

**SMALL BIOSCIENCE BUSINESSES:  
A PLAN TO CREATE 200,000 JOBS IN AMERICA** [www.biotechjobsforamerica.com](http://www.biotechjobsforamerica.com)

**Executive Summary.** This proposal offers a plan to President Obama and his economic recovery team to add **200,000 jobs** in the next four years in the biosciences sector by increasing funding to existing programs that target small businesses (Table 1).

At the end of 2006, the Biotechnology Industry Organization (BIO) [www.bio.org](http://www.bio.org) estimated that about 43,000 large and small biosciences businesses provided 1.3 million in direct jobs and 7.5 million jobs in related employment in America.

We can create 200,000 jobs in biosciences in the next four years by increasing funding totaling **\$6.7 billion** to five existing (“target”) programs: **SBIR/STTR, TIP, military medical research, Congressional Directed Medical Research Programs, and SBIC.** These target programs already operate with competitive funding guidelines; they are staffed and have proposal solicitation, review, and award infrastructure.

- This proposal focuses on increasing funding to **small bioscience businesses** with “**development ready**” projects, *ie* not research.
- Target funding programs would develop therapeutics, diagnostics, medical devices and biological tools where some proof-of-concept has been demonstrated. “Biosciences” may include applications for agriculture, biofuels, environmental protection and law enforcement.
- **This proposal focuses on military medical needs to improve the care given to our wounded warriors.** Pain is the single most challenging clinical and cost problem in treating our wounded warfighters. Treating their pain costs an estimated \$150 billion, affecting 25% of our troops from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF).

**Table 1. Summary of Funding Increases to Target Programs**

TARGET PROGRAMS, NEW FUNDS	New Funds		Total jobs created
	(four years)	60% salaries	
SBIR/STTR	\$ 2,080,750,000	\$1,248,450,000	62,423
Technology Innovation Program (TIP)	508,125,000	304,875,000	15,244
Military medical research	1,600,000,000	960,000,000	48,000
Congressionally Directed Medical Research Programs	2,150,000,000	1,290,000,000	64,500
Early-stage Bioscience Funds (SBIC)	400,000,000	216,000,000	10,800
<b>TOTAL, New biosciences</b>	<b>\$ 6,738,875,000</b>	<b>\$4,019,325,000</b>	<b>200,966</b>

The key assumptions behind job creation are given in the next section. It is assumed that 60% of funds awarded support jobs, with the remainder allocated to supplies, materials, small equipments and administrative costs.

Small biosciences businesses can help reduce the economic costs of a range of diseases and conditions. For example, chronic disease now accounts for \$1.2 trillion in economic cost to America,

<http://www.milkeninstitute.org/publications/publications.taf?function=detail&ID=38801018&cat=ResRep> , representing 1.7 million deaths, or 70% of all deaths each year.

<http://www.cdc.gov/nccdphp/> If we had a cure – not just treatment – for diabetes, we could better manage our Medicare costs: about 20% of Medicare patients have diabetes, accounting for 33% of Medicare expenditure.

<http://209.85.173.132/search?q=cache:4jYtIPBQlckJ:www.ncpanet.org/pdf/leg/dmegwu+study.pdf+study+cost+of+diabetes+Medicare&hl=en&ct=clnk&cd=14&gl=us> So the definition of “biosciences” here includes stem cell technologies that can cure, not just treat. <http://www.americansforcures.org/article.php?uid=6086>

Because of the profound impact on American society – OEF/OIF returnees are selling VA-prescribed opiate medicines on the street, and using opiates for suicide (see **Appendix C**) – specific funding for new non-opiate, effective, safe and affordable medications for pain is called for in this proposal.

**Section 1** gives key assumptions, reviews target programs, and then details plans to increase funding to target programs by \$6.7 billion in the four-year period 2009-2012.

**Section 2** presents the case for non-job benefits of federal investment in biosciences:

- 2.1 Early-stage private capital for biosciences is presently at a very low ebb;
- 2.2 The economic multiplier from “investment” in biosciences is very attractive (\$6.70 per \$1.00 “invested”) and represents a good use of taxpayer dollars. Micro case studies from three states are given; and
- 2.3 Funding these programs will strengthen America’s global competitiveness.

**Appendix A** gives a bio for the author, Constance McKee, President & CEO of Manzanita Pharmaceuticals, Inc. **Appendix B** gives historical data for success rates of the SBIR/STTR program. **Appendix C** gives more detail for the need for more effective, non-opiate pain medications for our wounded warfighters from OEF/OIF.

The increases proposed here will be leveraged by states’ efforts. “State economic development organizations ...are becoming increasingly sophisticated ...in building the biosciences sector and are adopting and implementing ...programs that support its growth.” [http://bio.org/local/battelle2008/State\\_Bioscience\\_Initiatives\\_2008.pdf](http://bio.org/local/battelle2008/State_Bioscience_Initiatives_2008.pdf)

In conclusion, supporting biosciences in America is not only good for job creation, it is a strategic investment that can improve the quality of healthcare provided to our veterans, minimize the human and cost burden of chronic disease, and maintain America’s competitiveness.

## SECTION 1

### Section 1. Target Programs & Proposed Increases in Funding Levels

**1.1 Key assumptions in funding models.** This proposal focuses on development of products by small bioscience businesses, not research by universities and institutes.

One key assumption is that increases to target programs for small biosciences businesses will be accompanied by an increase to the NIH, the “R” of the “R&D” budget of America. The scientific case for increasing funding for the NIH is given eloquently in the report “Broken Pipeline.” [www.brokenpipeline.org](http://www.brokenpipeline.org) The case for economic benefit of funding the NIH was illustrated in May 2000, when a “return on investment in [NIH] R” calculation was made by the U.S. Joint Congressional Committee. The Committee estimated the return on investment of NIH-funded medical research at about 15 times “taxpayers’ [then] annual NIH budget.” Subsequent advances in health care related to this “investment” increased life expectancy, with a net economic benefit to America of about \$2.4 trillion (1992 dollars). <http://www.nih.gov/news/070101wyden.htm>

Another key assumption is that the job multiplier effect used for small bioscience businesses differs from that for academic institutions. The complex infrastructure of universities appropriately consumes a higher percentage of funds than a small business. Increasing funding to the NIH will have a similar positive impact on biosciences jobs, but probably at a lower rate of job creation.

Section 1 summarizes the current status, recent funding levels and proposed additional funding for target programs. Where available, a program’s historical track record of success is given. No assumption is made as to whether additional personnel may be required to implement the increases proposed here.

**Table 1. Summary of Funding Increases to Target Programs**

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The key assumption in the model is that if a \$1 million award is made to a small bioscience business, 60% or \$600,000 will support 5 direct jobs and 25 indirect jobs. Thus every \$1 million in funding awards supports 30 jobs.

The following assumptions and terms are used throughout this proposal:

- \$120,000 in funding per year supports one bioscience job per year
- One direct job per year creates 5 additional jobs per year in related employment (“multiplier impact”), for a total of 6 (“total job creation effect’)
- For every funding award, 40% is allocated to non-employment expenses, for example materials and supplies, and other G&A expenses. Thus sixty percent (60%) of new funds support salaries for small bioscience businesses.
- The model is indifferent as to whether jobs are created or saved. Capital markets for 400 publicly-traded biotech companies has “seized,” and as of January 2009, 300 have less than a year’s cash. Funding awarded on a competitive basis from target programs may support these companies.
- In practice, larger firms and even some academic institutions may be awarded grants under some of the programs targeted here, for example the military medical research grants and the Congressionally Directed Medical Research Programs (CDMRP). Although focused on small businesses, the proposal is indifferent as to whether a job is created or saved by an emerging or established firm in the private sector.
- Very careful consideration has been given to the number of awards that each program can solicit, review, award and oversee. In other words, this proposal does not merely ‘throw money at the problem.’

## **SMALL BUSINESS INNOVATION AND RESEARCH (SBIR) SMALL BUSINESS TECHNOLOGY TRANSFER AND RESEARCH (STTR)**

**1.2 Background: SBIR/STTR** (Small Business Innovation and Research; Small Business Technology Transfer and Research) funds high-risk medical research. These programs are administered through the NIH (National Institutes of Health), the FDA (Federal Drug Administration), and the CDC (Centers for Disease Control). They are overseen by the Small Business Administration (SBA).

The SBIR program was founded in 1982, followed by the STTR program launched in 1994.<sup>1</sup> Because the SBIR/STTR program focuses on small businesses, it is distinct from other NIH programs that support academic endeavor.

In remarks to Congress on February 13, 2008, Jo Anne Goodnight of the SBIR/STTR Program Coordination, NIH Office of Extramural Research, described the aim and scope of the SBIR program. <http://www.hhs.gov/asl/testify/2008/02/t20080213a.html>

Among the eleven Federal agencies that participate in the SBIR program, the NIH is one of the largest funders, second only to the Department of Defense, and the single largest supporter of biomedical research.....

The NIH SBIR program is part of a complex innovation ecosystem that provides dedicated funding for small businesses to engage in innovative, early-stage biomedical and behavioral research and development (R&D) projects with commercial potential for medical solutions and breakthroughs. The program plays an important role in achieving our mission of improving human health, particularly in translating research findings and advancing medical discoveries into tangible products and services.

The NIH SBIR program encompasses 23 of NIH's 27 Institutes and Centers (ICs), each of which has a mandate to address science and health from a specific perspective, disease area (e.g., cancer), or area of concern (e.g., aging). The SBIR program is one means by which the ICs accomplish their R&D objectives. The unique feature of the SBIR program is a focus on commercialization of the outcomes of research. Thus, the SBIR program supplements the approach of the traditional research programs of NIH.<sup>2</sup>

**1.3 Current funding for SBIR/STTR.** Since its launch in 1983 until 2006, the SBIR/STTR programs have funded 20,590 projects with \$3.6 billion for "high risk" projects. There is no strict "one award-one company" rule, but in practice only a few small businesses win multiple awards which may be Phase 1, Phase 2 or combined Phase 1 and 2 awards known as "Fast Track."

Funds for the SBIR/STTR program are currently calculated as a set-aside percentage of each agency, for example, a percentage of the NIH extramural R&D budget. In 2007, the set-aside for SBIR was 2.5% (\$580.7 million); for STTR, the set-aside was .3% STTR (\$69.7 million) for a total of \$650 million.<sup>3</sup>

**Table 2. SBIR/STTR Recent Awards & Success Rate (2006)**

SBIR/STTR	Current Funding		Total	Percent	Average \$ of
	Annual Total	Awards	Submissions	Funded	Projects Funded
SBIR 2006	\$309,217,486	1,080	4,580	23.6%	\$286,312
STTR 2006	42,342,898	189	913	20.7%	\$224,036
Total 2006	\$351,560,384	1,269	5,493	23.1%	\$277,037

Table 2 illustrates the competitiveness of the SBIR/STTR program, where less than 25% of submissions are funded. **Appendix B** summarizes success rates for SBIR beginning in 1983, adding the STTR program in 1994, through 2006.<sup>4</sup> Historically, success rates for combined Phase 1, Phase 2 and Fast Track submissions for SBIR and STTR ranged between 19.0%-34.1%.

Of the total awarded since 1983, \$637 million has been awarded to firms working on therapies for orphan or rare diseases. These are diseases where patient populations are too small (less than 200,000) to attract the attention of major pharmaceutical

companies. Including Department of Defense SBIRs (\$6.5 billion), funding spent on orphan diseases represents about 10% of all SBIR grants,

**1.4 SBIR track record.** About 40% of NIH SBIR-funded projects reach the commercial market. <http://www.allbusiness.com/government/elections-politics-political-parties/6795536-1.html>

**1.5 Proposed additional funding to SBIR/STTR.** Table 3 outlines proposed increases to SBIR/STTR programs, beginning with awards made for the April 2009 submission date. The SBIR/STTR program solicits proposals three times a year, in April, August and December. Increases may be implemented almost immediately, with actual cash reaching small bioscience businesses in about a year.

Table 3 proposes that total funding be roughly doubled, that the number of submissions and thus total awards be increased, that the success rate be increased, and that per-award amounts be increased. Over a four-year time period this would represent a net increase of \$2 billion to the SBIR/STTR program.

**Table 3. Proposed Increases to SBIR/STTR Funding**

<b>SBIR/STTR</b>	<b>Current Funding Annual Total</b>	<b>Awards</b>	<b>Total Submissions</b>	<b>Percent Funded</b>
Total 2009	\$ 750,000,000	1,800	6,000	30.0%
Less, current funding	(350,000,000)	(1,280)	(5,400)	
Total 2010	\$ 825,000,000	1,980	6,600	30.0%
Less, current funding	(350,000,000)	(1,280)	(5,400)	
Total 2011	\$ 907,500,000	2,178	7,260	30.0%
Less, current funding	(350,000,000)	(1,280)	(5,400)	
Total 2012	\$ 998,250,000	2,396	7,986	30.0%
Less, current funding	(350,000,000)	(1,280)	(5,400)	
Additional funding	\$ 2,080,750,000	3,234	6,246	51.8%
Total funding	\$ 3,480,750,000	8,354	27,846	30.0%

The model reflects the following assumptions:

- Phase 1 awards will be increased to \$250,000 (from \$100,000). Phase 2 awards will be increased to \$1 million (from \$750,000).<sup>5</sup> Current levels of Phase 1 and Phase 2 awards have been in place for at least 10 years. Priority will be given to Fast Track applications, where Phase 1 and Phase 2 proposals are submitted together but technical milestones are clearly delineated prior to release of Phase 2 funding. As in the current practice, program officers would have discretion to make awards in excess of award levels, provided budget requests can be justified.
- To the baseline of total submissions of 5,400, the program will review another 6,000 submissions per year (2,000 more per funding cycle). The model assumes that demand doubles almost immediately, but in practice there is likely to be a steady increase. After the first year, the number of additional submissions is

assumed to increase by 10% each year to reach 7,986. Note that 8,000 total submissions is only slightly higher than the “high” of about 7,000 reached in 2004 without an increase in funding.

- It is assumed that the “reinterpretation” of SBIR/STTR funding eligibility in 2003, where companies that were more than 50% owned by institutional or venture investors were unable to submit to the SBIR/STTR program, dampened enthusiasm.<sup>6</sup> The historically highest number of submissions was in 2004, when almost 6,800 funding proposals were submitted. It is further assumed that demand for SBIR/STTR submissions will increase in the current difficult early-stage funding environment. The author respectfully suggests that job creation should be the focus, *ie* funding eligibility should not be constrained by capital structure. Further, since many venture firms are not investing, and many venture firms have limited partners who also have a strong interest in economic development, the distinction between public and private capital seems moot.
- Current levels of funding are roughly doubled from \$350 million per year to \$750 million in Year 1, and then increased by 10% for the next three years. Total new funds in four years would be about \$2 billion.
- The success rate would be increased to 30%.
- Noting public concern about so-called “grant hogs,”<sup>7</sup> limit the total number of new SBIR/STTR awards to two per year per firm.

## TECHNOLOGY INNOVATION PROGRAM (TIP)

### 1.6 Technology Innovation Program (TIP)

**Background:** TIP (Technology Innovation Program). In 2007 Congress passed legislation in the Omnibus Innovation and Competitiveness Bill (H.R. 2272) - also known as America COMPETES - for the Technology Innovation Program (TIP). The TIP is described as the successor to a previous program, the Advanced Technology Program (ATP), administered by NIST (National Institute of Standards and Technology). The ATP was originally introduced originally by Sen. Fritz Hollings, but was terminated in 2007. Variants of ATP have been replicated all over the world.

The founding statute states that the goal of the TIP is to assist “businesses and universities to accelerate the development of high-risk technologies that will have a broadly-based economic impact.”

Like the ATP, TIP will (1) fund small businesses in areas of strategic and clinical importance to the U.S.; (2) make awards that are large enough (\$3 million) to enable small businesses to reach significant commercial milestones; and (3) require cost-sharing. In a TIP award, cost-sharing may involve indirect as well as direct costs.

Legislation appropriating funds for TIP was passed. However, citing the view that innovation should be financed solely by private capital, President Bush threatened to veto this bill, so the TIP was never fully funded or implemented.

<http://www.aip.org/fyi/2007/103.html>

**1.7 Current status: gearing up and ready for business.** The Act currently authorizes at least \$45 million for new TIP awards each year [http://science.house.gov/legislation/leg\\_highlights\\_detail.aspx?NewsID=1774](http://science.house.gov/legislation/leg_highlights_detail.aspx?NewsID=1774) . Many of the former ATP staff, the ATP email outreach list, the website for information and grants submission remains in place, so that a rapid implementation of TIP is possible.

The first TIP competition in 2008 focused almost exclusively on civil infrastructure, on advance sensing technologies to strengthen our roads, bridges and water systems. The first awards were announced in January 2009.

[http://www.nist.gov/public\\_affairs/releases/20090106\\_TIP\\_2008\\_award\\_announce.html](http://www.nist.gov/public_affairs/releases/20090106_TIP_2008_award_announce.html)

Recently TIP asked for white papers on areas of competitive importance to America. [www.nist.gov/tip/call\\_for\\_white\\_papers\\_dec082.pdf](http://www.nist.gov/tip/call_for_white_papers_dec082.pdf) The portfolio for bioscience topics is still under development.

The author intends to present **Appendix C** to TIP for consideration as a topic for bioscience. **Appendix C** makes the clinical, economic and social case that America should fund the development of new, non-opiate medications to treat the pain of our wounded warfighters. The unsatisfactory treatment of pain is not only the largest single cost in the civilian healthcare system, it also represents the largest cost in our military healthcare system, driven by combat casualties from OEF/OIF. With the support of key constituents like the American Pain Society, Congress recently passed the Pain Management Act. However, this legislation focused on optimizing treatment using currently available drugs, not funding new drugs.

**1.8 TIP track record: ATP track record as proxy.** While TIP is not a reauthorization of ATP, the ATP track record provides a useful proxy. The founding statute for ATP established its “role in providing cost sharing support “for the purpose of assisting United States businesses in creating and applying the generic technology and research results necessary to commercialize significant new scientific discoveries and technologies rapidly.” <http://www.atp.nist.gov/clso/revolutions.html>.

Like the TIP, ATP was a competitive funding mechanism. In 44 competitions held between 1990 and 2004, 768 projects from over 6,000 proposals were selected for cost-shared funding. Approximately 30% percent of these awards (224 projects) involved biosciences or healthcare related technologies. The ATP provided funding up to \$2 million per firm, and could support multi-year budgets.

The ATP provided much needed “gap capital” not just for biosciences, but also for American competitiveness in manufacturing (NIST also administered the MEP, or

Manufacturing Extension Partnership), electronics, and green technologies. Examples of the economic contributions of ATP funding awards include:

- Manufacturing [www.atp.nist.gov/clso/mfg\\_paper\\_2006\\_01\\_24\\_full\\_version.pdf](http://www.atp.nist.gov/clso/mfg_paper_2006_01_24_full_version.pdf)
- Contributing to our aging population [www.atp.nist.gov/iteo/aging\\_technologies\\_final.pdf](http://www.atp.nist.gov/iteo/aging_technologies_final.pdf)
- Maintaining our competitiveness in semiconductor and micro-/nano-technologies [www.atp.nist.gov/iteo/semi-nanoelec.htm](http://www.atp.nist.gov/iteo/semi-nanoelec.htm) as well as photonics and optical technologies [www.atp.nist.gov/iteo/elec\\_phon.htm](http://www.atp.nist.gov/iteo/elec_phon.htm)
- Innovating in healthcare [www.atp.nist.gov/clso/revolutions.html](http://www.atp.nist.gov/clso/revolutions.html)
- Improving harmful industrial emissions through green technologies [www.atp.nist.gov/eao/gcr06-897.pdf](http://www.atp.nist.gov/eao/gcr06-897.pdf)

### 1.9 Proposed funding for TIP biosciences awards

- It is proposed that an additional \$500 million be allocated for TIP for biosciences, to create about 15,000 new biosciences jobs. Current levels of funding suggest limited support of \$18 million for biosciences, or about 7.2 awards per year.

The model for job creation from additional TIP funding assumes the following:

- The still-active ATP database can be augmented by further email and in-person conference outreach to reach the initial target number of 200 submissions the first year, and increasing 10% each year thereafter.
- A success rate of 25% (roughly twice that of 13%, the previous ATP success rate)
- An average of \$2.5 million per award
- Within the TIP portfolio, about 40% of awards will be made to biosciences.
- Call for proposals can be made by mid-2009, with first funding awards in 2010.

**Table 4. Proposed Funding of TIP Biosciences Awards**

<b>TIP, new biosciences funds</b>	<b>Current Funding Annual Total</b>	<b>Awards</b>	<b>Total Submissions</b>	<b>Percent Funded</b>
Total 2010 Biosciences only	\$ 125,000,000	50	200	25.0%
Less, current funding biosciences	(18,000,000)			
Total 2011 Biosciences only	\$ 137,500,000	55	220	25.0%
Less, current funding biosciences	(18,000,000)			
Total 2012 Biosciences only	\$ 151,250,000	61	242	25.0%
Less, current funding biosciences	(18,000,000)			
Total 2013 Biosciences only	\$ 166,375,000	67	266	25.0%
Less, current funding biosciences	(18,000,000)			
<b>Total new funds</b>	<b>\$ 508,125,000</b>	<b>232</b>	<b>928</b>	<b>25.0%</b>

<b>TIP, new biosciences funds</b>		
<b>Total new bioscience funds</b>	\$	508,125,000
Total number of awards (4 yrs)		232
60% salary support	\$	304,875,000
Per job	\$	120,000
Direct jobs created		2,541
Multiplier 5x		12,703
Total new jobs, new funds only		15,244

## MILITARY MEDICAL RESEARCH

**1.10 Background: the military medical research** programs considered here focus on technologies acquired by USAMRMC (U.S. Army Medical Research and Materiel Command) as administered by TATRC [www.tatrc.org](http://www.tatrc.org) (Telemedicine and Advanced Technology Research Center). Since its founding in 1991, TATRC has served as “central laboratory” to find and deliver “cutting edge medical technology for soldier healthcare.” TATRC currently supports over 500 projects in medical robotics, medical imaging technologies, advanced prosthetics, computational biology, biomonitoring, neuroscience, regenerative medicine, chronic disease management, nano-medicine and biomaterials, and medical logistics.

This proposal also details increases to programs administered by AFIRM (Armed Forces Institute of Regenerative Medicine).

The following agencies were not included in this proposal, but increased funding for small biosciences businesses may also be considered:

- BARDA (Biomedical Advanced Research and Development Authority)  
[www.hhs.gov/aspr/barda](http://www.hhs.gov/aspr/barda)
- DARPA (Defense Advanced Research Projects Agency)  
[www.darpa.mil](http://www.darpa.mil)
- DTRA (Defense Threat Reduction Agency)  
[www.dtra.mil](http://www.dtra.mil)

**1.11 The cost of treating Iraq and Afghanistan veterans: our other \$700 billion problem.** In November 2007, in an article entitled “Shock and Awe Hits Home,” Physicians for Social Responsibility (PSR) estimated that the economic cost to America for treating Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) returnees will be \$700 billion.  
<http://www.psr.org/site/DocServer/ShockandAwe.pdf?docID=3161> The PSR estimate was based on actual data from the DVA Gulf War Veterans Information System Report published in November 2006. At Harvard, Bilmes offered a similar estimate in “Soldiers

returning from Iraq and Afghanistan: the long-term costs of providing veterans medical care and disability benefits.”<sup>8</sup> [www.epsusa.org/events/aea2007/papers/bilmes.htm](http://www.epsusa.org/events/aea2007/papers/bilmes.htm)

In his very careful and detailed study entitled “Pain and Emotional Problems Among OEF/OIF Returnees,” Dr. Michael Clark, Clinical Director of the Chronic Pain Rehabilitation Program and Associate Professor, University of South Florida, Tampa, documents how pain is the most vexing clinical, as well as the most costly problem of treating our OEF/OIF veterans.

<http://www.vachronicpain.org/Downloads/PART%20%20Evolving%20paradigms%20OEF%20OIF%20Polytrauma%20Pain%20Clark.pdf>

Congress has enacted some legislation to help our veterans, for example, The Veterans Pain Care Act of 2008 passed in October 2008.

[http://www.painmed.org/advocacy/advocacy\\_news.html#veterans](http://www.painmed.org/advocacy/advocacy_news.html#veterans) The National Defense Authorization Act of 2009 passed in October 2008 contains some elements of a pain care act sought by a broad coalition of constituents. However HR 2994, the National Pain Care Policy Act, failed to pass in late 2008.

**Senior personnel at the VA are aware that our veterans are selling VA-prescribed opiates for street value. Despite this acute medical and social need, there are currently no specific funding programs in military medical research to address the pain of our OEF/OIF returnees, to provide them with new, more effective, non-opiate medications.**

**Recently passed legislation does not directly address the challenge of ineffective and addictive medications.**

To immediately and directly address this problem, the simplest legislative path for increased funding for novel pain medications may lie through a disease-specific program administered by Congressionally Directed Medical Research Programs (CDMRP). Another easy-to-implement legislative path would be to revise upward the appropriations for the related Deployment Related Medical Research Program (DRMRP) in 2009. Thus an increase to fund novel pain drug development is considered in the following section for CRMRP, not as part of USAMRMC or AFIRM programs described below.

**1.12 AFIRM (Armed Forces Institute of Regenerative Medicine).** The AFIRM was launched in April 2008 to focus on harnessing stem cell technology - “regenerative medicine” - to improve the care of our wounded warfighters.

<http://www.defenselink.mil/releases/release.aspx?releaseid=11842>

AFIRM’s scope is limited, focusing only on these selected aspects of regenerative medicine: “burn repair; wound healing without scarring; craniofacial reconstruction; limb reconstruction, regeneration or transplantation; and compartment syndrome (a condition related to inflammation after surgery or injury that can lead to increased pressure, impaired blood flow, nerve damage and muscle death).

<http://www.health.mil/Press/Release.aspx?ID=157> Funding for AFIRM was also limited to research and development with non-human embryonic stem cells (hESC) per President Bush's Executive Order dated August 9, 2001. This proposal assumes that this restriction on research within AFIRM will be lifted.

Ten years after hESC were discovered by Dr. Jamie Thomson at the University of Wisconsin, the current state of clinical progress in regenerative medicine is summarized in the white paper, "Making Stem Cell Research a National Priority" (September 2008).

<http://www.americansforcures.org/article.php?uid=6086> In January 2009 the private company Geron (Menlo Park, California) received the go-ahead from the FDA to start clinical trials in the first patients with acute spinal cord injury. The study uses "presidentially-approved stem cell lines" from hESCs.

<http://edition.cnn.com/2009/HEALTH/01/23/stem.cell/> What this means is that as a nation we are close to breakthrough medicine to repair spinal cord injury, one of the 'signature wounds' of the OEF/OIF conflict.

### **1.13 The United States Army Medical Research and Materiel Command**

**(USAMRMC)** is "the Army's medical materiel developer, with lead agency responsibility for medical research, development, and acquisition; medical information management and information technology; medical logistics management; and health facility planning. The USAMRMC's expertise in these critical areas helps establish and maintain the capabilities the Army needs to fight and win on the battlefield."

<https://mrmc.amedd.army.mil/index.asp>

The USAMRMC achieves many of its technology acquisition goals via Broad Agency Announcement (BAA) from established as well as small bioscience firms, in the public as well as private sector, for example BAA 08-1:

Broad Agency Announcement 08-1 is intended to solicit research ideas that work towards providing solutions to medical problems of importance to the American warfighter at home and abroad.

[http://www.usamraa.army.mil/pages/Baa\\_Paa/mrmcbaalist.cfm](http://www.usamraa.army.mil/pages/Baa_Paa/mrmcbaalist.cfm)

Research proposals are sought from educational institutions, nonprofit organizations, private industry, and domestic and foreign government agencies. This is a continuously open announcement; pre-proposals may be submitted and will be evaluated at any time throughout the year, unless otherwise noted or stated in a separate announcement.

**1.14 Current funding of military medical research.** Historically USAMRMC has partnered with small business through its Office of Small Business Program <http://www.mrmc.smallbusopps.army.mil/#> The Office of Small Business Programs (OSBP) reported that \$524 million was awarded to small businesses in FY08. [www.mrmc.smallbusopps.army.mil/pdf/FY\\_08\\_YEAR\\_END\\_SB\\_metrics.pdf](http://www.mrmc.smallbusopps.army.mil/pdf/FY_08_YEAR_END_SB_metrics.pdf) The Army strives to make 3% of its small business awards to Service-Disabled Veteran-Owned Businesses.

AFIRM was launched in 2008 with the funding of two consortia consisting of about 20 academic and private companies. The AFIRM currently has funding of > \$250M over five years that involves a unique blend of military, public sector and philanthropic funds. Funding from federal sources (Army, Navy, Air Force, VA and NIH) is \$100M, with \$68M in matching funds from state governments and universities that participate in the consortia. These funds are complemented by \$109M in pre-existing research projects, funding by NIH, DARPA, Congressional funding, NSF and philanthropy that directly support the deliverables of AFIRM.

<http://www.defenselink.mil/news/newsarticle.aspx?id=49610>

No funding is proposed to the current consortia. Rather, because of the potential of regenerative medicine, to repair, not just treat damaged nerves; because considerable progress has been demonstrated in CNS-related regenerative medicine; **and because of the great clinical need to treat the CNS-related wounds of OEF/OIF returnees – not just spinal cord injury, but also traumatic brain injury, PTSD, pain and nerve trauma** – this proposal envisions that an additional \$600 million be provided to AFIRM in a new program over a four-year period to focus on CNS-related injuries.

**1.15 Proposed increases to specific military medical research programs.** Table 5 illustrates proposed increases to these two programs:

- A 50% increase in the annual amount awarded to small businesses, to \$750 million, a net increase of \$250 million over four years (new funds \$1 billion); and
- New funds of \$600 million to AFIRM to support projects focused solely on CNS-related injuries (to include traumatic brain injury, spinal cord injury, pain, other forms of nerve trauma and PTSD).

**Table 5. Proposed Increases to Military Medical Research Programs**

<b>MILITARY MEDICAL RESEARCH</b>	<b>Current funds</b>	<b>New funds (four years)</b>
AFIRM - current	\$ 300,000,000	
AFIRM - proposed CNS-related		\$ 600,000,000
USAMRMC - small business only (FY08)	524,000,000	
USAMRMC - 50% increase (4 yrs)		1,000,000,000
	<u>\$ 824,000,000</u>	<u>\$1,600,000,000</u>

<b>MILITARY MEDICAL RESEARCH, NEW FUNDS</b>	
<b>Total new military research funds</b>	\$ 1,600,000,000
60% salary support	\$ 960,000,000
Per job	\$ 120,000
Direct jobs created	8,000
Multiplier 5x	40,000
Total new jobs, military research	48,000

## CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

**1.15 Background.** This section considers additional funding for **Congressionally Directed Medical Research Programs** (CDMRP) [www.cdmp.r.army.mil](http://www.cdmp.r.army.mil) and the recent variant, the **Deployment Related Medical Research Program** (DRMRP). The DRMRP first solicited proposals in FY08.

**A new CDMRP program to fund development of new, more effective non-opiate medications to treat acute and chronic pain is proposed.**

**Appendix C** gives additional detail on the clinical and treatment problems of chronic pain affecting OEF/OIF returnees.

For 2007 only, Congress appropriated and funded \$300 million of research to address PTSD (post traumatic stress disorder) and TBI (traumatic brain injury). This was authorized and awarded via a disease-specific CDMRP program.

**How CRMRP is funded.** The CRMRP is funded through DoD via the annual Defense Appropriations Act. A significant component of CDMRP's focus and funding comes from patient advocates:

“The Office of Congressionally Directed Medical Research Programs (CDMRP) is funded through the Department of Defense (DoD), via annual Congressional legislation known as the Defense Appropriations Act. For most programs, the DoD sends a multi-year budget request to Congress in the form of the President's Budget. However, dollars for the CDMRP are not considered part of the DoD's core mission, and are therefore not included in the DoD's requested budget. Rather, the dollars to fund CDMRP are added every year during the budget approval cycle by members of the House or Senate, in response to requests by consumer advocates and disease survivors.” <http://cdmp.r.army.mil/fundingprocess.htm>

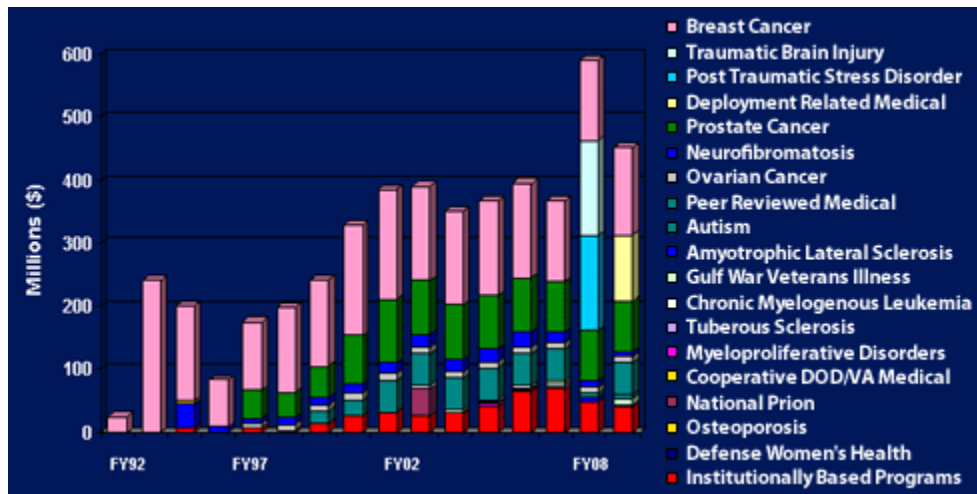
In its start-up year in 1992, the CDMRP initially focused on breast cancer. Over time the program was expanded to address other underserved diseases. Other diseases targeted with CDMRP funding include various cancers as well as “orphan diseases” (defined as having 200,000 or less patients in the U.S.).<sup>9</sup> Table 6 summarizes the funding history for CDMRP from 1992 through 2006, in which CDMRP reviewed 52,000 research proposals, of which 8,316 (16%) were funded.

**Table 6. Summary Funding History for CDMRP**

Research Program	FY	Amount for Research	Proposals Received	Proposals Funded
Breast Cancer	92-07	\$1,801.1 M	34,455	5,187
Defense Women's Health	1995	\$32.8 M	559	69
Osteoporosis	1995	\$3.7 M	105	5
Neurofibromatosis	96-07	\$158.6 M	799	209
Prostate Cancer	97-07	\$709.9 M	8,401	1,837
Ovarian Cancer	97-07	\$96.9 M	1,875	170
Peer-Reviewed Medical Research	99-06	\$295.7 M	2,307	247
DOD/VA	99-00	\$6.0 M	88	9
Chronic Myelogenous Leukemia	02-06	\$19.3 M	252	61
Prion Diseases	2002	\$37.2 M	136	38
Tuberous Sclerosis	02-06	\$11.9 M	173	48
Myeloproliferative Disorders	2004	\$3.6 M	18	9
Gulf War Illness	2006	\$4.5 M	31	9
Autism	2007	\$6.5 M	289	18
Amyotrophic Lateral Sclerosis	2007	\$4.5 M	21	3
Psychological Health	2007	\$277.3 M	2,110	201
Institutionally Based Programs	95-06	\$329.4 M	235	196
<b>TOTALS &gt;&gt;&gt;</b>		<b>\$3,798.9 M</b>	<b>51,854</b>	<b>8,316</b>

Tables 7A and 7B below give a different view of the funding history of CDMRP. Including 2007 and 2008 funding, CDMRP has managed \$4.8 billion in funding appropriations. <http://cdmrp.army.mil/fundinghistory.htm>

**Tables 7A & 7B. Summary of Funding History of CDMRP**



Research Program	FY	Appropriation
Breast Cancer	92-08	\$2,229.8 M
Defense Women's Health	1995	\$40.0 M
Osteoporosis	1995	\$5.0 M
Neurofibromatosis	96-08	\$190.3 M
Prostate Cancer	97-08	\$890.0 M
Ovarian Cancer	97-08	\$121.7 M
Peer-Reviewed Medical Research	99-06, 08	\$395.5 M
DOD/VA	99-00	\$6.8 M
Chronic Myelogenous Leukemia	02-06	\$22.1 M
Prion Diseases	2002	\$42.5 M
Tuberous Sclerosis	02-06, 08	\$17.5 M
Myeloproliferative Disorders	2004	\$4.3 M
Gulf War Illness	2006, 2008	\$15.0 M
Autism	07-08	\$13.9 M
Amyotrophic Lateral Sclerosis	2007	\$5.0 M
Psychological Health	2007	\$301.0 M
Deployment Related Medical	2008	\$105.2 M
Institutionally Based Programs	95-08	\$406.6 M
<b>TOTALS &gt;&gt;&gt;</b>		<b>\$4,812.1 M</b>

**Deployment Related Medical Research Program: DRMRP is a sub-program of CRMRP.** The goal of DRMRP funding is to “address prevention, diagnosis, treatment, and mitigation of deployment-related injuries and psychological health concerns.” The DRMRP program was established in FY08 to administer a total of \$235 million - of funds appropriated under the Fiscal Year 2008 Supplemental Appropriations Bill (P. L. 110-252). <http://cdmrp.army.mil/pubs/press/2008/08drrmpreann.htm> Of the total \$235 million, the FY08 solicitation (closed in October 2008) stated the goal of awarding \$92 million. Funding mechanisms and award amounts for DRMRP include:

Award Mechanism	Period of Performance	Funding Amount
Hypothesis Development Award	18 months	\$150,000 in direct costs
Advanced Technology/Therapeutic Development Award	Up to 5 years	Up to \$5,000,000 in total costs (direct and indirect) per year
Clinical Trial Award	Up to 5 years	Up to \$5,000,000 in total costs (direct and indirect) per year

The main Research Topic Areas in the DRMRP announcement in 2008 included:

- blood safety and blood products;
- final development of medical devices for use in theater (including portable suction machines and EKGs for theater hospitals);
- injury prevention;
- TBI and psychological health (including PTSD);
- trauma treatment and rehabilitation (including face, visual/ocular and nerve damage, dental, and auditory systems);

- wound infection and healing; and
- wound infection vaccines.

Topic Areas included “pain management to improve short-term outcomes and reduce the risk of long-term opioid dependence and/or abuse” as part of the treatment gap for TBI and Psychological Health. However, pain was only one out of 45 sub-topics listed in the Program Objectives for the DRMRP solicitation.<sup>10</sup>

From discussions with military physicians at the ATACCC conference (Advanced Technology Applications for Combat Casualty Care) in August 2007 and 2008, the author understands that no military medical research programs and no aspect of CDMRP presently **directly** address the lack of effectiveness of currently marketed pain medications, the social problems associated with opiate therapy, and the cost problems of treating our wounded warriors for pain.

**Traumatic Brain Injury Medical Research Program.** In 2007 supplemental DOD funding provided \$150 million for Post Traumatic Stress Disorder (PTSD) and \$150 million for Traumatic Brain Injury (TBI). The goal of this funding was to complement other DOD efforts. The program is administered by USAMRMC through CDMRP. <http://cdmrp.army.mil/pubs/press/2007/07ptsdtbipreann.htm> There is apparently no additional funding planned within CDMRP for therapeutic approaches to PTSD and TBI.

**1.16 Current funding for CDMRP and DRMRP.** The FY09 Defense Appropriation Act (Public Law 110-329) provides research funding for the following programs managed by the Department of Defense office of CDMRP (in US\$ millions):

**Table 8. Current (FY09) Funding for CDMRP**

<u>Congressionally Directed Medical</u>	
<u>Research Programs</u>	<u>FY09</u>
Breast cancer	\$ 150
Prostate cancer	80
Ovarian cancer	20
Neurofibromatosis	10
Tuberous Sclerosis	6
Autism	8
Gulf War Illness	50
Other peer reviewed programs	50
<b>Total, current funding</b>	<b>\$ 374</b>

Table 9 summarizes 22 programs that have been funded under CDMRP involving pain (\$12 million). Of the 22, 11 address cancer pain, 3 address pain associated with neurofibromatosis, 7 involve chronic pain, and one involves musculoskeletal pain. The CDMRP has made seven grants focused on non-cancer chronic pain totaling \$5.2 million. Of these, five represented \$5 million and two grants totaling approximately

\$225,000 were made in 2007 as part of the program on Psychological Health and Traumatic Brain Injury.

**Table 9. CDMRP Awards Involving Chronic Pain**

<b>CDMRP Programs Involving Chronic Pain</b>		
2004	University of Texas Health Science Center (Houston) PI: Lichtenberger, L.M. "Use of PC-NSAIDs in Chronic Pain" Program: Peer-Reviewed Medical Research Program	\$ 1,789,202
2005	University of Florida PI: George, S. Z. "Prevention of Low Back Pain in the Military: A Randomized Clinical Trial" Program: Peer-Reviewed Medical Research Program	1,008,426
2006	Rutgers PI: Devore, D. I. "Chronic Pain Treatment by Controlled Release of Local Anesthetics from Biocompatible Hydrogel Wound Dressings" Program: Peer-Reviewed Medical Research Program	650,810
2006	University of Texas (Southwestern Medical - Dallas) PI: Bezprozvanny, I. "Development of Novel Therapy for Chronic Neuropathic Pain" Program: Peer-Reviewed Medical Research Program	840,574
2006	University of Virginia PI: Laurencin, C.T. "Development of a Novel Injectable Controlled Analgesic Delivery System for Effective Pain Management" Program: Peer-Reviewed Medical Research Program	698,279
2007	Indiana University PI: Krebs, E. "Post-Traumatic Stress Disorder and Pain Comorbidity in Veterans" Program: Psychological Health and Traumatic Brain Injury	198,959
2007	Brentwood Medical Institute PI: Wallbom, A. "A Pilot Study to Identify Barriers to Treatment in OIF/OEF Veterans with PTSD and Low Back Pain in Establishing Transdisciplinary Complementary Interventions" Program: Psychological Health and Traumatic Brain Injury	26,796
Total		\$5,213,046

**1.17 Track record of CDMRP and DRMRP.** The track record of CDMRP in contributing to new therapies is not known. The DRMRP is too new to be able to assess its success or impact.

**1.18 Proposed increases to CDMRP and DRMRP.** Table 10 proposes an additional \$2.15 billion in funding to CDMRP to address veterans' issues over a four-year period. Of the total \$2.15 billion, \$400 million would be focused on developing new, non-opiate pain medications to treat chronic pain. By contrast, the NIH currently spends \$221 million a year on pain research, a figure which has remained virtually unchanged during the period 2001-2008.<sup>11</sup>

Table 10 also proposes increases for existing CDMRP programs, for the DRMRP awards, and renews funding for developing PTSD/TBI therapies.

**Table 10. Proposed Increases to Congressionally Directed Medical Research Programs & Deployment Related Medical Research Program**

<b>Congressionally Directed Medical Research Programs</b>	<b>Current funds</b>	<b>New funds (4 yrs)</b>
Congressionally Directed Medical Research Programs	\$ 375,000,000	\$ 750,000,000
Deployment Related Medical Research Programs	92,000,000	400,000,000
Deployment Related - Pain	-	400,000,000
Deployment Related - Traumatic Brain Injury (TBI), funded in 2007	300,000,000	600,000,000
	<u>\$ 767,000,000</u>	<u>\$ 2,150,000,000</u>

<b>CDMRP, NEW FUNDS</b>	
<b>Total new CDMRP funds</b>	\$ 2,150,000,000
60% salary support	\$ 1,290,000,000
Per job	\$ 120,000
Direct jobs created	10,750
Multiplier 5x	53,750
<b>Total new jobs, new funds CRMRP</b>	<b>64,500</b>

Key assumptions include:

- Increase CDMRP funding by 50% each year, total new funds would be \$750 million over the next four years
- Double the amount of funding available for DRMRP
- Initiate a new program for pain within Deployment Related program, funded at \$100 million per year
- Renew funding for PTSD/TBI at \$150 million per year for four years
- No assumptions were made about number of awards, average size of award, or number of firms funded, or whether public or private sector. Historically these have been made at the discretion of the Department of Defense as administrator for CDMRP, together with the patient advocates involved in the review process. The primary emphasis here is finding the best technologies for our veterans, with a secondary emphasis on job creation in small businesses.

## **SMALL BUSINESS INVESTMENT COMPANIES (SBIC) EARLY-STAGE BIOSCIENCES FUNDS**

**1.19 Background.** Small Business Investment Companies (SBIC) is a program of Small Business Administration (SBA) where private funds are leveraged with federal borrowing provided to venture investment companies.

This Section details the concept and rationale for a new SBIC program focused on early-stage bioscience investment, reviews the basics of the SBIC program as they currently exist, and quantifies potential job created from the proposed \$400 million funding amount.

The new SBIC program is considered in the context of the current shift in biosciences investment from a venture capital model to one more closely resembling private equity, where value is created for investors from development and sale of assets, not equity.

Venture capital plays a key role in job creation in America. A 2008 study (“Venture Impact”) by the National Venture Capital Association quantified the positive contribution of venture capital investment in all sectors of technology:

Together, the nation’s venture capital backed companies employed over 10.4 million American workers in high-quality jobs and generated \$2.3 trillion in revenue in 2006. The total revenue of venture capital financed companies comprised 17.6 percent of the nation’s gross domestic product (GDP) and 9.1 percent of U.S. private sector employment in 2006.

The payoffs for venture capital investments are enormous. Similar to recent years, \$26 billion was invested in 2006. This represented just 0.2 percent of U.S. GDP. Revenue generated by the universe of venture backed companies in 2006 corresponded to 17.6 percent of GDP.

Venture capital backed companies outperformed their non-ventured counterparts in job creation and revenue growth. Employment in venture backed companies jumped by 3.6 percent, while national employment grew by just 1.4 percent, between 2003 and 2006. At the same time, venture capital backed company sales grew by more than 11.8 percent, compared to an overall rise in U.S. company sales of 6.5 percent during the same period. <http://www.asiaing.com/venture-impact-the-economic-importance-of-venture-capital-backed-companies-to-the-u.s.-ec.html>

**1.20 Concept: Early-stage Bioscience Funds.** A new class of SBIC venture funds focused on early-stage biosciences is proposed with funding of \$400 million.

Capital from this SBIC program would be awarded to 16 firms, \$25 million per fund, allocated to eight regions where academic and entrepreneurial infrastructures can

support biosciences innovation: (1) California, (2) Northwest, (3) Rocky Mountains, (4) Midwest, (5) Southwest, (6) Southeast, (7) Midatlantic, and (8) Northeast. Fund managers may be established or emerging firms, but the program would have an emphasis on jumpstarting “debut” fund managers, providing they have a strong biosciences industry background supporting their application.

**1.21 Rationale for Early-stage Bioscience Funds.** There are several reasons for jumpstarting a new class of bioscience investment firms:

- As described by the headlines of recent news articles below, funding for early-stage biosciences, particularly for projects with long-term horizons like therapeutics, has all but disappeared. Capital markets have “seized.”
- One major hurdle to limited partners’ decision to fund new venture capital firms is track record. “Track record” considers (1) whether an investment team has worked together before, (2) whether the emerging firm will actually invest as it states it will, and (3) return-on-investment (ROI) history. In addition to filling the early-stage funding gap, this proposal would enable a new class of venture firms by supporting so-called ‘debut funds.’
- Using the job values and multiplier impact described above, not counting fund managers, \$400 million would support 1,800 direct and 9,000 indirect jobs in portfolio companies, for a total of 10,800 jobs created.

Funding cuts to the SBA since 2000 have weakened the agency. This proposal assumes that funding to the SBA will be restored to at least 2000 levels.

**1.22 Basics of the current SBIC Program.** From the SBA website [www.sba.gov](http://www.sba.gov) :

“The SBIC Program is one of many financial assistance programs available through the U.S. Small Business Administration. The structure of the program is unique in that SBICs are privately owned and managed investment funds, licensed and regulated by SBA, that use their own capital plus funds borrowed with an SBA guarantee to make equity and debt investments in qualifying small businesses..... Detailed regulations for SBICs are included in [www.sba.gov/tools/resourcelibrary/lawsandregulations/index.html](http://www.sba.gov/tools/resourcelibrary/lawsandregulations/index.html).

- “An SBIC can be organized in any state, as either a corporation, limited partnership (LP), or a limited liability company (LLCs must be organized under Delaware law). Most SBICs are owned by relatively small groups of local investors, although many are owned by commercial banks.....
- “SBICs may invest only in qualifying small business concerns as defined by SBA regulations. Generally speaking, SBICs may not invest in the following: other SBICs, finance and investment companies or finance-type leasing companies,

unimproved real estate, companies with less than 51% of their assets and employees in the United States, passive or casual businesses (those not engaged in a regular and continuous business operation), or companies which will use the proceeds to acquire farm land.....

- “SBA leverage is designed to operate on a zero-subsidy basis. To obtain leverage, SBICs issue debentures, which are guaranteed by SBA. Pools of these SBA guaranteed certificates are sold to investors through periodic public offerings. Debentures have a term of ten years and provide for semi-annual interest payments and a lump sum principal payment at maturity.....”

**1.23 Proposed funding of Early-Stage Bioscience Funds.** Table 11 quantifies the job creation effect from Early-Stage Bioscience Funds.

**Table 11. Proposed Increase to SBIC Early-Stage Bioscience Funds**

<b>Early-Stage Bioscience Funds</b>	
Principal	\$ 400,000,000
Number of firms @ \$25M	16
Operating costs @ 10%	\$ (40,000,000)
Funds available for investment	\$ 360,000,000
60% salary support	\$ 216,000,000
Per job	\$ 120,000
Direct jobs created	1,800
Multiplier 5x	9,000
Total new jobs, new funds only	10,800

**1.24 Limited investment time horizon.** The time horizon of these Early Bioscience Funds would be short: four years. In addition to the investment thesis, the relatively modest amount of capital will effectively constrain firms to focus on seed-stage investments of between \$250,000-\$500,000.

- **Criteria.** Criteria for SBA awards to new fund managers for Early-Stage Bioscience Funds will be as rigorous as for established firms, with an absolute requirement for hands-on project management and executive experience. In other words, this program would fund few Wall Street transplants, but rather individuals with a commitment to their own regional economies.
- **Follow-on capital.** After two or three years, SBIC Early-Stage Bioscience Funds would need to raise additional private or institutional capital and/or find other means of leveraging their early-stage investments.

**1.25 Shift to private equity model.** A key assumption in this proposal is that the venture capital model used in the past 25 years – where venture investors made money on increased equity value, and exit when initial public offering (IPO) markets are robust – is gone. The reason is the math: public markets demand later-stage clinical products

and investors have a pool of public companies to consider. The longer timeline requires entrepreneurs to raise additional equity capital. This means that time-to-exit and dilution has become increasingly disadvantageous to early-stage investors.

For example, when considering an investment in a company developing a novel therapeutic, a venture capital investor will logically prefer to invest \$5 million in a Series C investment with clinical data that promises an exit strategy within three years, than invest the same \$5 million in a Series A financing round to support development of a relatively unproven drug that is still in animal, or preclinical studies. The ROI on the second, earlier-stage investment is lower because of increased clinical risk, more capital and more dilution required and longer time-to-exit.

The industry average “probability of success” for investing in pharmaceutical products has remained relatively steady over the past 30 years. Only about 10% of drugs that make it to Phase 1 clinical studies eventually make it to market. Drugs that are further along in development, for example in Phase 3 clinical trials – where some clinical effectiveness has already been observed – have a 50% chance of garnering FDA approval. (Pharmaceutical Research and Manufacturers Association, PhRMA at [www.phrma.org](http://www.phrma.org))

Since Genentech’s IPO in 1982, as more bioscience companies have been funded and more have gone public, venture investors have had more choice. Logically they have sought less risk for the same amount of money. Over time, IPO markets have rewarded later- and later-stage companies. Thus bioscience firms have had to raise additional private and venture capital prior to tapping public markets. But exit valuations have remained stagnant. Put another way, when it takes \$150 million in venture capital to develop a drug so that the IPO market will accept a public listing, but the IPO valuation is \$150 million, the math doesn’t make sense, particularly for early-stage investors.

**1.26 Making the math work: new biosciences investment model.** The author supports a new biosciences investment model, where early-stage bioscience investors offset the risk of lengthy product cycles by minimizing corporate overhead, staying ‘virtual,’ and leveraging equity investment with non-equity funding.

For the math to work, a new biosciences early-stage investment model must pursue one or combine several of these strategies:

- Where possible, partner with, and leverage the infrastructure of academic institutions. For drug development, piggyback on existing bench infrastructure to carry out key preclinical studies. Partner with academic hospitals committed to running early clinical studies, for example, the Institute for Translational Medicine and Research at the University of Pennsylvania <http://www.itmat.upenn.edu/>
- Adapt to the private equity model, where the value lies in the asset or product, not in the company. Assume the liquidation event will be trade sale not IPO.

- Leverage private and institutional capital with philanthropic capital, state and federal funding programs. In 2007, the amount of philanthropic funding (“venture philanthropies”) invested as equity in emerging biosciences firms was \$75 million. <http://www.signonsandiego.com/news/business/biotech/20080620-9999-1n20groups.html>
- Access regional or state-based initiatives to keep bioscience R&D and manufacturing in America. As described below, locate in states that have programs that support biosciences with cash and/or infrastructure support, for example, Massachusetts, Connecticut, Pennsylvania and Colorado.
- Amortize the cost of project management and administrative personnel by having early-stage bioscience firms act as “business incubators” to portfolio companies, *ie* share bookkeeping, accounting, auditing and project management cost. This was the investment model followed by Cambridge Quantum Fund I (a seed investment fund focused on technologies from Cambridge University, 1990-1994, Cambridge, UK.<sup>12</sup>). In that model, about 80% of the Chief Executive’s time was directly allocated to portfolio companies as the “hands-on” financial and executive manager. Of the remaining 20% of total fund capital, approximately half, or 10% of the total represented the costs of due diligence that became part of the investment when deals were completed. The number of failed investments, where due diligence did not materialize into completed investments, was low.
- Operate portfolio investments as virtual companies, accessing specialized contract research organizations (CROs).

In other words, setting aside other key issues like luck, access to quality deal flow, hands-on experience, prudent use of funds and effective governance practices, early-stage bioscience investment firms can accept the long time horizons required in bioscience product development, but improve ROI by minimizing equity dilution by attracting non-dilutive public and philanthropic capital.

Very generally, the capital required for various products to reach their first key milestone - when trade sale is possible and attractive - is:

- \$ 5 million for diagnostics, tools
- \$10 million for medical devices, agricultural and environmental diagnostics
- \$20 million for novel therapeutics to reach Phase 2 clinical trials, or “clinical proof”

For example, a portfolio company involved in cancer diagnostics would need \$5 million to complete its first product prototype and two alpha-stage reviews from clients. At this point, based on 2008 trade sale data, a cancer biomarker would be worth about \$15 million to an acquirer. Say the early-stage equity investor contributes \$2 million, with the other \$3 million from non-equity sources. Thus a trade sale of \$15 million would represent a return of 7x on the early-stage investor’s money.

**1.27 Restore SBA funding to 2000 levels.** This proposal assumes that funding to the SBA itself will be increased. Since 2001, excluding new funding for disaster loans, the SBA budget has been cut by roughly 41 percent. Lending through the SBA's main 7(a) and 504 programs is down 55 percent and 36 percent, respectively, down about 50% since the financial meltdown. <http://www.allbusiness.com/economy-economic-indicators/economic-conditions-recovery/7388168-1.html>

"The SBA is not the organization it used to be," said Margot Dorfman, chief executive of the U.S. Women's Chamber of Commerce, during a recent congressional hearing. "Eight years of budget cuts and poor executive leadership have gutted the organization. Many longtime, skilled employees and managers have left. Even now, we continue to hear that the SBA is not adequately supporting the businesses who are struggling Katrina disaster victims, and again who have been impacted by [hurricanes] Gustav and Ike."

## SECTION 2

**Section 2. High Regional Benefit to Taxpayers of Life Sciences Economies.** This section reviews how financing for small bioscience businesses is drying up in the current financial crisis, discusses the methodology used to estimate the economic multiplier effect, and explores examples of states' efforts to support small biosciences businesses. Finally, American competitiveness in a global context is considered.

**2.1 Current funding for early-stage bioscience: a looming funding gap.** With the IPO window “nailed shut,”<sup>13</sup> as of mid-January 2009, about 300 companies – 75% out of total 400 publicly traded small bioscience businesses – have less than one year of cash. Of the 300, 120 have less than six months of cash. But the capital markets for small bioscience businesses have “seized” – there is effectively no capital for these emerging companies <http://www.burrillreport.com/article-1019.html> The current funding crisis is illustrated by selected headlines using titles like “littered with financial wreckage,” “crisis,” “drastic,” “bankruptcies,” and “doom and gloom”:

- “Biotech buyout spree ahead as values crumble”  
January 6, 2009  
<http://www.fiercebiotech.com/story/biotech-buyout-spreed-ahead-values-crumble/2009-01-06>
- “Biotechs claw for their lifeblood – financing”  
November 16, 2008  
<http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2008/11/16/BUHT1440RI.DTL&hw=biotech&sn=002&sc=849>
- “Drastic cuts among some biotech companies”  
November 30, 2008  
<http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2008/11/30/BUBM14CSKM.DTL>
- “Biotech’s Umbilical Cord Has Been Severed”  
December 1, 2008 (Vol. 28, No. 21)  
<http://www.genengnews.com/articles/chitem.aspx?aid=2701>
- “Economic crisis hammers small, mid-sized biotechs”  
November 17, 2008  
[http://www.fiercebiotech.com/story/economic-crisis-hammers-small-mid-sized-biotechs/2008-11-17?utm\\_medium=nl&utm\\_source=internal&cmp-id=EMC-NL-FB&dest=FB](http://www.fiercebiotech.com/story/economic-crisis-hammers-small-mid-sized-biotechs/2008-11-17?utm_medium=nl&utm_source=internal&cmp-id=EMC-NL-FB&dest=FB)
- “Credit crisis pushes biotechs to the brink”  
November 24, 2008  
<http://www.fiercebiotech.com/story/credit-crisis-pushes-biotechs-brink/2008-11-24>
- “VCs forecast: Doom and gloom for next two years”  
November 29, 2008  
<http://www.fiercebiotech.com/story/vcs-forecast-doom-and-gloom-next-two-years/2008-11-19>

- “Crisis in the lab: biotech bankruptcies are looming”  
November 2008

<http://www.pharmalot.com/2008/11/crisis-in-the-lab-biotech-bankruptcies-are-looming/>

**2.2 Case for economic multiplier effect from the biosciences industry.** Without distinguishing between small and established firms, in 2004 the Milken Institute quantified the multiplier effect for biotechnology:

<http://www.milkeninstitute.org/publications/publications.taf?function=detail&ID=377&cat=ResRep>

“For every \$1.00 invested in a biotech company, another \$6.70 “biotech job value” finds its way into the regional economy. Only 25 years after the first scientific discovery, the industry accounts for 2.7 million jobs and \$172 billion in real economic output (2003).

<http://www.biopharmaimpact.com/index.taf?page=mul&section=stateimpact>

A subsequent Milken Institute analysis in June 2008 quantified benefits to states and regional economies that actively support biosciences.

<http://www.milkeninstitute.org/pdf/StateTechScienceIndex.pdf>

**2.3 Economic development in biosciences reaps benefits for states.** The biotechnology industry emerged without public sector support in the late 1970s, led originally by California and Massachusetts. Since then other states have invested aggressively and wisely in biosciences, with impressive results. About 30 of the 50 states (California has none) have some form of economic incentive to attract small biosciences businesses, or keep big pharma from moving out of state. The economic development efforts of states – and concomitant successes - are well documented in “Technology, Talent and Capital: State Bioscience Initiatives 2008” (“Battelle report”)

[http://bio.org/local/battelle2008/State\\_Bioscience\\_Initiatives\\_2008.pdf](http://bio.org/local/battelle2008/State_Bioscience_Initiatives_2008.pdf)

Three different approaches to state economic development by supporting biosciences as practiced by Colorado, Pennsylvania and North Carolina are given below.

**Colorado.** In 2003 the state of Colorado acted together with the Colorado Bioscience Association to support bioscience companies, including launching a state-backed \$30 million investment fund. Five years later, Colorado has 430 bioscience companies, up from 230 companies. Job creation also jumped, from 12,000 direct jobs to more than 18,000 in the state. Prior to the last quarter of 2008, venture capital investment in these firms had also quadrupled, to almost \$350 million. <http://www.ddmag.com/article-economic-development-Colorado-Bioscience.aspx>

**Pennsylvania.** Twenty years ago the Commonwealth of Pennsylvania established regional Technology Partnerships, for example, Ben Franklin Technology Partners Southeastern Pennsylvania, to support small innovative businesses in the state. [http://www.sep.benfranklin.org/capital/funding\\_bio.html#application](http://www.sep.benfranklin.org/capital/funding_bio.html#application) The BFTPs support technology as well as biosciences. The investment remit of BFTPs is to (1) support seed start-ups in the range of \$100,000 - \$500,000 and/or (2) coinvest between

\$200,000 - \$3 million alongside other sources, including SBIR, angel or other early-stage venture sources.

After 20 years, the Commonwealth reported a 23x multiplier effect [http://www.benfranklin.org/our\\_impact/index.asp](http://www.benfranklin.org/our_impact/index.asp) :

“...the Commonwealth’s investment in the BFTP has yielded substantial returns for Pennsylvania taxpayers. From 1989 to 2001, BFTP boosted the state’s economy by \$8 billion and helped to create 93,105 job-years\*. In addition, during the same period, **every public dollar invested by BFTP yielded nearly \$23 of additional state income.** [Job years are defined as the number of jobs created that lasted a full year or more multiplied by the number of years they have existed to date].....The state garnered more than \$400 million in additional tax revenue as a direct result of the program, which more than covered the operating costs of the program over the same period.....BFTP boosted Pennsylvania’s economy by \$8 billion.”

**North Carolina.** A recent report from Battelle Institute quantified the state of North Carolina’s investment in life sciences over the past decade: \$1.2 billion in research, infrastructure, incentives, and workforce training. <http://www.ncbiotech.org/billion/> The payoff was substantial: this “investment” of \$1.2 billion yielded a thriving industry with more than 500 companies, with a net impact of \$56.6 billion and 180,000 jobs:

- 180,007 jobs
- \$9.4 billion in employment compensation
- \$45.8 billion in North Carolina business volume
- \$1.44 billion in taxes generated for state and local government

**2.4 Strengthen America’s global competitiveness in life sciences.** As Small Business Majority [www.smallbusinessmajority.org](http://www.smallbusinessmajority.org) notes:

“The backbone of the American economy, 25 million small businesses make up 52% of private sector workforce. Small business creates 75% of all new jobs and anchors our communities.”

The life sciences industry dates back to 1973, when the basic research of Cohen and Boyer yielded a technique known as recombinant DNA technology. Thirty-five years later about 2,000 small pharmaceutical businesses – a selected subset of total bioscience businesses - have gone public,<sup>14</sup> contributing more than 200 approved drugs and vaccines with estimated sales of \$60 billion. Another 2,000 drug products are in the FDA pipeline.<sup>15</sup>

[http://www.phrma.org/news\\_room/press\\_releases/more\\_than\\_2000\\_new\\_medicines\\_in\\_development\\_for\\_older\\_americans/](http://www.phrma.org/news_room/press_releases/more_than_2000_new_medicines_in_development_for_older_americans/) . In addition to new medicines, biotechnology-based products have improved agriculture, law enforcement (DNA fingerprinting), and helped protect the environment.

By continuing to practice an almost exclusively *laissez faire* approach at the federal level to funding biosciences innovation, America places its indigenous biosciences businesses at a significant global strategic disadvantage: lack of access to early-stage capital. As shown in the examples below, other countries are building all around us, and American biosciences businesses are outsourcing key aspects of R&D.

**Spain.** After investing 1 Billion Euros, in 2008 Genoma España (the Spanish Foundation for the Development of Genomic and Proteomic Research) reported growth of 25% a year in biotech in job creation, attracting investment, and spurring sales and exports in Spain. From 2000-2006, the Spanish government invested this amount via its Ministry of Education and Science and Ministry of Health and Consumers. Overall, subsidies for R&D and scientific infrastructure increased by over 200%.  
<http://www.genengnews.com/articles/chitem.aspx?aid=2696>

**France.** In 1998, France founded Genopole® as an entire biotechnology complex – “gene city and biotech city” - near Evry, a city south of Paris. [www.genopole.fr](http://www.genopole.fr) The biosciences complex was created at the initiative of the French Government, local authorities and the Association Française contre les Myopathies to bring together “academic and private research laboratories, biotechnology companies and higher education in one place.” In addition to a shared facility with a state-of-the-art biological and computing center, there is a services- and facilities-based incubator and now a Stem Cell Research Centre Project <http://www.genopole.fr/html/en/recherche/institut-cellules-souches/index.htm> with bioreactors for pilot scale GMP cellular tissue for clinical studies.

Genopole hosts a seed fund known as Genopole® Premier Jour (“Day One” or G1J), an early-stage vehicle that has been funded over ten years with about US\$10 million. Since founding G1J has invested in 25 companies. These companies currently employ 200 people in 21 companies, with 25 products in preclinical and clinical development. Following seed funding from G1J, these companies attracted several hundreds of millions more in investment capital.

**New Zealand (population 4.1 million).** As of 2006, after increasing the government’s support for biotechnology by 20% between 2004 and 2005 to NZ\$640 million, New Zealand saw biotech export revenue increase by 30%, contributing NZ\$300 million per year. There are now 126 private and public sector life sciences companies in New Zealand employing 2,200 people.

**Scotland (population 5 million).** Scotland has perhaps made the most concerted effort of any country to invest in biosciences, both in terms of per capita figures and actual results. The country is now home to 600 life sciences organizations. In infrastructure alone the Scottish government has invested \$1 billion in the Edinburgh BioQuarter; \$118 million for the Scottish Center for Regenerative Medicine encompassing translational medicine capabilities; and \$50 million for the Division of Signal Transduction Therapy. <http://www.dddmag.com/article-Scotland-Incubator-For-Drug-Discovery.aspx> The pharma company Wyeth has established a Translational

Medicine Research Collaboration with the country via Scotland's economic development arm, Scottish Enterprise.

In addition, Scottish Enterprise Investments (SEI) manages three funds that provide risk capital investment for Scottish-based companies: the Scottish Seed Fund, the Scottish Co-investment Fund and the Scottish Venture Fund. [http://www.scottish-enterprise.com/sedotcom\\_home/grow-your-business/find-money-to-grow/equity-funding.htm](http://www.scottish-enterprise.com/sedotcom_home/grow-your-business/find-money-to-grow/equity-funding.htm) This is a tiered strategy to address funding gaps in seed capital, venture capital to growth capital. In about five years, the SEI funds have invested an estimated \$250 million in emerging bioscience businesses in Scotland.

**India.** India may be considered to be a major partner in America's health. India is home to 43% of the 1,154 pharmaceutical plants registered with the FDA that make all of America's generic medicines. And half of Americans take these medicines. We have moved much of our generics manufacturing offshore in part to avoid the costs of regulation. <http://www.nytimes.com/2009/01/20/health/policy/20drug.html?src=linkedin>

But now India is emerging from its "generics only" mindset. It is unlikely in the present financial downturn that the Indian government will continue with plans for 20 life sciences bioparks, but clearly the strategic thinking has been done. [http://economictimes.indiatimes.com/News/News\\_By\\_Industry/Healthcare\\_Biotech/20\\_more\\_biotech\\_parks\\_to\\_come\\_up\\_in\\_India\\_Sibal/articleshow/3805437.cms](http://economictimes.indiatimes.com/News/News_By_Industry/Healthcare_Biotech/20_more_biotech_parks_to_come_up_in_India_Sibal/articleshow/3805437.cms)

In addition to generic drugs manufacture, American-based big pharma and biotech companies are increasingly turning to India – with China as a main competitor – for cost savings in discovery and clinical development:

- Merck and AstraZeneca are considering cost-savings by outsourcing to India and China. <http://www.fiercepharma.com/story/astrazeneca-outsource-manufacturing/2007-09-17>
- Ranbaxy recently announced entering into clinical trials for a drug it is developing jointly with GSK [http://economictimes.indiatimes.com/News/News\\_By\\_Industry/Healthcare\\_Biotech/Pharmaceuticals/Ranbaxy\\_GSK\\_drug\\_starts\\_initial-stage\\_trials/articleshow/3956043.cms](http://economictimes.indiatimes.com/News/News_By_Industry/Healthcare_Biotech/Pharmaceuticals/Ranbaxy_GSK_drug_starts_initial-stage_trials/articleshow/3956043.cms)
- Genzyme (Boston) The \$4.6 billion biotech leader Genzyme is planning to carry out clinical trials, set up R&D centers and transfer manufacturing to India. **“Now India is the driver of innovation.”** [http://economictimes.indiatimes.com/News/News\\_By\\_Industry/Healthcare\\_Biotech/Biotech/Genzyme\\_to\\_set\\_up\\_RD\\_centres\\_in\\_India/articleshow/3734330.cms](http://economictimes.indiatimes.com/News/News_By_Industry/Healthcare_Biotech/Biotech/Genzyme_to_set_up_RD_centres_in_India/articleshow/3734330.cms)

In conclusion, the global playing field for biosciences jobs is no longer flat as long as our competitors invest in innovation.

## PROPOSAL ENDNOTES

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<sup>1</sup> Small Business Innovation Development Act of 1982, P.L. 106-554. Reauthorization was signed 12/21/2000 that extended the program through 09/30/2008). Since founding, the goal has remained the same, to stimulate technological innovation with “high-risk” projects.

<sup>2</sup> Jo Anne Goodnight’s remarks to Congress, February 2008

<http://209.85.173.132/search?q=cache:O4js8pPPAZwJ:www.house.gov/smbiz/hearings/hearing-02-13-08-sbir-sub/testimony-02-13-08-goodnight.pdf+goodnight+SBIR+2008&hl=en&ct=clnk&cd=3&gl=us>

<sup>3</sup> [http://209.85.173.132/search?q=cache:Ad3nT-XGGLwJ:www.tip.uconn.edu/Files/Goodnight\\_UnivStartups\\_Jan2008.ppt+goodnight+SBIR+2008&hl=en&ct=clnk&cd=8&gl=us](http://209.85.173.132/search?q=cache:Ad3nT-XGGLwJ:www.tip.uconn.edu/Files/Goodnight_UnivStartups_Jan2008.ppt+goodnight+SBIR+2008&hl=en&ct=clnk&cd=8&gl=us)

Presentation by Jo Anne Goodnight, January 2008, University of Connecticut.

<sup>4</sup> Derived from the cached copy of

[http://grants.nih.gov/grants/funding/sbir\\_success%20rate\\_sbir\\_sttr\\_fy2003\\_2006.xls](http://grants.nih.gov/grants/funding/sbir_success%20rate_sbir_sttr_fy2003_2006.xls) Accessed 28 November 2008.

<sup>5</sup> <http://grants.nih.gov/grants/guide/pa-files/PA-08-050.html> Accessed 28 November 2008.

<sup>6</sup> September 4, 2003. Position paper by BIO. <http://www.bio.org/reg/SBIRFactSheet.pdf> Accessed 27 Nov 2008.

<sup>7</sup> [http://www.biotechtransferweek.com/issues/1\\_18/features/140896-1.html](http://www.biotechtransferweek.com/issues/1_18/features/140896-1.html)

<sup>8</sup> Faculty Research Working Papers Series, John F. Kennedy School of Government, Harvard University, January 2007.

<sup>9</sup> Additional programs now being managed by the CDMRP are as follows: Amyotrophic Lateral Sclerosis Research Program \$5 Million; Bone Marrow Failure Research Program \$5 Million; Multiple Sclerosis Research Program \$5 Million; Peer Reviewed Cancer Research Program \$16 Million; Peer Reviewed Lung Cancer Research Program \$20 Million. Research topics under the FY09 Peer Reviewed Medical Research Programs are restricted to: Alcoholism, Autoimmune Diseases, Blood Cancer, Childhood Asthma, Drug Abuse, Epilepsy, Kidney Cancer, Listeria Vaccine for infectious disease and cancer, Lupus, Mesothelioma, Molecular Signatures in Tumors, Neuroblastoma, Osteoporosis and related bone disease, Paget's Disease, Pediatric Cancer, Polycystic Kidney Disease, Social Work Research, Tinnitus, West Nile Virus Vaccine.

<sup>10</sup> Department of Defense Congressionally Directed Medical Research Programs, Deployment Related Medical Research Program <http://cdmrp.army.mil/drmrp/default.htm> Accessed 14 Sept 2008.

<sup>11</sup> <http://www.nih.gov/news/fundingresearchareas.htm> Accessed 14 Sept 2008.

<sup>12</sup> Cambridge Quantum Fund I was a £1 million seed fund spearheaded by 3i. It was launched in 1994 with the author as first Chief Executive, followed by successive Chief Executives from 1994-1999. In 1999 Avlar Limited assumed management responsibilities for five bioscience investments in the CQF portfolio. Cambridge University has continued to make strategic investments in early-stage technologies via Cambridge Challenge Funds I and II.

<sup>13</sup> Comments by venture capital panelist from Interwest Partners LLC at San Jose BioCenter event, Redwood City, December 13, 2008.

<sup>14</sup> BIO statistics accessed 3 January 2009. <http://bio.org/speeches/pubs/er/statistics.asp>

<sup>15</sup> Pharmaceutical Research and Manufacturers Association

[http://www.phrma.org/news\\_room/press\\_releases/more\\_than\\_2000\\_new\\_medicines\\_in\\_development\\_for\\_older\\_americans/](http://www.phrma.org/news_room/press_releases/more_than_2000_new_medicines_in_development_for_older_americans/) Accessed 3 January 2009. Data as of 20 November 2008.

## **APPENDIX A**

### **Bio for Constance McKee**

Constance McKee is co-founder, President & CEO of Manzanita Pharmaceuticals, Inc. [www.manzanitapharmaceuticals.com](http://www.manzanitapharmaceuticals.com) Manzanita is developing a “targeted” glucocorticoid for treatment of chronic pain. Constance is a named co-inventor on Manzanita’s three issued patents.

She was founder, President & CEO of the precursor to Manzanita, Asilomar Pharmaceuticals, Inc. Constance served as co-Principal Investigator under the founding DARPA grant to Asilomar (1999-2001). Asilomar filed for bankruptcy in 2006. Constance led the group of private investors who purchased the intellectual property assets of Asilomar in 2007 to form Manzanita.

She has written grant proposals for most of the programs cited here.

Constance earned her BA from Stanford with honors. Following completion of her MBA at Yale University, she was awarded a Fellowship from the Robert Bosch Foundation that supported internships in corporate finance in Frankfurt, Germany.

From 1987-1995, Constance lived in Cambridge, UK, where she launched Cambridge Quantum Fund I in 1990. CQF was the first seed capital fund that focused on commercializing technologies emerging from Cambridge University. CQF was funded with £1 million (US\$1.5 million) contributed by Cambridge University, four Cambridge colleges, and the investment firms **3i** and Hambros Technology Fund.

Constance returned to the US in 1995. She is a co-founder and Board member of BioE2E [www.bioe2e.org](http://www.bioe2e.org), an all-volunteer organization that presents programs to support bioentrepreneurs. BioE2E has presented over 60 programs, including “Alternative Funding Fairs” to connect start-ups with non-equity sources of capital. From 2007-2008 she served as Co-Executive Director of Americans for Cures Foundation (2007-2008), where she wrote the white paper, “Making Stem Cell Research a National Priority.”

With Dr Jay Levy at UCSF, Constance is currently involved in co-founding California Antiviral Foundation. About 5% of HIV-infected individuals never develop AIDS because of a naturally-occurring phenomenon known as innate immunity. California Antiviral Foundation is a nonprofit organization that will elucidate the molecular basis for this protective effect. The goals of the Foundation are to (1) find the protein(s) responsible for innate immunity, and (2) drive the commercialization of diagnostic and drug products to the point where other organizations can develop the Foundation’s prototype products and bring them to patients.

**APPENDIX B  
HISTORICAL SBIR/STTR SUCCESS RATES**

<b>SBIR/STTR</b>	<b>Current Funding Annual Total</b>	<b>Awards</b>	<b>Total Submissions</b>	<b>Percent Funded</b>	<b>Average \$ of Projects Funded</b>
1983	\$ 6,943,400	131	664	19.7%	\$53,003
1984	22,108,278	259	885	29.3%	85,360
1985	26,062,066	328	961	34.1%	79,458
1986	36,740,590	419	1,796	23.3%	87,686
1987	39,313,089	410	1,672	24.5%	95,886
1988	42,544,795	425	1,860	22.8%	100,105
1989	45,606,920	482	1,953	24.7%	94,620
1990	50,599,330	540	2,111	25.6%	93,702
1991	57,374,907	609	2,102	29.0%	94,212
1992	61,269,577	680	2,206	30.8%	90,102
1993	82,035,727	807	2,573	31.4%	101,655
1994	80,535,886	709	3,737	19.0%	113,591
1995	140,365,768	921	4,039	22.8%	152,406
1996	125,681,376	805	3,555	22.6%	156,126
1997	188,149,841	1,110	3,443	32.2%	169,504
1998	169,505,387	1,037	3,348	31.0%	163,457
1999	223,887,786	1,250	4,163	30.0%	179,110
2000	232,758,128	1,285	4,558	28.2%	181,135
2001	282,377,896	1,348	3,987	33.8%	209,479
2002	299,336,046	1,375	4,394	31.3%	217,699
2003	327,651,122	1,488	5,551	26.8%	220,196
2004	369,778,690	1,596	6,798	23.5%	231,691
2005	329,290,432	1,307	6,139	21.3%	251,944
2006	351,560,384	1,269	5,493	23.1%	277,037
	<u>\$ 3,591,477,421</u>				

## APPENDIX C

### The need to fund improvements in pain medications

Treating pain is the most costly and difficult clinical problem in America, for our civilian patients and for our wounded warriors.



**Introduction.** With the headline “The New War on Pain,” the June 2007 issue of Newsweek brought the issue of the pain of our wounded warfighters to the attention of America.

As of January 2009, just over 44,000 servicemembers have been injured in Operation Enduring Freedom (OEF, Afghanistan) and Operation Iraqi Freedom (OIF, Iraq). Polytrauma is defined by the VA as “...two or more injuries to physical regions or organ systems, one of which may be life threatening, resulting in physical, cognitive, psychological, or psychosocial impairments and functional disability.”<sup>1,2</sup>

For those wounded warriors with polytrauma, there is a direct correlation to pain: 98% of those with polytraumatic injury are in pain.

Pain is the single largest, most difficult to treat and costly element in VA healthcare:

**“...it is expected that about 50% of all OIF/OEF servicemembers will eventually access VA healthcare”<sup>3</sup> ....about half of OEF/OIF returnees (47%) will seek treatment for pain....of which about half will receive opiate therapy along with other pain drugs.”**

In the civilian population, pain represents the most frequent reason that patients sought medical care. About 1.5% of all healthcare visits in America are for pain.<sup>4</sup> Prior to OEF/OIF, the economic cost to America of treating pain was estimated at \$100 billion in direct and \$100 billion in indirect costs.<sup>5</sup> To this must be added the cost of treating OEF/OIF returnees – in 2007 the total was estimated at \$350 - \$650 billion.<sup>6</sup> Using the benchmark that 47% of OEF/OIF returnees will seek treatment for pain, **the cost of treating just the pain of OEF/OIF returnees will be \$150 - \$300 billion.**

**With the conflicts in Iraq and Afghanistan, we have doubled the economic and clinical burden of our nation’s largest medical problem.**

**Characterizing the clinical problem.** Pain may be described as acute (immediately after the time of injury), subacute (pain after injury, but usually a pain that resolves with the healing process) and chronic pain (pain that persists after injury). Very generally, acute and subacute pain is treated by the Department of Defense (DOD), and chronic

pain is treated by the Veterans Affairs (VA) after soldiers have completed a tour of duty or granted a medical discharge.

The neurobiology of pain, and in particular how and why chronic pain persists after acute pain, is poorly understood. Morphine – first isolated from opium in 1803 and introduced as a surgical anesthetic in the Civil War<sup>7</sup> - is still the best option for managing acute and sub-acute pain. However, morphine can itself lead to an increase in pain (“hyperalgesia”) if used on a prolonged basis.

**How and why the need for new pain medications arises.** There are multiple reasons why the public sector should step forward to develop new pain medications that are more effective, non-addicting, safe and affordable:

- 1) No single drug is effective in controlling either acute or chronic pain. Doctors may prescribe one or several of different drug classes, for example the morphine derivatives like Oxycontin®, Percocet®, and non-opiates, for example, non-steroidal anti-inflammatory drugs (NSAIDs) like Celebrex® or anti-convulsant (anti-epileptic) drugs like Neurontin®.
- 2) Addiction and crime related to veterans’ untreated pain is increasing. Senior VA physicians are aware that substance abuse is rising as OIF/OEF veterans sell VA-prescribed OT medications on the street. For some, opioid pain medication represents a means of ending their lives. Some veterans have committed armed robbery for pain medication:

"This wasn't to make money or better myself in any other way. This [act of stealing] was to feed an addiction."

<http://sfgate.com/cgi-bin/article.cgi?f=/c/a/2007/09/03/MN2VRJ8MV.DTL>

- 3) Almost all currently prescribed pain medications have side effects, some serious. Opioids impair thinking and in large doses suppress breathing. Non-opiates can also be deadly: the NSAID agent Vioxx® was pulled off the market in 2004 after patients died from related heart failure.
- 4) Treatment is costly, with three factors driving cost in the system. First, most pain medications are generic, so it is the continual use of, and use of multiple drugs that drives cost. Second, because there is no “drug of choice,” servicemembers may require repeated doctor visits to find pain relief through different combinations of medications. Third, new treatment paradigms for non-drug treatment may involve multiple healthcare providers like physical therapies, psychotherapists, neurophysiologists, specially trained neuropharmacologists and alternative treatment like acupuncture. This comprehensive approach to treatment can yield results, but dramatically increases the cost of care.

- 5) Any new drug would compete against the high number of marketed generic drugs. This diminishes the economic incentive for small businesses to explore new, non-addictive therapies for chronic pain.

**It is imperative to develop new, effective, safe, non-addictive and affordable drugs to treat pain, to better care for our wounded warfighters' pain conditions.**

Key sources for the data presented in this document are Walker 2007,<sup>8</sup> Clark 2007,<sup>9</sup> Clark 2006,<sup>10</sup> and Clark 2005.<sup>11</sup> Further references are given for in-depth reading.

**Department of Defense and VA responses to date.** The Department of Defense and the VA have shown extraordinary leadership in treating pain by improving protocols using currently marketed drugs: the DOD, in treating acute and sub-acute pain,<sup>12</sup> and the Tampa VA in its award-winning Chronic Pain Rehabilitation Program.<sup>13</sup> The VA site in Tampa is the single specialist site for treatment of chronic pain.<sup>14</sup>

<http://www.vachronicpain.org> At the Tampa site is the Chronic Pain Rehabilitation Program (CPRP), part of the James A. Haley Veterans Hospital. The CPRP is “an award-winning, comprehensive, **in-patient** chronic pain treatment program established in 1988 to help veterans with chronic pain cope with their condition.”

The “need for rapid detection and intervention” in pain management for OEF/OIF returnees was recognized as early as 2004, but the scope and cost of the problem was not brought into focus until 2006.<sup>15</sup> A Pain Outreach program was funded and implemented in November 2007.<sup>16</sup> The military recognizes that a key outcomes issue is to treat acute and subacute pain so that it resolves, *ie* preventing the occurrence and reducing the severity of chronic pain by identifying and treating risk factors in acute pain.<sup>17</sup> Combat physicians recognize the need to intervene early to reduce post-deployment pain.<sup>18</sup> However, even with advanced pain management immediately after combat and new protocols for management of chronic pain, the quality of life of OEF/OIF returnees with pain can be severely diminished.

**Section 1** gives further detail on the scope of the clinical problem, including a review of the interdisciplinary approach to pain management involving more than drug therapy.

**Section 2** considers how treating the pain of OEF/OIF returnees is difficult both because of the nature of wounds – complex injuries and polytrauma – but also because of a high correlation with mental and behavioral problems. Effective management of pain is made more difficult because all the drugs given to treat mental and behavioral problems also affect the brain.

**1 The Scope of the Clinical Problem.** Since 2001, 1.64 million Americans have been deployed served in OEF and OIF. As of 12 January 2009

- 4,909 have died since 19 March 2003 (4,226 in OIF, 638 in OEF)<sup>19</sup>
- Almost 44,000 have been wounded in Iraq<sup>20</sup> and 2,648 WIA (Wounded in Action) in or around Afghanistan as of mid-January 2009<sup>21</sup>

- Of these, 47% have sought relief from pain<sup>22</sup>
- Historically about 44% of veterans with pain have been given opioid therapy,<sup>23</sup> a figure that appears consistent with findings with recent studies. Despite their frequent prescription, opioids may in fact not be as effective as believed, particularly against neuropathic pain.<sup>24</sup> Many placebo-controlled trials involving opiates have serious flaws in developing baseline and ongoing data collection.<sup>25</sup> Finally, multiple studies of opiate therapy use also report reduced activity levels, cognitive impairment and increased depression.<sup>26</sup>
- Soldiers presenting with pain have a high correlation with PTSD (28.3% met PTSD criteria on initial screening)<sup>27</sup> and fatigue, with 75.6% reporting fatigue<sup>28</sup>

**“Rates of substance abuse (opioids abuse, opioid non-adherence, or opioid addiction) concerns associated with [opioid therapy] are significant.” (Clark 2005)**

**1.2 The focus on the battlefield for treating wounded warfighters is survival, not pain management.** About 61% of combat wounds in OEF/OIF are related to blasts or fragments, resulting in orthopedic injuries (70%) and polytrauma (27%).<sup>29</sup> Buckenmaier and colleagues (see References, Buckenmaier *et al* 2003; 2005) have pioneered the use of regional anesthesia and peripheral nerve blocks during stabilization and air evacuations.<sup>30</sup> Buckenmaier reports that combat casualties about to be airlifted from Iraq to Landstuhl Regional Medical Center (Germany) are more afraid of unmanaged pain during transport than of their injuries.<sup>31</sup>

**1.3 In one sampling of returnees taken at the Tampa site, 96% reported pain.**<sup>32</sup> Seventy per cent experienced pain in more than one site. The level of pain reported was moderately severe to severe. Using pain scales of 1-10, where 4 is considered barely tolerable, pain scores in this study averaged 5.6.

**1.4 Inadequate pain control.** Inadequate pain control is cited as main problem at admission; the second-most frequent problem is sedation which can result from pain medications. One study noted the average duration of pain as 55.1 months.<sup>33</sup>

Pain Duration	
Average	55.1 months
< 36 months	46.5 months
36-72 months	33.3 months
> 72 months	20.2 months

**1.4 Need for multi-disciplinary care drives system cost.** Much of the cost in treating pain lies in frequent office visits, for “aggressive multi-disciplinary pain management.”<sup>34</sup> “Aggressive management” means frequent office visits to a range of clinical experts for frequent evaluation and re-prescription. For example, in one study where 63% of returnees reported pain, 18% were also referred to the Musculoskeletal Pain Clinic, 15% were referred to the Inpatient Pain Program, 28% were referred to the

Mental Health and PTSC Clinics, and 8% were referred to the Blast Injury Clinic and Neurology.<sup>35</sup>

<b>Cost of Treating Pain Driven By Need for Multidisciplinary Care<sup>36</sup></b>	
Medications	89.4%
Physical Therapy	67.0%
Injections	23.3%
Surgery	23.3%
Prosthetics/Orthotics	16.4%
Chiropractic	12.6%
Massage	10.2%
Occupational therapy	05.6%
Kinesiotherapy	05.6%
Implants	0.8%
Accupuncture	0.8%

**1.5 Range of drug medications used.** Pain is rarely “cured,” but outcomes can be improved or “managed” by combining types of medications, often mixing several types of pain medications at the same time.<sup>37</sup> The drugs may be standardized, but applying them, in what mix, in what sequence, and in what dose, can improve pain control.

There are several classes of drugs used to treat neuropathic and chronic pain, including ion channel blockers such as anti-convulsants carbamazepine and gabapentin (Neurontin®) and its more recent analog Lyrica®, antidepressants, NMDA antagonists, opioids and capsaicin are prescribed to treat focal and systemic forms of neuropathic pain, but no single drug offers relief to more 30% of patients.<sup>38,39,40,41,42</sup> One study of classes of pain medications given to OEF/OIF returnees reflected this range:

<b>Classes of Pain Medications Currently Given<sup>43</sup></b>	
Class of pain agent	Percent Use
Anti-inflammatories	62.9%
Opioids	16.8%
Muscle relaxant	15.0%
Anti-convulsant	11.7%
Anti-depressant	06.3%
Anxiolytics	0.8%
Other	10.7%

Pain management can reduce opiate use, for example, in one study where the number of polytrauma patients require opioids dropped to 48% from 58% after new treatment protocols were introduced. In that study, pain intensity declined from 5.6 to 3.3.<sup>44</sup>

“Nevertheless, pain continues to be a problem at discharge....there is some indirect evidence that chronic pain and chronic pain syndromes may be more likely to develop than in other acute pain injuries.”<sup>45</sup>

“Aggressive multidisciplinary pain management incorporating medical and behavioral pain specialists is needed at all levels of care.”<sup>46</sup>

**Section 2. Complex injuries, complex treatment.** One reason pain is difficult to treat is because other drugs given to treat depression and polytrauma also act on the brain. Such drug regimens often have knock-on sedative or dilutive effects with pain medications.

<b>High Correlation Between Pain, Polytrauma &amp; Mental Health<sup>47</sup></b>	
89%	≥ 1 pain problem
67%	Reported pain at admission (DOD)
4.6	Mean pain score (0-10, where 10 is high)
67%	Patients reporting pain > 1 site
44%	Pain-related impairments
67%	Also received mental health diagnosis
82%	Also received mental health treatment

**2.2 Pain is not an isolated symptom.** Pain is frequently involved with other emotional issues such as depression (36%), post-deployment adjustment problems (23%), anxiety (20%), family/marital problems (19%) or difficulties with anger (15%).<sup>48</sup> Fatigue is highly correlated with pain, with 81% reporting chronic pain, of which 48% reported chronic pain occurring 6-7 days per week.<sup>49</sup>

<b>Other Emotional Issues</b>	
Depression	36%
Post-deployment adjustment problems	23%
Anxiety	20%
Marital/family problems	19%
Alcohol abuse	19%
Anger difficulties	15%

<b>Pain Related Impairments<sup>50</sup></b>	
Recreational or physical activity	42%
Emotional functioning	34%
Social activity	18%
Family relationships	18%
Sleep	14%
Sexual functioning	2%

**2.3 Barriers to VA care.** Finally, seeking treatment for pain in the military setting is part of the problem in managing pain: **“some [of our veterans] are very angry at the military.”**

<b>Barriers to Adjustment &amp; Barriers to VA Care<sup>51</sup></b>
Significant survivor guilt
Conflict between their actions in combat and their moral beliefs
Concern about re-deployment
Feeling “changed” and “isolated” <ul style="list-style-type: none"> <li>• Difficulty relating to family or friends</li> <li>• Frequent marital or relationship conflict</li> </ul>
Reluctance to take medications
Less likely to report pain than other medical conditions
Scheduling (time off when employed full-time)
Belief they are undeserving compared to their severely injured comrades
<b>“Some are very angry at the military”</b>

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## APPENDIX C ENDNOTES

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- <sup>2</sup> Walker 2007.
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