolism"
2006	

Investigators

Celi, Francesco	MD	NIDDK
Sachdev, Vandana	MD	NHLBI
Shuldiner, Alan	MD	University of Maryland
Horenstein, Richard	MD, JD	University of Maryland
Fried, Susan	PhD	University of Maryland

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#89	"Pilot Trial of Intravenous Nitrite for Sickle Cell Vaso-Occlusive Pain Crisis"
2006	

Investigators

Gladwin, Mark	MD	NHLBI
Kato, Gregory	MD	CC
Hsu, Lewis	MD	CC
Mack, Kyle	MD	NCI
Machado, Roberto	MD	NHLBI
Shiva, Sruti	PhD	NHLBI
Taylor, James	MD	NHLBI
Wang, Xunde	MD	NHLBI
Schechter, Alan	MD	NIDDK

Protocols

The protocol for use in human subjects is still in the development phase. We expect to have this multi-center protocol ready for submission to the IRB in the summer of 2007.

Patents and Licenses

A provisional patent application by the NIH for use of nitrite as treatment for cardiovascular disease (which includes sickle cell disease) has been filed. This patent is not licensed yet and neither the inventors nor the NIH is receiving royalties at this time.

Publications

A paper is in preparation utilizing the data from the animal studies using nitrite in transgenic sickle cell mice.

Other Accomplishments or Comments

Bench work and animal work has begun in preparation for the clinical protocol. Baseline whole blood, plasma nitrite and met hemoglobin levels have been collected on 15-20 sickle cell and control subjects which provide pilot data regarding the variability and technical challenges of these measurements. Hydroxyurea was found to possibly be a significant confounder of nitirite levels.

Animal studies with transgenic sickle cell mice indicate a significant protective effect of nitrite injection. The mechanism of protection may involve the effects on hypoxic mitochondrial respiration.

B2B#90	"The effect of HIV-1 Infection on Endogenous miRNA Expression in vivo"
2006	

Investigators

Jeang, Kuan Teh	MD, PhD	NIAID
Smith, Stephen M.	MD	St. Michaels' Medical Center, NJ

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

This is a new project which is ongoing. To date, we have developed a rapid microarray assay which allows us to monitor human miRNA changes in HIV-1 infected individuals. We have stratified HIV-1 infected individuals based on viral load and CD4 cell counts. Ongoing results indicate that miRNA profiling minimally provides useful biomarker monitoring of disease progression. We are hopeful that upon further analyses, specific miRNAs can be mechanistically characterized that may causally explain different aspects of immunodeficiency.

B2B#91	"Genetic Characteristics of HIV-1 During Suppressive Antiretroviral Therapy"
2006	

Investigators

Maldarelli, Frank	MD, PhD	NCI
Persaud, Deborah	MD	Johns Hopkins School of Medicine
Coffin, John	PhD	NCI
Palmer, Sarah	PhD	NCI
Wiegand, Ann	MS	NCI
Kottilil, Shyamasundaran	MD, PhD	NIAID
Kearney, Mary	MS	NCI

Protocols

Collaborative study has not started.

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#92	**"Evaluation of Molecular Methods for the non-invasive Diagnosis of Pneumocystis and Tuberculosis and Molecular Evaluation of Non-subtype B HIV Quasispecies in the Lung"**
2006	

Investigators

Kovacs, Joseph	MD	CC
Huang, Laurence	MD	MAS, SFGH, UCSF
Fischer, Steven	MD	CC
Maldarelli, Frank	MD	NCI
Imamichi, Hiromi	PhD	NCI
Davis, J. Lucian	MD	SFGH/UCSF
Worodria, William	MBChB, MMed	Makerere University, Mulago Hospital
Yoo, Samuel	MD	Makerere University, Mulago Hospital

Protocols

Evaluation of oral wash specimens for the diagnosis of Pneumocystis pneumonia and tuberculosis in HIV-infected patients in Uganda.

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Through a collaboration with investigators at UCSF and Makerere University, we have undertaken a preliminary evaluation of the utility of oral wash combined with PCR for the diagnosis of both Pneumocystis pneumonia and tuberculosis in HIV-infected patients in Uganda. In a preliminary evaluation of ~100 patient samples, we found very few samples that were positive for Pneumocystis, but a high proportion that were positive for tuberculosis. This demonstrated that detection of tuberculosis in oral wash samples was feasible. Based on these data, we are in the process of collecting ~150 sputum or BAL samples from patients with suspected tuberculosis together with matched oral washes. The sputum and BAL samples will be processed using conventional techniques (culture, AFB staining) and will serve as the gold standard for diagnosis. Results will be compared to PCR results of oral wash samples. To date we have obtained ~100 such paired samples and are in the process of evaluating them as noted above.

B2B#93	**"Microalbuminuria and Podocyturia in Patients with HIV disease: Detection, Characterization, and Therapy"**
2006	

Investigators

Kopp, Jeffrey	MD	NIDDK
McBryde, Kevin	MD	Children's National Medical Center

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#94	"Hemolysis, HIV/AIDS and Parasitic Infections Associated Secondary Pulmonary Arterial Hypertension in Sickle Cell Diseases"
2006	

Investigators

Gladwin, Mark	MD	NHLBI
Aliyu, Zakari Y.	MD	NHLBI
Rodgers, Griffin	MD	NIDDK
Taylor, James	MD	NHLBI
Kato, Gregory	MD	CC
Machado, Roberto	MD	NHLBI

Protocols

06-H-N189: Prevalence of Secondary Pulmonary Hypertension (PAH) in Patients with Sickle Cell Disease in Nigeria and the Role of HIV/AIDS and Endemic Parasitic Infections in the Natural History of Pulmonary Hypertension in Sickle Cell Disease

Patents and Licenses

No data available

Publications

None to date.

Other Accomplishments or Comments

The protocol was approved by the NHLBI IRB on 6/13/06. Dr. Aliyu has traveled to Nigeria several times and has enrolled 308 subjects (181 sickle cell patients and 127 controls). Echocardiocraphy and blood samples have been collected on 300 subjects and are being analyzed. Dr. Aliyu will return to Nigeria in June 2007 to enroll and collect samples on another 300 subjects.

B2B#95	"Novel Bench-to-Bedside Research Methods for Drug Addiction: Development, Validation and Application"
2006	

Investigators

Peoples, Laura L.	PhD	University of Pennsylvania
Stein, Elliot	PhD	NIDA
Childress, Anna	PhD	NIDA

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

Novel animal neuro-imaging procedures and protocols were developed by the laboratory of Dr. Elliot Stein at NIDA IRB. My lab [at the University of Pennsylvania] additionally modified the instrumentation and surgical procedures we use to carry out intravenous cocaine self-administration sessions so that the animals can be placed in the neuro-imaging equipment. We have also developed procedures that are new for our laboratory and that are required to complete the proposed experiments. For example, we have established odorant discrimination in rats. Animals are trained to associate one odor with availability of drug and another with the non-availability of the drug. We developed this procedure because we have proposed to characterize the neuronal response to drug-paired cues in the imaging studies and odors are the only cues that we can feasibly present to animals during the imaging. Technical development in my lab atht of Dr. Stein is sufficient that we are now running our first set of animals through the proposed research protocols.

My [extramural] laboratory plans to write an R01 application in 2008. Data collected in the context of the bench-to-bedside project will be used as the preliminary data for that application. The plan is to use the R01 funds to continue the novel work that Dr. Stein and I have initiated

B2B#96 2006	**"Breast Cancer among African American Women: The role of Missense Changes in the BRCA1 and BRCA2 Breast Cancer Susceptibility Genes Using a Population-Based Approach"**

Investigators

Ostrander, Elaine	PhD	NHGRI
Malone, Kathleen	PhD	Fred Hutchinson Cancer Research Center, Seattle

Protocols

No data available

Patents and Licenses

No data available

Publications

Malone K.E., Daling J.R., Doody D.R., Hsu L., Bernstein L., Coates R.J, Marchbanks P.A., Simon M.S., Mcdonald J.A. Norman, S.A. Strom, B.L., Burkman R.T., Ursin G., Deapen D., Weiss L.K. Folger S.F., Madeoy J.J. Friedrichsen D.F., Suter N.M., Humphrey M.C. Spirtas R., Ostrander E.A. (2006). Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. Cancer Research 66: 8297-308.

Trabert B., Malone K.E., Daling J.R., Doody D.R., Bernstein L., Marchbanks P.A., Strom B.L., Ursin G., Langlois M., and Elaine A. Ostrander. Vitamin D receptor polymorphisms and breast cancer risk in a large population-based case control study

Malone KE, Doody DR, Hsu L, Ostrander EA. Re: How reliable are BRCA1/BRCA2 mutation estimates? Cancer Research, 2007 (in press).

Other Accomplishments or Comments

Studies are ongoing to develop the yeast in vitro system to test 13 missense changes found in the BRCT domain of BRCA1 in African American women. This represents a novel effort. We are developing an inducible yeast BRCA1 construct and will be testing it in a variety of yeast strains that show sensitivity to DNA damage. We will then introduce the missense changes into individual constructs and test each. If this works it will prove to be a useful tool for other labs interested in investigating BRCA1 and BRC2 mutations. We have also interrogated the African American women in our cohort for variants in the vitamin D receptor and have a paper ready to submit on that work. This work profiles the variants and exposures that place African American women at increased risk for breast cancer, and are distinct from those observed in Caucasian women.

All missense changes observed in the 696 African-American women in CARE have been examined with a series of web-based computational tools that predict which variants are likely to be disease-associated. A thorough review was first done to identify programs that are validated and that vary in classification methodology, drawing from variant properties such as sequence homology and protein structure/ conservation. Align-GVGD, SIFT (Sorting Intolerant From Tolerant), PolyPhen (polymorphism phenotyping), nsSNPAnalyzer, and PMUT were used to characterize each variant. Similarities and differences between functionality prediction output will guide our characterization of the functional and clinical significance of each missense change. We have also incorporated data from the Breast Cancer Information Core (BIC), missense position within functional motifs, as well as haplotype assignment for variants mapped in the literature. Currently, we are examining co-occurrence with known deleterious mutations and haplotype structure within our dataset.

B2B#97	"Melanocortin 3 receptor Mutations as an Etiology for Obesity in African American and Caucasian children"
2006	

Investigators

Yanovski, Jack	MD, PhD	NICHD
Schoeller, Dale	PhD	University of Wisconsin
Gavrilova, Oksana	PhD	NIDDK
Ning, Cong	MD, PhD	NICHD
Koo, Ja Shin	PhD	NICHD
Westphal, Heinrich	MD	NICHD

Protocols

Amendment to protocol 96-CH-0101 to study 300 additional subjects

Patents and Licenses

No data available

Publications

Tanofsky-Kraff M, Haynos AF, Kotler LA, Yanovski SZ, Yanovski JA. Laboratory-Based Studies of Eating during Meals among Children and Adolescents. Curr. Nutr. Food Sci. 3, 55-74, 2007

Ning C, Fleisch A, Feng N, Theim KR, Mirch MC, Adler-Wailes D, Jan J, Roberts M, Yanovski JA. Thr6Lys and Val81Ile Missense Mutations of the Melanocortin-3-Receptor Gene are Associated with Increased Trunk Fat Mass in Children. Endocrine Soc., 2006

Other Accomplishments or Comments

Transgenic mouse project has first 4 pups for knock-in of wild type MC3R.

B2B#98 2006	"Vitamin E Pharmacokinetics and Oxidative Biomarkers in Normal and Obese Women"

Investigators

Levine, Mark	MD	NIDDK
Traber, Maret	PhD	Oregon State University

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

The project "Vitamin E Pharmacokinetics and Biomarkers In Normal And Obese Women" by Mark Levine, MD, PhD (NIDDK) and Maret G. Traber, PhD was submitted for NIH Scientific Review in December 2006. The reviewers' comments have been addressed, the protocol and consent forms are being written and are expected to be submitted for review by mid-June 2007.

The 30 page clinical protocol details α-tocopherol turnover studies that are planned, including the main trial where dual stable-isotope labeled (deuterium) α-tocopherols are administered orally and intravenously to healthy lean and obese women. Because ascorbic acid (vitamin C) concentrations may alter α-tocopherol pharmacokinetics, subjects will be studied first at low and then high steady state vitamin C concentrations. Before this main study is initiated, two preliminary trials will be performed. In preliminary trial 1, fat content for optimal absorption will be assessed because fat-content of a meal may alter vitamin E absorption. The fat content will be varied from 0 - 40% of calories in the breakfast meal. Carbohydrate and fat will vary, and protein will remain constant. Remaining meals during test days will not be restricted in fat. A single vitamin E dose of 30 mg will be given orally and intravenously. In preliminary trial 2, optimal fat content from preliminary trial 1 will be used, and the vitamin E dose will be varied. Vitamin E dose amount could non-specifically alter vitamin E kinetics. We will therefore determine the largest dose (2-30 mg) that does not non-specifically increase vitamin E turnover, with fat held constant.

Deuterated (d6)-alpha tocopherol has been synthesized and its purity assessed and found acceptable for preparation of the intravenous vitamin E dose. Scheduling of the synthesis of the lipid emulsion containing this deuterated vitamin E for the IV dose has been set for July 2007.

The use of the new biomarker, ascorbyl HNE, a putative adduct between vitamin C and a lipid oxidation end-product, has been under intense investigation in collaboration with Dr. F. Stevens, OSU. Currently, it appears that the adduct is not present in human plasma; previous reports have not been confirmed. Currently, we are continuing to assess other potential biomarkers for our human study.

We have also investigated a new biomarker, a urinary F2-isoprostane metabolite, 2,3-dinor,5,6-dihydro15-F2t-IsoP (F2t-IsoP M), a ß-oxidation product of F2-isoprostanes. We hypothesize that both the urinary and plasma F2t-IsoP M concentrations may be excellent biomarkers of oxidative stress related specifically to vitamin E status. We are currently developing assays of these biomarker to test this hypothesis. Available data suggests that the metabolite is at 10-fold higher concentrations in the urine than is the parent compound, with less variability, so that statistically significant differences are detectable between smokers and non-smokers for the metabolite, but not the parent compound. (Abstract to be presented: 55th ASMS Conference on Mass Spectrometry, entitlted "Quantitation of Human Urinary F2-Isoprostanes and their Metabolites by Mixed-Mode SPE and HPLC-MS-MS; AW Taylor, RS Bruno, MG Traber).

B2B#99	"Immunosuppression Minimization by Biological Response Monitoring"
2006	

Investigators

Kirk, Allan	MD	NIDDK
Light, Jimmy	MD	Washington Hospital Center

Protocols

No data available

Patents and Licenses

No data available

Publications

No data available

Other Accomplishments or Comments

No data available

B2B#100 2006	**"A Preliminary Assessment of the use of Ocular Coherence Tomography and Magnetic Resonance Imaging as Outcome Measures for Studying the Optic Nerve in Studies of Neuroprotection in Multiple Sclerosis" project to evaluate**	
Investigators		
McFarland, Henry	MD	NINDS
Nussenblatt, Robert	MD	NEI
Calabresi, Peter	MD	Johns Hopkins School of Medicine
Balcer, Laura J.	MD	University of Pennsylvania
Protocols		
No data available		
Patents and Licenses		
No data available		
Publications		
No data available		
Other Accomplishments or Comments		
No data available		

Journals publishing Bench-to-Bedside reports

Am J Hum Genet 77:999-1010, 2005
Am J Med Genet A. 2006 Sep 25; [Epub ahead of print]
Am. J. Resp. Crit. Care Med. 159: 1368-1376, 1999.
Amer J Med Genet 132A: 278-282
American Journal of Respiratory and Critical Care Medicine. 169(7): A155, 2004
Anesthesiology 103:1052-1059, 2005
Annals of Neurology 2004;55:654-659
Biology of Blood and Marrow Transplantation, 13, 292a, 2007.
Blood 100:72-79, 2002.
Blood 104:120a, 2004
Blood 104:810, 2004
Blood 105:1992-99, 2005
Blood 106, 571a, 2005. Selected for podium presentation
Blood 107:3892-3901, 2006
Blood 2004;104:1217-1223
Blood 2004;104:3412-3
Blood 2005;105:420-5.
Blood Cells Mol. Dis. 27:971-7, 2001
Blood In press
Blood, 2005 Feb 1;105(3):1010-5. Epub 2004 Sep 21.
Blood. 2006 107:3091-7
Blood. 2006 Feb 15;107(4):1680-7
Blood. 2007 109:78-84
Blood. 2007 Mar 15;109(6):2399-405. Epub 2006 Nov 7.
Blood. 2007 Mar 19; [Epub ahead of print]
Brain 2004;127:1182-1190.
Cancer Gene Therapy 9, 1001-1012; Dec. 2002.
Cancer Research 59, 5875-5877, 12/1/99
Cancer Research 61, 8751-8757; Dec. 15, 2001
Cancer Research 63:8984-8995, 2003
Cancer Research 65, 9991-999; Nov. 2005.
Cancer Research 66: 8297-308
Cancer Research, 2007 (in press).
Circulation 112: II-219, 2005.
Clin Cancer Res. 2005 Dec 15;11(24 Pt 1):8799-807
Clinical Genetics (in press), 3/2007
Clinical Immunology, in press
Curr. Nutr. Food Sci. 3, 55-74, 2007
Cytotherapy. 2002;4: 395-406
Development 130: 4539-4552, 2003
Exp Hematol. 2004 32:709-19, 2004
Exp Hematol. 2005 33:460-8
Free Radic Biol Med. 41: 339-346, 2006
Gene Therapy, 11: 1425-26, 2004
Genetics in Medicine, 4 (30), p. 117, 2002.
Glycobiology. 2005 Nov;15(11):1102-10. Epub 2005 Jun 29.
Hum Mol Genet. 12: 1631-1641, 2003
Hum. Mol. Genet. 15: 839-851, 2006

Appendix C: Journals publishing Bench-to-Bedside reports

Human Gene Therapy 10:1251-1257, 1999
Human Gene Therapy 16, 435-444; April 2005
Human Gene Therapy 17, 31-45; Jan 2006
Human Gene Therapy 2004;15:351-360.
Int J Cancer, 105: 210-216, 2003
Int. J. Rad. Oncol. Biol. Phys. 63:1400-1412, 2005.
Invest. Ophthalmol. Vis. Sci. 45: E-Abstract 5141
Investigative Opthamology 41: 3402-3409, 2000
Investigative Opthamology and Visual Science, 2002 Mar;43(3):679-85
J Allergy Clin Immunol. 2006 117:865-9.
J Assoc Genet Technol. 2005;31(4):163-7. PMID: 16354942 [PubMed]
J Autism Dev Disord. 2006 Mar 29; [Epub ahead of print] PMID: 16570214
J Chromatography B 780: 245-247, 2002
J Chromatography B 823:184-188, 2005.
J Clin Invest. 115:2139-2148, 2005
J Exp Med. 194:12, 1731-1741, 2001
J Immunol 166: 5817-5825, 2001
J Immunol 168: 338-347, 2002
J Leukocyte Biol. 2004;76:1214-9
J Neuroimmunol 2003;141:125-131
J Neurosurg. 102:522-525, 2005.
J Transl Med. 2005 Apr 14;3(1):15
J. Acquired Immunodeficiency 43 (No. 3): 304-312
J. Clin. Endo. Metab., in press
J. Clinical Investigation. 113:1344-1352, 2004 (note: credit in acknowledgement to bench-to-bedside program)
J. Immunol, 173: 5863-5871, 2004
J. Neurotoxicology 24:895-908, 2003
J. Virol. 80:2092-2099, 2006
Jour Surg Oncol, 94(7):555-564, 2006
Journal of Clinical Investigation 115:1888-1895, 2005
Journal of Neurochemistry 98: 860-875, 2006
Journal of Neuroscience Research In Press, 2007
Journal of Neuroscience, 25:7840-7846, 2005
Journal of Virology, in press
Jpn J Infect Dis. 2004 57:S27-8.
Kidney International 60: 2118-2128
Leukemia. 2005;19:69-76.
Methods in Enzymology 2004;386:275-299
Mol Genet Metab. 85: 96-107, 2005
Mol Ther. 2006 14:202-11
Mol Ther. 2006 14:202-11
Molec Brain Res 90:17-25, 2001
Molecular Genetics and Metabolism 2004; 81: 196-202.
Molecular Imaging 2004;3:24-33
Molecular Therapy (March 20, 2007; e-pub)
Molecular Therapy 3:565-573, 2001
Molecular Therapy 9:389-395, 2004
Nat Rev Genet. 2006 Dec;7(12):940-52. Review.PMID: 17139325
Nature Biotechnology 18:176-180, 2000
Nature Med. 6:1147
Nature Medicine 7: 478-484

Appendix C: Journals publishing Bench-to-Bedside reports

Nature Neuroscience, 8:991-993, 2005. (NIH PRESS RELEASE: http://www.nih.gov/news/pr/jul2005/nimh-10.htm)
Nature Reviews Neuroscience, 7:38-393, 2006
NEJM, 2004; 350:886-895.
NEJM; 348: 593-600; 2003**In this NEJM article, the authors write in the concluding acknowledgments "This work was funded by the NIH Bench to Bedside Award Program"
Neurology 50: 485-491, 1998
Neuron, 43:623-631, 2004. see accompanying commentary entitled "Fulfilling the Promise of the Cognitive Neurosciences" (NIH PRESS RELEASE: http://www.nih.gov/news/pr/sep2004/nimh-01.htm)
NMR in Biomedicine 2005;18:383-389
NMR in Biomedicine 2005;18:383-9
Pain 104:219-228, 2003
Pediatr Neurol. 2006 May;34(5):337-50. PMID: 16647992 (TOP 10 papers downloaded on the web in 2006.)
PLoS Biology. 2004 Dec;2(12):e423. Epub 2004 Nov 23
Proc Natl Acad Sci U S A. 2007 Mar 14; [Epub ahead of print] PMID: 17360355
Radiology 2003;228:480-487
Radiology 2003;229:838-846
Radiology In Press
Stem Cells 18:155-156, 2000
Stem Cells 2006:24:671-78
Steroids. 68: 497-502, 2003
Toxicol. Pathol. 30:254-252, 2002
Trends Mol Med 10: 585-590, 2004
Vaccine, 23: 2591-2601, 2005