Overview of NCI-Frederick support to NIAID

H. Clifford Lane, MD
Deputy Director for Clinical Research and Special Projects
National Institute of Allergy and Infectious Diseases
January 25, 2012
<table>
<thead>
<tr>
<th>IC</th>
<th>FY 2011 Enacted</th>
<th>FY 2012 Enacted</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>$5,058,577</td>
<td>$5,072,183</td>
<td>0.3%</td>
</tr>
<tr>
<td>NIAID</td>
<td>4,478,668</td>
<td>4,490,711</td>
<td>0.3%</td>
</tr>
<tr>
<td>NHLBI</td>
<td>3,069,723</td>
<td>3,079,021</td>
<td>0.3%</td>
</tr>
<tr>
<td>NHGRI</td>
<td>511,497</td>
<td>512,873</td>
<td>0.3%</td>
</tr>
<tr>
<td>NCRR</td>
<td>1,257,754</td>
<td>-</td>
<td>-100.0</td>
</tr>
<tr>
<td>NCATS</td>
<td>-</td>
<td>575,366</td>
<td>-</td>
</tr>
<tr>
<td>NIGMS</td>
<td>2,033,782</td>
<td>2,430,036</td>
<td>19.5%</td>
</tr>
<tr>
<td>Other ICs</td>
<td>12,913,127</td>
<td>13,037,334</td>
<td>1.0%</td>
</tr>
<tr>
<td>Subtotal</td>
<td>$29,323,128</td>
<td>$29,197,524</td>
<td>-0.4%</td>
</tr>
<tr>
<td>OD</td>
<td>1,166,963</td>
<td>1,459,117</td>
<td>25.0%</td>
</tr>
<tr>
<td>B &amp; F</td>
<td>49,900</td>
<td>125,344</td>
<td>151.2%</td>
</tr>
<tr>
<td>Total</td>
<td>$30,539,991</td>
<td>$30,781,985</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

FY 2011 excludes the $297.3M passed through to the Global Fund to allow comparison with FY 2012.
NIAID Research: A Dual Mandate

Maintain and “grow” a robust basic and applied research portfolio in microbiology, infectious diseases, immunology and immune-mediated diseases

Respond rapidly to new and emerging disease threats

New/Improved Interventions
Detrick labs to house gene manipulation work

By ROLLIE ATKINSON  
Staff Writer

Once a tiny airfield in the 1930s, and then the home of the U.S. Army Chemical Corps' massive effort into biological warfare research from 1945-1952, Frederick's Fort Detrick is now destined to become the home of the nation's major containment laboratory for genetic manipulation research.

In between, the complex of highly specialized scientific research facilities has been used for basic cancer research and continuing investigations into infectious diseases and development of new medical protection for the nation's armed forces. It remains the home of the Frederick Cancer Research Center and the U.S. Army Medical Research Institute of Infectious Diseases.

Friday, officials of the National Institutes of Health (NIH) announced the launching of controversial recombinant DNA experiments at Fort Detrick in recovred germ warfare labs.

The international scientific community continues to express interest in Fort Detrick—the home of the first attempts in biocontainment procedures and the testing ground for much of today's knowledge into biosafety and work with hazardous organisms and substances.

When NASA sought expertise in developing a containment facility to receive and study its "moon rocks"—it borrowed designs and practices developed through the years of Detrick's experience with germ warfare.

The national Communicable Disease Center in Atlanta, Ga., also looked to Fort Detrick's experience and personnel in derailing new laboratories to contain studies with dangerous disease organisms.

And, when NIH sought a location for elaborate and expensive maximum containment facilities they logically turned again to Fort Detrick, with its former germ warfare labs standing idle.

Now, with $250,000 worth of renovation and new equipment, Frederick will gain new notoriety as the home of the nation's major effort into controversial gene-splicing experiments.

That notoriety may not always be positive.

Friday, for the first time since Vietnam War days, protesters bearing placards reading "Who should play God?" and "Do the ends always justify the means?" stood vigil at Fort Detrick outside a large press briefing near build-

(Continued On Page A-6)

Are DNA hazards underrated?

By ROLLIE ATKINSON  
Staff Writer

Dr. Malcolm Martin, who will direct the risk assessment experiments here into recombinant DNA techniques, believes, as many other scientists now do, that the precautionary measures, public controversy and elaboration and expensive safety facilities of gene-splicing may all be "exaggerated."

"But there was a time, a short three years ago, when many scientists like Dr. Martin issued public warnings on the potential hazards of recombinant DNA work.

A group of prominent scientists led a successful move to ban certain recombinant DNA tests with known pathogens and human institutions, and instigated the formation of the National Institutes of Health (NIH) safety guidelines on the research.

Now, however, some of those same scientists regret sounding the alarm which also created widespread public protest and debate, such as a large demonstration by local people Friday at Fort Detrick.

"You will never be able to answer all the possible risk scenarios involved in recombinant work," Dr. Martin admit-

Scientists and pickets

Members of the international press filled a meeting room at Fort Detrick Friday morning to hear presentations on the recombinant DNA experiments to be conducted there. Shown here speaking before still and television cameras is Dr. Bernard Talbot, special assistant for Intramural Affairs. While the meeting progressed smoothly indoors, demonstrators from the People's Business Committee and Western Maryland Clergy and Laity Concerned remained present but peaceful outside. For more photos see page A-8. (Photos by C. Kurt Hailer)
NIAID / NCI Frederick Timeline

- 1978 – Recombinant DNA experiments in Bldg. 550
- 1985 – Immunologic monitoring of patients with AIDS in Bldg. 560; later moved to Bldg. 469
- 1986 – Mike Baseler hired
- 1994 – Virologic monitoring of patients with AIDS in Bldg. 550
- 2005 – Vaccine Pilot Plant
Support Provided by NCI-Frederick to NIAID

- Clinical Research Infrastructure
- Support to “Special Projects”
Clinical Research Infrastructure Support Provided by NCI-Frederick

- MDs, Nurses, Pharmacists
- Protocol Development
- IND Management
- Clinical Research Monitoring

- Laboratory Support
  - Monitoring
  - Biomarker analysis
  - Repository
  - Biopharmaceuticals
  - Vaccine Production
  - Education
Clinical Research Infrastructure Support Provided by NCI-Frederick

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  - Biopharmaceuticals
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- Education
Barriers to Clinical Research Project (2007)

- Identify key policies, practices, Regulations, and legislation governing NIH-sponsored human subject clinical research that limit the effectiveness and efficiency of clinical research
- Make recommendations to facilitate and improve effectiveness and efficiency of clinical research
Initial Targeted Barriers-Based on Frequency and Ranking

- Scientific Review / Approval Protocols
- Interaction – Industry / Tech Transfer
- Bio-Safety Committee Review
- IRB & Ethical Issues
- Site Registration / Approval
- Informed Consent & Documentation
- Conflict Of Interest
- Adequacy Of Resources
- Conflicts – U.S. / Local Requirements
- Adverse Event reporting
- FDA / OHRP Interactions
- Protocol Monitoring & Compliance
- Management Of Samples
- Research-related Injury
- Work In International Settings
- Collaborations
Identified that Clinical Research Support Services were inadequate to meet the increasingly complex demands of clinical research.

In response to this need, NIAID moved forward to develop a Protocol Navigation/Protocol Development Program.
The Protocol Navigator Interface

Scientific Review

APPROVED
CONCEPT

• Hypothesis,
• Endpoints,
• Design
• Statistics

NIH
NIAID
RCHSPB

Office of Ethics
IRB Office
Medical Writers
IND
Safety Office/DSMB
Site Establishment/Monitoring
CRF Production
ORS
OHSRP

PROTOCOL NAVIGATORS

Clinical Protocol
Factors Leading to Choice of NCI-Frederick for a Given Task

- Need for an ongoing, close working relationship
- Recurrent similar tasks, minimize need for training new staff
- Rapid response
- Complement other awards
NCI-Frederick Support to NIAID Clinical Research and Special Projects

NIAID DCR Leadership
Dr. C. Lane / Ms. L. McNay / Ms. J. Metcalf

SAIC-F Leadership
Dr. M. Baseler / Ms. B. Baseler

Laboratory Operations

Applied/Developmental Research Directorate
Dr. C. Lane / Ms. J. Metcalf

Dr. M. Baseler

- Dr. A. Fauci / Dr. C. Lane
  - AIDS Monitoring
    - Dr. M. Baseler
  - Virus Isolation & Serology
    - Dr. R. Dewar
  - Lab of Human Retrovirology
    - Dr. T. Imamichi
  - Lab of Molecular Cell Biology
    - Dr. V. Natarajan
  - Lab of Immunopathogenesis and Bioinformatics
    - Dr. R. Lempicki

- Dr. J. Gallin / Dr. H. Malech / Dr. S. Holland
  - Neutrophil Monitoring
    - Dr. D. Kuhns

- Dr. W. Strober / Dr. J. Cohen
  - Immunological Monitoring
    - Dr. R. Hornung

Clinical Research Support

Clinical Monitoring Research Program
Dr. C. Lane / Ms. L. McNay

Ms. B. Baseler

- Regulatory Program Support
  - Dr. J. Pierson
    - Ms. B. Baseler

- Operational Support
  - Ms. L. McNay
    - Ms. B. Baseler

Support to NIAID Clinics
Dr. R. Davey / Ms. R. Eckes

- Dr. J. Powers
  - Ms. T. Foltz

Support to Special Projects
Ms. L. McNay / Dr. C. Lane

- Ms. B. Baseler
Clinical Research Infrastructure Support Provided by NCI-Frederick

- MDs, Nurses, Pharmacists
- Protocol Development
- IND Management
- Clinical Research Monitoring
- Laboratory Support
  - Monitoring
  - Biomarker analysis
  - Repository
  - Biopharmaceuticals
  - Vaccine Production
  - Education
Development of IL-15 as a Potential Treatment for HIV/AIDS

- Common gamma-chain using cytokine with potent effects on CD8+ T cells
- Studied by Tom Waldmann for many years but no commercial development
- Working together with Tom and NCI-Frederick, clinical grade IL-15 has been produced and is in clinical trials
100-Fold Increase in Effector CD8+ T Cells in Non-Human Primates Treated with a 10-Day Continuous IV Infusion of IL-15
Support Provided by NCI-Frederick to NIAID

- Clinical Research Infrastructure
- Support to “Special Projects”
Characteristics of NIAID Special Projects

- Identified by NIAID Director
  - High priority
  - Urgent and compelling
  - No other mechanism could easily meet the need
  - Often involve other governments
Current Special Projects in NIAID

- Influenza
  - Observational cohort studies
  - Interventional studies
- Project Phidisa (US-South Africa)
- DC Partnership for HIV/AIDS
- US DoD ID Clinical Research Program
One Never Knows Where the Next Influenza Pandemic Will Arise
INSIGHT- Observational Cohort Study FLU 002

Cumulative enrollment over time by geographic region.
## D-dimer and Risk of Bad Outcome in FLU 002 and FLU 003

<table>
<thead>
<tr>
<th>D-dimer Tertile*</th>
<th>FLU 002</th>
<th>FLU 003 General Ward</th>
<th>FLU 003 ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (lowest)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.9 (0.6-6.1)</td>
<td>3.3 (0.8-12.9)</td>
<td>4.9 (0.9-25.7)</td>
</tr>
<tr>
<td>3 (highest)</td>
<td>4.2 (1.3-13.8)</td>
<td>6.8 (1.9-24.9)</td>
<td>22.0 (3.1-157.3)</td>
</tr>
</tbody>
</table>

*Univariate model; tertiles computed separately for each cohort
Special Project: La Red - Mexico

Signing of the Letter of Intent with the Mexico Minister of Health
2009
LOI between NIAID and MoH of Mexico in 2009
5 clinical sites in Mexico City
Observational Study of Influenza-like illness in Mexico
Influenza Combination Therapy Trial
n=1,776
Special Project: Phidisa


- Goals
  - Provide treatment to HIV-positive SANDF members and their dependents in the context of clinical research
  - Answer research questions relevant to S. Africa
  - Build research capacity within the South African Military Health Service (SAMHS)

- Over 6000 volunteers enrolled as of December, 2011
Signing of Formal Agreements between US and RSA by US Embassy and South African Officials

Amb. Frasier and Minister Lakota
April 26, 2005

DCM La Lime and MG Motumi
October 5, 2010
Comparison of Outcomes in Untreated vs. Treated Pts.

K–M Estimates of Mortality Rates Over Follow-up by CD4; p<0.0001

At Risk: 142 77 52 34 31 22 16
At Risk: 77 46 37 25 23 20 13
At Risk: 122 72 52 42 35 29 24
At Risk: 476 440 414 363 339 307 246

CD4 <25
CD4 25-49
CD4 50-99
CD4 100-199

Months from Randomization

At Risk: 140 119 98 84 72 51
At Risk: 201 161 136 112 97 89 75
At Risk: 118 106 95 85 75 67 54
At Risk: 196 182 166 151 136 119 93
The mission of DC PFAP Sub specialty Clinics is to reduce the burden of HIV in DC by developing an innovative community-based clinical research program that will inform health care strategies and impact the AIDS epidemic and create a model for other urban areas and globally.
NIAID Review of Projects Supported by NCI-Frederick

- Board of Scientific Counselors for Projects led by Intramural Investigators

- For Special Projects there are Two Levels of Review
  - NIAID Research Initiative Committee
  - Project-Specific External Scientific Advisory Committees
Summary

- NCI-Frederick is a critical component of the NIAID clinical research effort
- This is especially true for the support of intramural investigators and “Special Projects”
- Consistency, flexibility and rapid response time are key factors in choosing NCI-Frederick for select activities within the NIAID portfolio