# Transformational Medical Technologies Initiative (TMTI)

## OUSD (AT&L)
## FY 2007

# Report Documentation Page

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| **2007** | **N/A** | **-** |

| 4. TITLE AND SUBTITLE | 5a. CONTRACT NUMBER |
|---|---|
| **Transformational Medical Technologies Initiative (TMTI)** | 5b. GRANT NUMBER |
| | 5c. PROGRAM ELEMENT NUMBER |
| 6. AUTHOR(S) | 5d. PROJECT NUMBER |
| | 5e. TASK NUMBER |
| | 5f. WORK UNIT NUMBER |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br>**Under Secretary of Defense for Acquisition, Technology and Logistics and the Assistant to the Secretary of Defense for Nuclear and Chemical Biological Defense Programs Washington, DC** | 8. PERFORMING ORGANIZATION REPORT NUMBER |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | 10. SPONSOR/MONITOR'S ACRONYM(S) |
| | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) |

12. DISTRIBUTION/AVAILABILITY STATEMENT
**Approved for public release, distribution unlimited**

13. SUPPLEMENTARY NOTES
**The original document contains color images.**

14. ABSTRACT

15. SUBJECT TERMS

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | |
| **unclassified** | **unclassified** | **unclassified** | **SAR** | **21** | |

# Preface

It is our responsibility to provide our warfighters the best capability and support in the world. America remains a nation at war. The Armed Forces of the United States are engaged in a global war on terror while simultaneously deterring further attacks on Americans here at home. In doing so, our military faces many challenges, but one in particular—the threat posed by weapons of mass destruction (WMD)—is among our greatest challenges.

The Department of Defense is pursuing a comprehensive strategy to counter this threat. To effectively execute this Program, the Department is depending in part upon continued Congressional support for stable funding for the Transformational Medical Technologies Initiative (TMTI) to fully exploit the advanced science and technology innovation necessary to successfully counter future genetically engineered biological weapons.

TMTI represents a new way of doing business. Best practices from both successful Department of Defense programs as well as the hard won lessons from the pharmaceutical industry are benchmarks for TMTI success. Through this approach, the TMTI program will accelerate the discovery and development of broad-spectrum medical countermeasures that will benefit the warfighter and ultimately the nation.

## Table of Contents

**Transformational Medical Technologies Initiative (TMTI)**
**Fiscal Year 2007 (FY 2007) Congressional Report**

## I. PURPOSE

This report responds to the tasks identified by the SAC-D Report No. 109-292. First, it highlights the reporting requirement. Second, it provides background information on the TMTI program. Third, it includes our reporting requirement response to the three specified Senate Appropriations Committee-Defense questions. Finally, it provides a summary.

## II. REPORTING REQUIREMENT

Senate Appropriations Committee-Defense (SAC-D) Committee Report No. 109-292 (Page 215) to Accompany H.R. 5631, Department of Defense (DoD) Appropriations Bill, 2007:

> *The Committee directs the Special Assistant for Chemical and Biological Defense to provide the congressional defense committees with the budget submission for fiscal year 2008, a list of programs funded under TMTI in fiscal years 2006 and 2007, performance metrics and benchmarks, and the results of the programs' quarterly reviews.*

## III. BACKGROUND

The mission of TMTI is to protect the warfighter from conventional or genetically engineered biological threats, known or emerging, by accelerating the seamless discovery and development of broad-spectrum medical countermeasures through the use of novel technology platforms and innovative management approaches. The TMTI program implements one of the key decisions in the *Quadrennial Defense Review (QDR) 2006*: develop broad-spectrum medical countermeasures against advanced bio-terror threats, including genetically engineered, intracellular bacterial pathogens and hemorrhagic fevers. Technological advances in genetic manipulation, biotechnology and advanced biochemistry increase the possibility that future state or non-state adversaries could develop and deploy new genetically engineered biological threats for which current countermeasures would be ineffective and the time needed to develop defense would be insufficient. The QDR 2006 directed that the DoD invest $1.5 billion over the next five years to resolve the challenge of emerging and bioengineered threats.

Traditional approaches to developing medical biodefense countermeasures have focused on developing medical biodefense countermeasures targeted against specific disease-causing pathogens and their effects, effectively implementing a single solution to each threat (i.e. "one bug: one drug"). TMTI aims to develop countermeasures that are truly "broad-spectrum" and effective against a range of pathogens. Some of these countermeasures will be developed by targeting pathogen pathways or mechanisms of action, while others will enhance the host innate immune response.

### A. TMTI Goals

A deliverable expected from many of the TMTI performers is the submission of an Investigational New Drug (IND) application. The most promising products will continue through the development process towards Food and Drug Administration (FDA) licensure

(potentially with industry partners) to meet warfighter requirements. Maturity of the most promising products and/or enabling technologies for each portfolio will determine the investments made in Advanced Development (AD).

The goals of TMTI are as follows:

1. Within five years develop two (or more) platform technologies that can be used to identify unknown pathogens and rapidly develop countermeasures to newly identified threats.
2. Within five years identify the genetic sequences for all pertinent threat agents against which to screen, characterize and identify potential biodefense threats.
3. Within five years develop and submit two (or more) IND broad spectrum countermeasures.
   a) One product will be active against viruses (especially hemorrhagic fever viruses).
   b) One product will be active against intracellular pathogens.

## B. Project Thrust Areas

The *Chemical and Biological Defense Program Medical Research and Development, Testing & Evaluation (RDT&E) Plan* was approved for execution by the Deputy Secretary of Defense (DepSecDef) on December 27, 2006. This plan described four thrust areas to support the TMTI goals. As illustrated in Table 1, these thrust areas have evolved into five thrust areas, which better characterize the approaches being pursued in the implementation of the TMTI goals. Two of the thrust areas (Genomics and Proteomics & Small Molecules) split into two component parts. Metabolomics was incorporated as an important subcomponent into the remaining thrust areas.

**Table 1. TMTI Thrust Areas**

| Initial Thrust Areas | Current Thrust Areas |
|---|---|
| • Innate Immunity and Cytokines | • Host Immune Enhancement |
| • Genomics | • Genomic Identification |
| | • Nucleotide Therapeutics |
| • Proteomics & Small Molecules | • Protein Based Therapeutics/Biologics |
| | • Small Molecule/Drugs |
| • Metabolomics | |

The evolution of the thrust areas occurred after receipt of the October 2006 TMTI Broad Agency Announcement (BAA) proposals. Elements of each of the original four thrust areas described in the *Chemical and Biological Defense Program Medical RDT&E Plan* were integrated in many of the proposals. Therefore, the original thrust areas were converted to better align with the pharmaceutical product development process that many of the proposals reflected. The current TMTI portfolio will include projects for improving foundational technologies and capabilities in the product-development-adjusted thrust areas.

### C. TMTI Approach

TMTI is "transformational" not only in leveraging technologies and generating products, but also in its approach to managing research and development activities. Under TMTI, the DoD will expand on current efforts partnering with the pharmaceutical and biotechnology industries, academia, and other government agencies to meet program goals. Furthermore, TMTI represents an integrated approach, with both Science & Technology (S&T) and AD activities being managed by a single, integrated Program Office (PO) following established DoD 5000 acquisition guidelines.

The portfolio of TMTI projects is being actively managed to maintain alignment with program strategy and to ensure that TMTI goals are met. A technology scanning campaign will be performed to identify technologies for potential addition to the TMTI portfolio. Multiple mechanisms will be used to solicit and rapidly establish contracts with performers, supplementing traditional BAA solicitations.

The TMTI program is aimed at achieving success of the overall program goals within five years to meet the emerging threat. By integrating S&T with AD, challenges related to transitioning products across multiple development portfolios are minimized. Furthermore, the integrated PO will maintain an end-to-end view of the development process, manage a dynamic product portfolio, coordinate performer activities to ensure timely product outputs, and manage overall program risk.

## IV. OFFICE OF SECRETARY OF DEFENSE (OSD) OVERSIGHT

As stated in the *Chemical and Biological Defense Program Medical Biodefense RDT&E Plan*, the Special Assistant for Chemical and Biological Defense and Chemical Demilitarization Programs (SA(CBD&CDP)) will provide oversight, coordination, and integration of the TMTI program, including strategy direction and policy guidance as deputy to the Assistant to the Secretary of Defense for Nuclear and Chemical and Biological Defense Programs (ATSD(NCB)). As part of this strategy direction, the SA(CBD&CDP) will provide a five year oversight strategy for the TMTI. The Joint Science and Technology Office (JSTO) and the Joint Program Executive Office (JPEO) are refining the *TMTI Business Plan* for the management of the TMTI. The SA(CBD&CDP) will work with the JSTO and JPEO to ensure the *TMTI Business Plan* is compliant with the *Chemical and Biological Defense Program Medical Biodefense RDT&E Plan*, includes the five year plan, and ensures continuous review of projects to facilitate necessary program adjustments.

#### a. Metrics

The five year TMTI program oversight strategy will provide a means for assessing program performance. The oversight strategy will incorporate the pharmaceutical product development model, where appropriate, as well as metrics for assessing success of the enabling platform technologies and the genetics sequencing projects. It will also compare and assess the ability of the contracts awarded to meet the product goals as stated in the *Chemical and Biological Defense Program Medical Biodefense RDT&E Plan*.

Other metrics included in this strategy are:

- Measurement of the obligation, disbursement, and execution of contracts according to the five thrust areas outlined in section IIIB of this report.
- Measurement of project progressions through medical technology readiness levels (TRLs) over a five year period and an intermediate period to identify early program successes. Projects will be assessed for both technology maturity and adherence to schedule by the Program Manager (Figure 1).

## V. REPORTING REQUIREMENT RESPONSE

### A. Budget Submission for FY 2008

Table 2 shows top level TMTI program funding and objectives through FY 2009. Table 3 shows current program expenditures, which, as of January 31, 2007, consisted solely of FY 2006 funding executions as the FY 2007 BAA responses are still under evaluation.

**Table 2. TMTI Program Funding and Objectives through FY 2009**

| | | FY 2006 | FY 2007 | FY 2008 | FY 2009 |
|---|---|---|---|---|---|
| **Funding ($M)** | Total Funding in Budget Activities 6.1-6.3 | 74 | 124 | 248 | 301 |
| **Annual Program Objectives** | | • Broad project selection across Budget Activities 6.1-6.3<br>• Define potential products, platforms, and enabling technologies | • Determine approved products for label expansion<br>• Identify near-approval products (e.g. shelved products)<br>• Identify projects expecting to reach IND filing status within 1-2 years | • Identify products expected to transition at the end of FY 2010 or early FY 2011<br>• Realign investments per thrust area as determined by gap analysis<br>• Continuance of current products' progression | • Identify performers for enhanced development capabilities<br>• Continuance of selected current products' progression |
| **Contracting Mechanism** | | BAA for new projects | Multiple (BAA and others) | Multiple | Multiple |
| **Timing** | | Oct 2005 | Dec 2006 and TBD | TBD | TBD |
| **Targeted performer** | | Industry, Academia, Government | Industry | Industry | Industry (if needed) |
| **Projected size of program portfolio** | | 20-30 projects | 28-39 projects | 13-34 projects | 12-19 projects |
| **Actual size of program portfolio** | | 25 projects<br>- 15 Extramural<br>- 10 Intramural | 50 BAA responses received in mid-Feb 2007<br>- 19 proposals invited<br>- 17 proposals submitted | | |

**Table 3. FY06 Funding Execution ($K) (As of: Jan 31, 2007)**

| Budget Activity (BA) | Item Code | Current Program Budget | OSD Obligation Goal (93%) | Current Obligations | Percent Obligated |
|---|---|---|---|---|---|
| BA1 | TB1 | 27,204 | 25,300 | 21,612 | 79% |
| BA2 | TB2 | 17,486 | 16,262 | 14,702 | 84% |
| BA3 | TB3 | 29,096 | 27,059 | 23,440 | 81% |
| **Total TMTI** | | **73,786** | **68,621** | **59,754** | **81%*** |

*Remedy: Contract award and associated funds obligation are pending for two FY 2006 projects

## B. List of Programs Funded in FY 2006 and 2007 (Response 1)

The funded projects have been organized into the appropriate Thrust Areas based on the type of product being developed. The funded FY 2006 projects are shown in Table 4. FY 2007 projects are in the selection process.

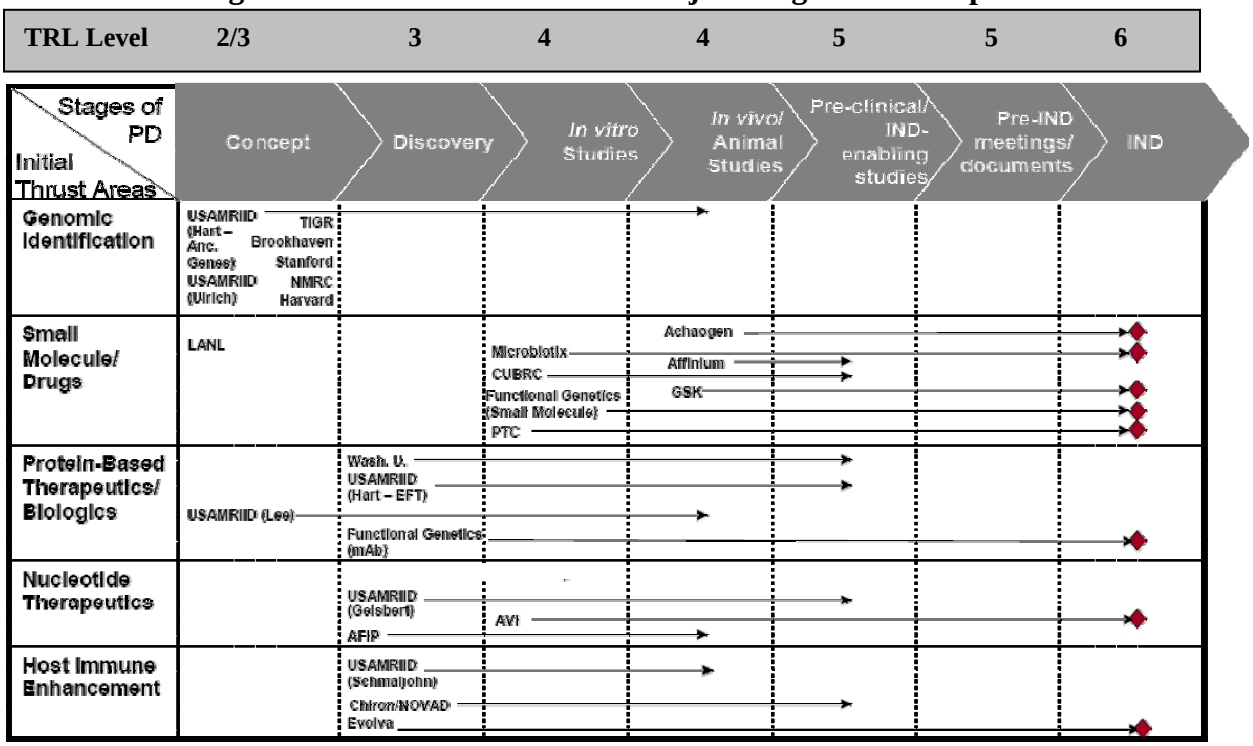
**Table 4. FY 2006 TMTI Selected Programs by Thrust Area**
**(*Intramural projects are in italics.*)**

| Goal | Primary Thrust | Program Title [Intramural and Contract] | Program Description |
|---|---|---|---|
| **I** | Genomic Identification | Brookhaven National Laboratory | Development of a toxin knowledge database |
| | | *USAMRIID* - Ulrich | Construct interactome of *Yersinia pestis* proteome |
| **II** | Genomic Identification | The Institute for Genomic Research (TIGR) | Evaluate potential of quorum sensing genes as therapeutic targets |
| | | *Naval Medical Research Center*-Read | Genomic sequencing of bacterial pathogens |
| | | *USAMRIID* - Parker | Development of monoclonal antibodies (Mab) protein based therapeutics against viral hemorrhagic fevers (VHF) |
| **IIIa** | Small Molecule/ Drugs | CUBRC Prosetta, Inc | Development of inhibitors of VHF viral capsid assembly |
| | | Functional Genetics, Inc | Development of TSG101 agonists (host protein recruited in VHF viral budding) |
| | Protein Based Therapeutics/ Biologics | Functional Genetics, Inc | Development of TSG101 Mab (host protein recruited in VHF viral budding) |
| | | *USAMRIID* - Olinger (in negotiation) | Development of Mab as tissue factor antagonist and therapeutic vaccine |
| | | *USAMRIID* - Lee | Discovery of potential therapeutics against VHF |
| | | Washington University | Discovery of anti-apoptotic peptides and small molecules against intracellular bacteria and VHF |
| | Nucleotide Therapeutics | AVI, Inc. | Investigating the use of Phosphodiamidate Morpholino Oligomers (PMOs) against VHF |
| | | *USAMRIID* - Hensley | Development of siRNAs against VHF |
| | Host Immune Enhancement | Chiron Novartis (OTA Pending) | TBD |
| | | *USAMRIID* - Schmaljohn | Determine if interferon (INF)-antagonism can be countered by recombinant INF |
| **IIIb** | Genomic Identification | Harvard University | Development of library of host (macrophage) genes that are up/down regulated in *Francisella tularensis* infection |
| | | Stanford University | Development of a library of host cellular genes exploited by pathogens |
| | Small Molecule/ Drugs | Achaogen, Inc | Development of small molecules to combat drug resistant bacterial pathogens |
| | | Affinium, Inc | Evaluation of *F. tularensis* 4 fatty acid synthesis inhibitors |
| | | GlaxoSmithKline (Pending) | Evaluation of novel DNA gyrase inhibitors |
| | | Los Alamos National Laboratory | Identification of mechanism/targets of bacterial resistance to MEP pathway inhibitors |
| | | Microbiotix, Inc | Development of bis-(imidazolinylindole) class of antibiotics |
| | | PTC Therapeutics | Development of tRNA hydrolase inhibitors of intracellular bacteria |
| | Nucleotide Therapeutics | *Armed Forces Institute of Pathology* | Discovery of new classes of RNA-based therapeutics and animal models of efficacy against intracellular bacteria |
| | Host Immune Enhancement | Evolva, Inc | Development of novel, biosynthesized small molecule libraries that induce targets of human defense responses against intracellular bacteria |

## 1. Development Schedule

Product development profiles are outlined for the selected FY 2006 projects in Figure 1. The X-axis indicates where in the normal pharmaceutical development (PD) process each project stood upon entry into the TMTI Program. No time scale is intended or implied. Red diamonds indicate an intended IND filing. Some projects constitute supporting or early development efforts and are therefore not themselves intended to result in a medical countermeasure. As such, these projects are not expected to file an IND.

**Figure 1. FY 2006 Thrust Area Project Stages of Development**




*Timelines based on proposal review

The majority of the projects selected are in the Protein-Based Therapeutics/Biologics and Small Molecules/Drugs Thrust Areas; nearly half of which have already begun *in-vitro* or *in-vivo* studies of a target compound.

Progression through medical TRLs will be used to assess program performance as traditionally utilized by the DoD medical acquisition community. A table describing the TRLs for Medical Product Development is provided in Annex A. Rapid transition through the TRLs will be one metric used to identify the early successes of the TMTI.

## 2. Oversight Performance Metrics

The following are the initial oversight metrics. As the program evolves, these criteria may change over time**.**

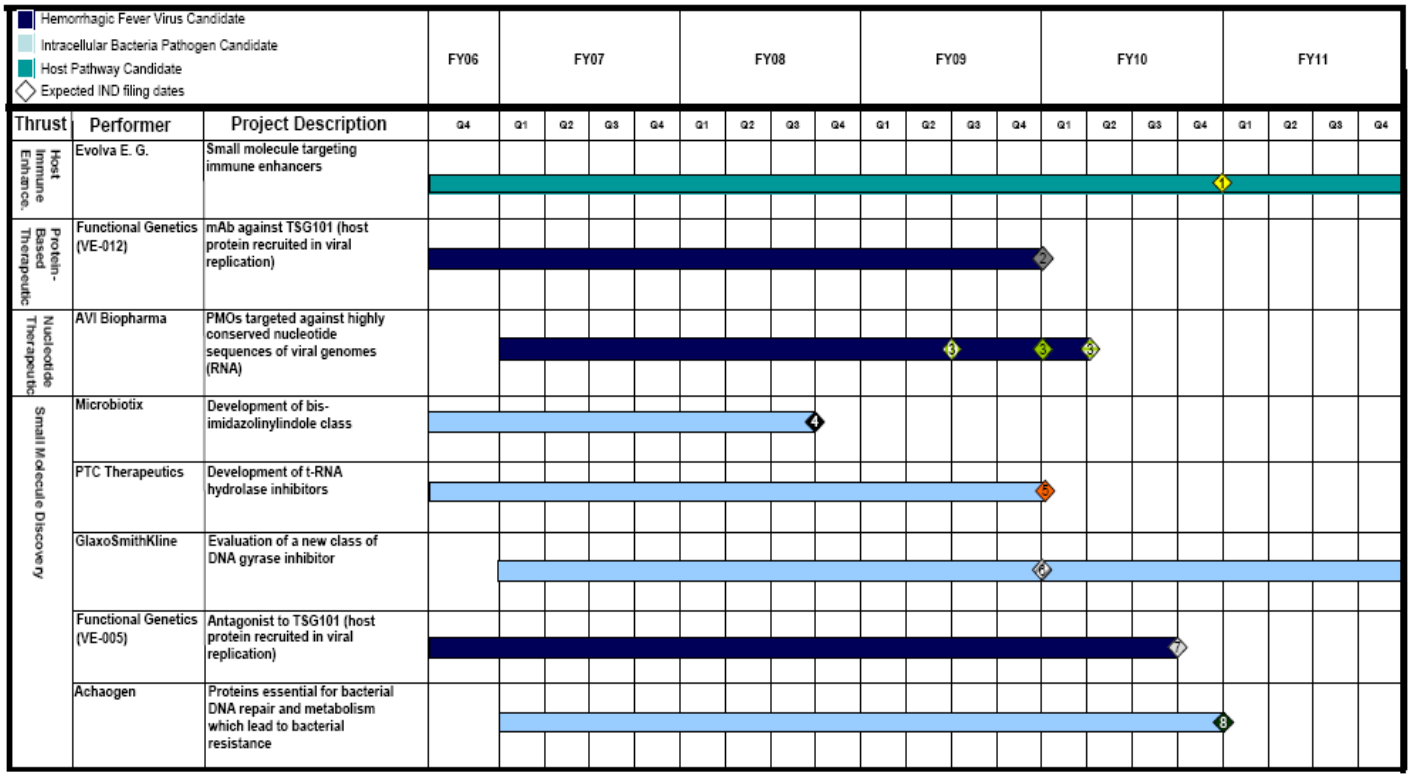
a) Align the TMTI project portfolio with strategic product goals (i.e., the number of projects funded per thrust area to support the TMTI product goals).

b) Assess the internal business processes and funds execution to include:
    1) Number of contracts awarded, and
    2) Obligate and execute contract funds (percentage of projects on time versus slipped).
c) Assessment of product goal achievement, metrics to include:
    1) Project maturity (i.e., percentage of Basic Research, etc.),
    2) Percentage of projects with defined Target Product Profile (TPP),
    3) Number of projects transitioning through decision points,
    4) Number of projects advancing through TRLs, and
    5) Number of projects filing INDs, where appropriate.
d) Assess program pace to include:
    1) Average time to TPP,
    2) Average time between decision points, and
    3) Average time between TRLs.

### 3. Project Timelines

Figure 2 shows the TMTI FY 2006 timelines. The projects are grouped by primary Thrust Area. Timelines are color coded by model system (viral, bacterial, host pathways).

**Figure 2. FY 2006 Thrust Area Project Timelines**




Note: Each diamond represents an expected IND filing.

### C. Performance Metrics and Benchmarks (Response 2), and Results of the Programs' Quarterly Reviews (Response 3)

A BAA was posted in October 2005 targeting performers across industry, academia, and government. This BAA solicited projects across S&T funding categories as a means to gather an array of potential products, platforms, and enabling technologies. Given the possibility of product failure and the inclusion of enabling and platform research, the size of the TMTI portfolio will logically grow rapidly after initiation of the program and then will gradually decrease in size in order to manage the number of products needed to transition into AD. As previously mentioned, the funding available for AD is limited. Thus, careful choices must be made both in initial selection and at go/no-go (down select) decision points.

### 1. FY 2006 Accomplishments

In FY 2006, 26 incrementally funded contracts were selected to receive awards across the three product goals and five Thrust Areas. Two of the projects listed are pending awards and one proposal was withdrawn by the offeror. Table 5 shows the contract amounts per fiscal year. FY 2008-FY 2011 funds shown represent funds that are anticipated, but not committed. The Government has not obligated for any funds beyond the current year.

**Table 5. FY 2006 TMTI Contract Awards by Fiscal Year**
**(*Intramural projects are in italics.*)**

| Goal | Primary Thrust | Program Title [Intramural and Contract] | Duration (years) | Total | FY06 | FY07 Option | FY08 Option |
|---|---|---|---|---|---|---|---|
| **I** | Genomic Identification | Brookhaven National Laboratory | 2 (2yr base, no opt) | $941,281 | $458,820 | $120,615 | $361,846 |
| | | *USAMRIID* - Ulrich | 3 (3yr base, no opt) | $4,791,761 | $1,420,841 | $412,255 | $1,236,766 |
| **II** | Genomic Identification | The Institute for Genomic Research (TIGR) | 3 (3yr base, no opt) | $4,940,249 | $1,604,808 | $411,171 | $1,690,756 |
| | | *Naval Medical Research Center* - Read | 3 (3yr base, no opt) | $13,381,100 | $4,837,368 | $1,381,216 | $3,018,867 |
| | | *USAMRIID* - Parker | 4 (4yr base, no opt) | $2,028,389 | $178,416 | $186,000 | $558,804 |
| **IIIa** | Small Molecule/Drugs | CUBRC Prosetta, Inc | 2 (1 base, 1yr opt) | $8,300,922 | $4,017,013 | $1,070,977 | $3,212,932 |
| | | Functional Genetics, Inc | 4 (4yr base, no opt) | $28,041,647 | $3,086,010 | $820,010 | $5,400,651 |
| | Protein Based Therapeutics/ Biologics | Functional Genetics, Inc | 3 (3yr base, no opt) | $12,953,396 | $1,744,421 | $1,076,716 | $6,902,110 |
| | | *USAMRIID* - Olinger (in negotiation) | 2 (2yr base, no opt) | $11,581,388 | $6,313,744 | $1,317,000 | $3,950,644 |
| | | *USAMRIID* - Lee | 3 (3yr base, no opt) | $2,132,000 | $714,000 | $179,000 | $535,000 |
| | | Washington University | 4 (1 base, 3-1yr opt) | $11,119,520 | $1,279,179 | $445,253 | $1,781,324 |
| | Nucleotide Therapeutics | Ambion (proposal withdrawn) | 4 (1 base, 3-1yr opt) | | | | |
| | | AVI, Inc. | 2 (2yr base, no opt) | $28,034,018 | $17,962,021 | | $10,071,997 |
| | | *USAMRIID* - Hensley | 2 (2yr base, no opt) | $3,600,286 | $1,800,000 | $450,000 | $1,350,286 |
| | Host Immune Enhancement | Chiron Novartis (OTA-Pending) | 5 (5yr base, no opt) | Pending | | | |
| | | *USAMRIID* - Schmaljohn | 2 (2yr base, no opt) | $1,101,576 | $545,468 | $139,000 | $417,108 |
| **IIIb** | Genomic Identification | Harvard University | 3 (3yr base, no opt) | $2,730,330 | $959,504 | $233,998 | $834,833 |
| | | Stanford University | 3 (3yr base, no opt) | $7,104,131 | $1,987,811 | $626,672 | $2,597,631 |
| | Small Molecule/ Drugs | Achaogen, Inc | 4 (1 base, 3yr opt) | $24,630,144 | $5,262,948 | $2,546,106 | $4,297,188 |
| | | Affinium, Inc | 2 (1 base, 1 opt) | $4,849,098 | $1,800,557 | $762,135 | $2,286,406 |
| | | GlaxoSmithKline (Pending) | 5 (3yr base,2-1yr opt) | Pending | | | |
| | | Los Alamos National Laboratory | 1 (1 yr, no opt) | $998,807 | $998,807 | | |
| | | Microbiotix, Inc. | 2 (2yr base, no opt) | $5,064,555 | $2,388,096 | $669,115 | $2,007,344 |
| | | PTC Therapeutics | 3 (3yr base, no opt) | $17,152,272 | $4,122,385 | $1,486,039 | $7,085,730 |
| | Nucleotide Therapeutics | *Armed Forces Institute of Pathology* | 3 (3yr base, no opt) | $1,722,815 | $554,717 | $143,413 | $594,448 |
| | Host Immune Enhancement | Evolva, Inc | 5 (2yr base, 3-1yr opt) | $26,866,882 | $3,882,915 | $866,458 | $7,968,946 |

## 2. FY 2007 Program

The TMTI plan was approved by the DepSecDef in December 2006. A FY 2007 BAA was published in October 2006 with the goal to provide rapid and effective medical countermeasures against genetically engineered or emerging Biological Warfare (BW) threat agents. The BAA focuses on products within two to three years of filing an IND application and initiating a Phase 1 clinical study or on products already licensed for another indication. Fifty pre-proposals were received and reviewed. From these, 19 were invited to submit full proposals. To date, 17 full proposals have been received. The source selection board met March 16, 2007, to make recommendations. The source selection authority will review these recommendations and will make award decisions in April 2007. In addition, TMTI will perform a complete technology sweep with an additional 2007 BAA to identify other candidates to be integrated into program.

## 3. Impact of FY 2007 Reductions

FY 2007 funding reductions forced the program to focus on more mature technologies to reduce risk of failure. In addition, it forced a shift in emphasis to near term gains versus a more balanced portfolio of "less" and "more" mature technologies. In order to successfully meet the program goals, TMTI must contain a portfolio of projects that represent diverse technological approaches to each Thrust Area. In order to accomplish the goals expeditiously, the approaches must be conducted in parallel instead of sequentially. Fully funding the program will allow this approach.

## 4. FY 2008 Objectives

TMTI follows the pharmaceutical model that pursues multiple candidate thrust areas simultaneously, to include new thrust areas that might be identified in stride. We expect this to allow the submittal of best candidate(s) from the FY 2006 and FY 2007 efforts to the FDA for IND approval and place into Advanced Technology Development. Also, TMTI will continue to collaborate with the interagency as well as industry to confirm no duplication of efforts. In FY 2008, a targeted solicitation mechanism will be used to address any portfolio gaps. In FY 2009 and beyond, solicitations will occur as determined by the needs of the program.

## 5. Program Management and Oversight

The TMTI program is managed in accordance with section 1522, title 50, USC, the *Chemical Biological Defense Program Implementation Plan*, April 2003, and the *Chemical and Biological Defense Program Medical RDT&E Plan*, December 2006. The size and complexity of the TMTI program requires frequent and in-depth oversight. This is accomplished by the Overarching Integrated Process Team (OIPT). The first OIPT meeting is planned for March 2007.

The ATSD(NCB) exercises oversight of the TMTI program as part of the OIPT process. As the deputy for CBDP matters, the SA(CBD&CDP) provides oversight, coordination, and integration of the TMTI program. This includes chairing the OIPT which will meet quarterly to review program results and next steps.

A Joint Program Management Office for the TMTI (JPM/TMTI) has been established and is staffed by personnel from the JSTO and the JPEO for day-to-day execution of the program. The TMTI PO reports to a TMTI Executive Office (EO) comprising the Director, JSTO and the Director, JPEO.

Two advisory boards will provide assistance to the OSD offices with TMTI oversight responsibilities. A Board of Senior Advisors, with membership drawn from government agencies, and chaired by the SA(CBD&CDP), will meet quarterly to review integration and oversight of program performance, incorporation of FDA guidance, coordination of research efforts among the agencies, alignments and planning of technology transitions toward product development, and other matters related to achieving the goals of the program. In addition, a Senior Steering Group, chaired by the ATSD(NCB), meets semi-annually to

monitor progress and provide guidance. Senior Steering Group membership will be drawn solely from within the DoD and will hold its first meeting in April 2007.

## 6. Performance Metrics and Benchmarks

The industry standard program management suite of metrics (based on cost, schedule, and performance) will be applied to each funded TMTI Project as well as across collections of projects that make up higher level Thrust Area Programs. These parameters will be used to communicate overall TMTI portfolio status.

Clear measures of success are critical for TMTI, both in managing the program and in communicating progress to stakeholders. As stated earlier, TMTI represents a new paradigm for rapid development of medical countermeasures. This paradigm has been developed, in part, by benchmarking the program's structure, metrics, and goals against both DoD program management best practices as well as the successful practices of the pharmaceutical industry.

Key measurable traits, or benchmarks, of successful complex DoD programs that have been incorporated into the management and oversight of the TMTI program include:

- Funding and program stability,
- Program responsibility of the system's entire lifecycle from development through operations support,
- Continuity of key personnel and technical expertise, and
- Good management practices as evidenced by open communications, independent internal evaluations, and a contracting environment that values innovation.

Similarly, the TMTI program has incorporated the following key benchmarks of the pharmaceutical industry:

- Clearly defined and widely acknowledged mission focus,
- Limiting unknowns and risk elements to the program early stages, and
- Identifying frequent Project Go/No-Go/Modification decision points.

Program direction and alignment with these benchmarks and associated cost, schedule, and performance metrics will be assessed on a continual basis by the Thrust Area Managers, the TMTI Program leadership, and by senior DoD oversight leadership. Constant and transparent program status will be communicated throughout all levels of the program through both informal and formal program reviews. This will enable the JPM/TMTI to reallocate funding within the TMTI portfolio as may be required to achieve product goals faster and to develop early corrective action for off-track projects.

**Table 6. Individual Project and Thrust Area Program Metrics**

| | Management Metrics | Purpose | Representative Metrics Used in FY 2006 Program Assessments (Specific metrics tailored to individual project performance) |
|---|---|---|---|
| | **Individual Project Metrics** | | |
| **Cost** | • Project level development budget is established<br>• Cost of individual project phases established and tied to the Project Performance Timeline | • To determine if Thrust area Product Development Tasks are being accomplished within the budget estimate set at the initiation of the Development Project | • $1,120,000 for first 15 months<br>o $373,333 for mutant preparation<br>o $373,333 to extract RNA<br>o $373,333 to prepare and perform a microarray hybridization analysis |
| **Schedule** | • Establish Project Performance Timeline | • Ties performance objectives to specified timeline<br>• Identifies dependent tasks and critical path | • Map expressed genes (15 Months)<br>• Prepare mutant construct (Months 1-9)<br>• *In vitro* time course growth and RNA extraction (Months 3-12)<br>• Microarray hybridization and Analysis (Months 6-15) |
| **Performance** | • Project performance vs defined cost and schedule milestones<br>• Project performance vs defined Go/No Go criteria | • Determination of successful completion with respect to anticipated time and cost<br>• Determination on successful achievement of desired research and development results | • Were mutant constructs successfully prepared within 9 months for $373,000?<br>• Was RNA extraction successfully completed on budget & schedule?<br>• Was the Microarray work started on time? Was it successfully completed within budget? Was a map prepared for expressed genes? |
| | **Overarching Thrust Level Program Metrics** | | |
| **Cost** | • Establish Program Budget<br>• Establish secondary project budget goals | • Determine if Program Overarching Thrust areas goals are being accomplished within budget | • $47.6 million to develop an Ebola therapeutic |
| **Schedule** | • Establish Overarching Program Timeline | • Ties performance objectives to specified timeline<br>• Identifies dependent tasks and critical path | • Projects involving antibody production, purification, process development, scale-up, Fill/Finish, preclinical trials and IND submission are scheduled |
| **Performance** | • Overarching Thrust Area Program performance versus cost/schedule<br>• Determination of Thrust Area Program technical success | • Determination of successful completion with respect to time and cost not only for each independent project but also for the development program in its entirety | • For projects involving antibody production, purification, or process development was the program successful in that preclinical trials in animals indicated that the therapeutic was effective and safe? Was an IND submitted to and accepted by the FDA for approval? |

**a) Metrics Used to Determine Stoplight Color**

**1) On Track (Green):**

All aspects of the program are progressing satisfactorily toward the supported TMTI Goal. Some minor problem(s) may exist, but appropriate solutions are available. Performance toward the specific program outcomes, within the primary focus and thrust area, is on-track with risk mitigation strategies identified and implemented. Schedule slippages, if any, can be rescheduled without requiring a significant amount of additional effort on the part of the executing entity or contractor. Costs are not expected to exceed planned funding levels or exceed contract target costs by more than 10%. Obligations and expenditures are at or above program plan.

**2) Potential or Actual Problem (Yellow):**

Some event, action, or delay has occurred that impairs progress toward the supported TMTI Goal. While appropriate solutions are within the TMTI PO's ability to solve, timely action or decisions by higher management outside the office may also be required to realign the effort. Required actions may include developing a revised technical approach, or a similar type action.

**3) Major Weakness (Red):**

An event, action, or delay has occurred that seriously impedes successful accomplishment of supported TMTI goal. Such a setback to the effort requires reorientation or reprogramming, with the advice and consent of higher management. Such a problem may be beyond the ability of the TMTI PO to resolve without significant action by higher echelons. A major weakness includes identified high risk area with no mitigation plan to reduce risk.

**b) Program Quarterly Reviews**

The EO conducts monthly reviews of the program with the PO. These reviews include a project status reflecting updates on metrics as well as discussion of potential issues based on cost/schedule/performance. Table 7 shows the project results following the first quarter of performance. The projects are categorized by Product Goal (defined in the *Chemical and Biological Defense Program Medical RDT&E Plan*) and by the Thrust Areas (defined in the *TMTI Business Plan*).

A successfully implemented program metrics analysis will allow program gap analysis and point toward additional Projects that need to be performed to complete the Program. These metrics and the DoD and industry benchmarks they measure will assist in the formation of future BAAs, Request for Proposals, Cooperative Research And Development Agreements and other contracting mechanisms that will be employed to assure successful program accomplishment.

**Table 7. Project Results following the First Quarter of Performance**

| Goal | Primary Thrust | Program Title [Internal and Contract] | Cost | Schedule | Performance* |
|---|---|---|---|---|---|
| I | Genomic Identification | Brookhaven National Laboratory | Green | Yellow | |
| | | USAMRIID - Ulrich | Green | Yellow | |
| II | Genomic Identification | The Institute for Genomic Research -TIGR | Yellow | Yellow | |
| | | Naval Medical Research Center - Read | Green | Green | |
| | | USAMRIID - Hart | Green | Yellow | |
| IIIa | Small Molecule/Drugs | CUBRC Prosetta, Inc | Yellow | Yellow | |
| | | Functional Genetics, Inc | Green | Green | |
| | Protein Based Therapeutics/ Biologics | Functional Genetics, Inc | Green | Green | |
| | | USAMRIID - Olinger (under negotiation) | Project not started yet | | |
| | | USAMRIID - Lee | Green | Yellow | |
| | | Washington University | | Yellow | Yellow |
| | Nucleotide Therapeutics | AVI, Inc | Green | Green | |
| | | USAMRIID - Hensley | Green | Yellow | |
| | Host Immune Enhancement | Chiron Novartis (OTA Pending) | Project not started yet | | |
| | | USAMRIID - Schmaljohn | Green | Yellow | |
| IIIb | Genomic Identification | Harvard University | Green | Green | Green |
| | | Stanford University | Green | Green | |
| | Small Molecule/ Drugs | Achaogen, Inc | Yellow | Yellow | Yellow |
| | | Affinium, Inc | Green | Green | |
| | | GlaxoSmithKline (OTA Pending) | Project not started yet | | |
| | | Los Alamos National Laboratory | Green | Yellow | |
| | | Microbiotix, Inc. | Green | Green | |
| | | PTC Therapeutics | Green | Green | Yellow |
| | Nucleotide Therapeutics | Armed Forces Institute of Pathology | Green | Green | |
| | Host Immune Enhancement | Evolva, Inc | Green | Green | |

* Recent program starts result in insufficient information to accurately measure performance for most projects.

These results as well as future monthly reviews will be reviewed quarterly by the TMTI OIPT. As previously discussed the initial OIPT meeting is planned for March 2007, and specific attention will be directed at those projects rated less than green.

## VI. SUMMARY

The *Chemical and Biological Defense Program Medical RDT&E Plan* outlines goals and approaches for implementing the TMTI in the context of the broader biodefense program. While the focus of the research is on accelerating advances in biotechnology leading to expedited development of specific products and countermeasures, the effective execution of the program relies on cooperative research and oversight among the performing organizations. Broad goals and the technologies to achieve them have been identified as a means of providing guidance to the research efforts and specific research thrusts have been identified as key focus areas for attention.

## VII. ANNEX A

### *Technology Readiness Levels for Medical Product Development*

| Technology Readiness Level | DoD Description (Acquisition Guidebook Oct 2002) | Medical Description[1] (Oct 2004) |
|---|---|---|
| 1. Basic principles observed and reported. | Lowest level of technology readiness. Scientific research begins to be translated into applied research and development. Examples might include paper studies of a technology's basic properties. | Earliest level of technology readiness. Active monitoring of scientific knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies. |
| 2. Technology concept and/or application formulated. | Invention begins. Once basic principles are observed, practical applications can be invented. Applications are speculative and there may be no proof or detailed analysis to support the assumptions. Examples are limited to analytic studies. | Focus efforts on practical applications based on basic principles observed. Generation of scientific "paper studies" that review and generate research ideas, hypothesis, and experimental designs for addressing the related scientific issues. |
| 3. Analytical and experimental critical function and/or characteristic proof of concept. | Active research and development is initiated. This includes analytical studies and laboratory studies to physically validate analytical predictions of separate elements of the technology. Examples include components that are not yet integrated or representative. | Research, data collection, and analysis begin in order to: test hypothesis; explore alternative concepts; identify and evaluate critical technologies and components; and research and eventual development of candidate countermeasure(s). Conduct non-clinical studies to support models based on presumed battlefield conditions. |
| 4. Component and/or breadboard validation[2] in laboratory environment. | Basic technological components are integrated to establish that they will work together. This is relatively "low fidelity" compared to the eventual system. Examples include integration of "ad hoc" hardware in the laboratory. | Laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous experimental design.<br>Exploratory study of critical technologies for effective integration into candidate(s).<br>Assess safety and efficacy utilizing animal model(s).<br>Propose assays, surrogate markers, and endpoints to be used during non-clinical and clinical studies to evaluate and characterize candidate(s). |

[1] TRL Medical descriptions are generally accepted across the medical acquisition community.
[2] Not "validation" as defined by FDA. FDA-type validations will be done at TRL 6-8 and are needed for licensure.

| | | |
|---|---|---|
| 5. Component and/or breadboard validation[3] in relevant environment. | Fidelity of breadboard technology increases significantly. The basic technological components are integrated with reasonably realistic supporting elements so it can be tested in a simulated environment. Examples include "high fidelity" laboratory integration of components. | Conduct non-clinical research studies involving data collection and analysis in well-defined systems with highly characterized lots of candidate(s) produced and further development of selected candidates.<br>Develop a robust and reproducible manufacturing process amenable to cGMP.<br>Qualify assays for potency, purity, identity and quality.<br>Qualify surrogate markers for efficacy in animal models. |
| 6. System/sub system model or prototype demonstration in a relevant environment. | Representative model or prototype system, which is well beyond that of TRL 5, is tested in a relevant environment. Represents a major step up in a technology's demonstrated readiness. Examples include testing a prototype in a high-fidelity laboratory environment or in simulated operational environment. | Manufacture, release and stability test GMP pilot lots.<br>Conduct GLP safety studies.<br>Prepare and Submit IND.<br>Conduct Phase 1 clinical trial. |
| 7. System prototype demonstration in an operational environment. | Prototype near, or at, planned operational system. Represents a major step up from TRL 6, requiring demonstration of an actual system prototype in an operational environment such as an aircraft, vehicle, or space. Examples include testing the prototype in a test bed aircraft. | Conduct Phase 2 clinical trial.<br>Establish final dose, dose range, schedule, and route of administration.<br>Data collected, presented, and discussed with FDA at meeting (Type B).<br>Clinical endpoints and supporting animal test plans agreed to by FDA.<br>Complete process validation and initiate consistency lot production. |
| 8. Actual system completed and qualified through test and demonstration. | Technology was proven to work in its final form and under expected conditions. In almost all cases, this TRL represents the end of true system development. Examples include developmental test and evaluation of the system in its intended weapon system to determine if it meets design specifications. | Complete production & testing of consistency lots.<br>Conduct Phase 3 clinical trials, if applicable.<br>Submit BLA/NDA to FDA<br>Obtain FDA approval. |
| 9. Actual system proven through successful mission operations. | Actual application of the technology in its final form and under mission conditions, such as those encountered in operational test and evaluation. Examples include using the system under operational mission conditions. | Post licensure/approval use of product.<br>Fulfill post-licensure commitments, if required. |

[3] Not "validation" as defined by FDA. FDA-type validations will be done at TRL 6-8 and are needed for licensure.