The Congressionally Directed Medical Research Programs

A Storyboard Approach to Charting Research Progress and Demonstrating Impact

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Outline

- CDMRP Overview
- NFRP Overview
- NF Storyboard
WHO is the CDMRP?

Department of Defense

Department of the Army

Army Medical Command

Medical Research and Materiel Command

Congressionally Directed Medical Research Programs
Grassroots consumers heightened political awareness of breast cancer that led to increased funding for cancer research and the 1992 creation of the CDMRP. The voices and experiences of consumers continue to play a pivotal role in the establishment and growth of research programs.

Over 2,100 consumers representing over 1,000 organizations have served on Peer Review and Programmatic Review panels.
## FY16 Funding

<table>
<thead>
<tr>
<th>Program</th>
<th>$M</th>
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<tr>
<td>Alcohol and Substance Abuse Disorders</td>
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<td>Peer Reviewed Alzheimer’s</td>
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<td>Amyotrophic Lateral Sclerosis</td>
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<td>Peer Reviewed Cancer (13 Topics)</td>
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<td>Autism</td>
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<td>Peer Reviewed Medical (39 Topics)</td>
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<td>Peer Reviewed Orthopaedic</td>
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<td>Reconstructive Transplant</td>
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<td>Epilepsy</td>
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<td>Spinal Cord Injury</td>
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<td>Tuberous Sclerosis Complex</td>
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<td>Vision</td>
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<td>Multiple Sclerosis</td>
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<td>Neurofibromatosis</td>
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<td>Orthotics and Prosthetics Outcomes</td>
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<td>Psychological Health and Traumatic Brain Injury*</td>
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<td><strong>TOTAL</strong></td>
<td><strong>$1.468B</strong></td>
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* CDMRP is assisting with the management of a specified portion of a larger appropriation(s)
Vision
Transform healthcare for Service Members and the American public through innovative and impactful research

Mission
Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans and the American public
Hallmarks

- Targeted research funds added to DoD budget by Congress
- Consumers participate throughout process
- National Academy of Medicine (IOM) recommended model for application review
- Funds high-impact innovative research
- Each program’s vision and investment strategy are adapted annually, allowing rapid response to changing needs
- Avoid Duplication with other funding agencies
  - Fills Unfunded/Unmet Gaps
- Funding flexibility
  - Funds obligated up-front; limited out-year budget commitments
  - Limited continuation funding
  - No “pay line;” funding recommendations based on portfolio composition, adherence to intent of mechanism, relative impact in addition to technical merit
Mission: Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans and the American public.

Peer Review

- Criterion-based evaluation of full proposal
- Determination of “absolute” scientific merit
- Outcome: Written critique and scores for individual criteria and overall merit
  - No standing peer review panels
  - No contact between reviewers and applicants

Partnership

Programmatic Review

- Comparison among proposals of high scientific merit
- Determination of adherence to intent and program relevance
- Outcome: Funding recommendations
  - No “pay line” (portfolio balance)
  - Funds obligated up front; no out-year budget commitments (but milestones imposed)
  - No continuation funding
Neurofibromatosis Research Program

Vision
Decrease the clinical impact of neurofibromatosis

Mission
Promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2 and Schwannomatosis to enhance the quality of life for persons with those diseases.

Key Facts
$287.85 million in FY96-14
332 awards in FY96-14
20 awards recommended for funding in FY15

Mechanisms supported: Clinical Trials, Consortium, Investigator Initiated, New Investigator, Exploration Hypothesis Development

Funding History

US Army Medical Research and Materiel Command
What is Neurofibromatosis?

Genetic disorder causes tumors to grow along various types of nerves. Classified as a rare disorder but more common than Cystic fibrosis, Muscular Dystrophy, Huntington’s disease and Tay Sachs combined.

**NF1**
- Von Recklinghausen NF
- Peripheral NF
- 1 in 3,000 births
- Autosomal dominant
- 50% sporadic, 50% genetic
- Neurofibromas under/on skin,
- Enlargement and deformation of bones and curvature of spine
- Tumors in brain, cranial nerves or spinal cord
- 50% have learning disabilities

**NF2**
- Bilateral Acoustic NF (BAN)
- 1:25,000
- Multiple tumors on cranial and spinal nerves
- Lesions on brain and spinal cord
- Tumors on both auditory nerves
- Hearing loss in teens/twenties first symptom
Measuring Impact

• Return on Investment
• Research Outcomes- Publication, patents
• Research Products- Drugs, devices
• Evaluate collaborations created
• New investigators recruited and retained
• Storyboards
Goals:

1. Identify gaps in research funding
2. Access impact of NFRP funding
3. ID key advances in NF in visual format

Audience:

1. Consumers (patients and advocates)
2. Congress
3. Programmatic panel
4. CDMRP
Ongoing program evaluation effort at the CDMRP, the NFRP has developed NF1 and NF2 “story boards” identifying key research advances in the fields of NF1 and NF2 through the years.
Process:

1. Identified key research advances from publications, regardless of source of funding
2. Identified NFRP research project results
3. Mapped each advancement to year
4. Mapped to specific area of science
   - (i.e.) Molecular biology, genetics, cell biology, pathobiology
5. Mapped to disease type (NF1)
   - NF1 or NF2
6. Color coded for links between research
Findings:

1. More research advances in basic vs. clinical prior to 2004
   » Most in area of molecular biology and genetics, cell biology and pathobiology, animal model development

2. NFRP has had an impact in shaping the progress of NF research

3. Gaps identified not necessarily a priority in NF research

4. Primarily a retrospective tool to look at program accomplishments

5. Not particularly useful for strategic decision making

6. Useful as a PR tool
NFRP Research Milestones

1996
- Genotype/phenotype analysis in NF1 (Pilchman) and NF2 (MacCollin)
- Development of mouse models of NF1 and NF2 (Paada and Jacks)

1997
- Natural history studies of NF1 (Korf) and NF2 (Slattery)

1998
- Genetic evaluation of NF1 tumors (Viskochil)

1999
- Natural history of psychological aspects of NF1 (North)
- Preclinical evaluation of gene therapy for NF2 (Breakfield)
- Mouse models of NF (Shannon)

2000
- NF2 natural history consortium (Slattery)
- Phase II trial of RU577 for NF1 (Widemann)
- Gene expression profiling of NF1 (Korf) and NF2 (Pilchman) cells

2002
- Identification of the schwannomatosis locus (MacCollin)
- Studies of NF1 modifier genes (Bernard)

2003
- Generation of a new class of Ras inhibitors for NF1 (Kloog)
- Development of an HSV vector therapy for NF2 (Marras)
- NF1 microarray consortium (Rabin)

2004
- Identifying PI3K inhibitors as a treatment for NF2 (Pilchman)
- Mouse models of NF (Slattery)

2005
- Phase II clinical trial of rasafenarin chemotherapy for NF1 (Widemann)
- Stains for the treatment of NF1 cognitive deficits (Silva)
- Whole body MRI evaluation of NF1, NF2, and schwannomatosis patients (Poikil)

US Army Medical Research and Materiel Command
Goals:

- Identify impact of NFRP on specific research topics
- Focus on current clinical trials
- Identify collaborations leading to clinical trials
- Show history of interventions
MEK Inhibitor Storyboard

- MEK inhibitors - active area of research
- MEK inhibitors - act to inhibit MEK1 and/or MEK2
- Affects the MAPK/Erk pathway which is overactive in NF1 and certain cancers
- Currently in clinical trials

QUESTION: What has been the impact of NFRPs funding of MEK studies
Step 1

- Identify Clinical Trials using MEK inhibitors
- Map to year and funding source on storyboard
MEK162

NFRP

CTF

NIH

Biotech & Intl

Co-funding

Clinical trial

PD0325901

MEK162

AZD6244

PD0325901

Combination Therapies

29 Clinical trials

AZD6244

GSK112022

2012

Co-funding

Clinical trial

PD0325901

Combination Therapies

80 Clinical trials

2016
Step 2

- Literature review of references for clinical trials
- Identify basic and preclinical studies that served as rational for MEK trials
- Map to storyboard
**NFRP**
- Developed first animal model of NF1-related MPNSTs
- Identified that the loss of neurofibromin is associated with tumorigenesis

**CTF**
- C1-1040 (PD184252)

**NIH**
- PD098059
- U0126
- Established MPNSTs cell lines and xenografts that could be utilized to identify potential therapeutics

**Biotech & Intl**
- PD098059
- C1-1040 (PD184252)
- JTP-70902
- GSK112022 (JPT-74057)
- Trametinib (GSK112022): First MEK inhibitor to receive FDA approval for the treatment of BRAF-mutated Melanoma.

**Clinical Trials**
- 29 Clinical trials
- 80 Clinical trials
Step 3

• Show how basic, preclinical and clinical trials are related
Developed first animal model of NF1-related MPNSTs

Identified that the loss of neurofibromin is associated with tumorigenesis

C1-1040 (PD184252)

Established MPNSTs cell lines and xenografts that could be utilized to identify potential therapeutics

Same study as above

PD098059

U0126

AZD6244

PD0325901

Combination Therapies

Trametinib (GSK112022): First MEK inhibitor to receive FDA approval for the treatment of BRAF-mutated Melanoma.

Biotech & Intl

Co-funding

Clinical trial

PD0325901

MEK162

CTF

NIH


29 Clinical trials

80 Clinical trials
Conclusions

- NFRP funded basic and preclinical studies have impacted current clinical trials with MEK inhibitors

- Funding from NFRP, CTF, NIH and Others were critical to the progress of MEK research currently in trials
Next Steps

• Further analyze our findings
• Develop whitepaper
• Develop dynamic MEK storyboard using online tools
  • i.e Tiki-Toki (www.tiki-toki.com)
• Create additional storyboards for NF specific topics
BRCA Storyboard

Breast Cancer Research Program
Ovarian Cancer Research Program

Contributions to advances in BRCA research

Advances in BRCA
Advances in BRCA
A Proud Consumer Legacy

Thank you