MILITARY BENEFIT

DEPARTMENT OF DEFENSE
Neurofibromatosis Research Program

Neurofibromatosis (NF) research offers insight into many disease areas and the Department of Defense NF Research Program (NFRP) is providing critical research that is of benefit to the military and the general population. Below are examples of recently funded NFRP research that could have broad impact for those with NF, as well as the military.

- Modifying Radiation Effects
- Bone Repair
- Pain
- Eye Disease
- Psychosocial and Cognitive Dysfunction
- Cancer

- **Neurofibromatosis (NF) is a group of genetic disorders that cause widespread, severe medical complications.** This includes tumors of brain, nerves, skin, breasts; deafness; blindness; paralysis; cognitive disabilities; unmanageable chronic pain; bone abnormalities; psychosocial issues; and cardiovascular defects.

- **Anyone can be affected by NF.** There are three forms of NF: NF1, NF2 and schwannomatosis. Together, these affect 1 in 3000 people. Half of NF cases are inherited from a parent, but half occur sporadically due to random genetic mutation during development. This means that NF may affect any person from any family.

- **NF research can benefit the military as a model for advancing treatments for many relevant conditions.** The same genes that are mutated in NF are often mutated in diseased tissues in people who don't have NF. Further, the proteins made by those NF genes play key roles in many normal body processes. Drugs that restore normal NF-associated cellular function are being developed to treat the manifestations of NF, but may also help people without NF who are suffering from various conditions including diseases of the nerves, brain, bones, blood vessels, and pain.

- **The Department of Defense fills a special role by providing peer-reviewed funding for cutting-edge medical research through the Congressionally Directed Medical Research Program (CDMRP).** The well-executed and efficient programs within the CDMRP, including the Neurofibromatosis Research Program (NFRP), demonstrate responsible stewardship of taxpayer dollars. Funding is awarded through a competitive, two-tier review process that involves clinicians, researchers, and patient advocates. CDMRP programs, including the NFRP, support the most innovative and impactful research, and are open to researchers in every state in the country.

- **NFRP grants do not duplicate or supplant National Institutes of Health (NIH) research efforts, but rather enhance and complement NIH efforts**. Since 1996, the NFRP has been a critical partner in supporting major NF research discoveries and moving them forward into new treatments for the benefit of NF patients, the military and the general population. The Department of Defense offers awards to fill gaps in ongoing research and compliments initiatives sponsored by other agencies, such as NIH. The NFRP and the NIH work in harmony with each other and have proven to be an excellent partnership to advance NF research. NFRP funding often allows researchers to explore new ideas and gather quality data making successful research more competitive in the larger science arena at NIH.

Bone Repair

Skeletal abnormalities affect up to one-third of patients with NF1. Included among these is improper fracture healing that may lead to permanent bone damage and amputation. Research involving NF1-associated bone disease and healing is likely to be more broadly applicable, including to military-associated injuries.

- **Dr. Elizabeth Schorry** (*Cincinnati Children's Hospital*) and the entire Neurofibromatosis Clinical Trials Consortium, which is an NFRP funded entity, are presently conducting a clinical trial to accelerate bone healing after surgery for tibial fractures. Approximately 10% of children with NF1 have a propensity for repeated fractures and leg bone malformation (pseudoarthrosis), which often requires surgical repair or even amputation. BMP-2 is a naturally occurring human protein that induces bone cell growth in normal development and can now be re-created in a laboratory as rhBMP-2. This trial is evaluating whether application of rhBMP-2 to the surgical site for tibial fracture repairs may improve healing. This has a strong possibility of directly impacting orthopedic surgery for other indications, including trauma such as is seen in the military.

Pain

Pain is one of the most common and most troubling symptoms for patients with NF, as it is in both active duty and retired members of the military. Advances in the field of NF-associated pain may extend to benefit the military through better understanding of biology and discovery of non-opioid therapeutics.

- **Dr. Rajesh Khanna** (*University of Arizona*) and colleagues developed a synthetic peptide to recreate the regulatory effect of the lost neurofibromin protein on the pain regulating protein CRMP2 for patients with NF1. Using this synthetic peptide in rodent models led to reduced pain for inflammatory, post-surgical and nerve related pain types. They also developed a medication that directly targets CRMP2 and reverses abnormal pain sensation in rats with NF1. This work not only advanced our understanding of the molecular basis for pain in NF1, but more importantly it identified two non-opioid treatments that improved pain in various rodent models.

- **Dr. Scott Plotkin** (*Massachusetts General Hospital*) and colleagues determined that pain is significantly worse in patients with schwannomatosis mutations in the *LZTR1* gene than those with *SMARCB1* mutations, while tumor burden was not different between these groups. This suggests that the severe pain in schwannomatosis may relate to an individual's disease genetics and suggests a potential target for developing new pain therapies. This could be an important development in personalized medicine.

Cancer

Both NF1 and military service are associated with increased risks of certain cancers, including breast cancer and sarcomas. Therefore, discoveries involving the biology or treatment of NF1-associated cancers are relevant and important to military service members and veterans.

- **Dr. Xia Wang** (*Moffitt Cancer Center*) identified that NF1-associated breast cancers have marked overexpression of the protein HER2 when extra copies of the *ErbB2* gene are present. This suggests an important interplay between the *NF1* gene and the *ErbB2* gene in breast cancer development, and potentially an opportunity for therapeutic development since FDA-approved HER2-targeting drugs already exist.

- **Dr. Brigitte Widemann** (*National Cancer Institute*) and colleagues performed a clinical trial to study chemotherapy response rates for a particular soft tissue sarcoma; sarcomas (especially malignant peripheral nerve sheath tumor) are seen with increased frequency with NF1 and are also a service-connected cancer for military personnel with certain chemical exposure history. Although this study was not designed to compare head-to-head results, the investigators identified that patients with

sporadic sarcomas responded to chemotherapy relatively better than those with sarcomas related to NF1. Nonetheless, disease stabilization was achieved in most patients with the chemotherapy regimen evaluated. Together, this provides the groundwork for new treatments for malignant peripheral nerve sheath tumors and reinforces that NF1-associated sarcoma research findings likely extend to benefit sporadic – and potentially military-connected – sarcomas.

Modifying Radiation Effects - Tumor and Radiation Biology

Many of the same genes that are mutated in NF-associated tumors are also mutated in non-NF tumors. Understanding the biology of NF-associated tumors will result in better treatments for all patients. Moreover, understanding radiation effects on these tissues is likely to extend help to military personnel who encounter radiation through their service.

- **Drs. Lei Xu and Konstantina M. Stankovic** (*Massachusetts General Hospital, Massachusetts Eye and Ear*) determined that the protein cMET, which is commonly increased in cancers and is a marker of poor prognosis, is upregulated in vestibular schwannoma cells after radiation therapy. They further found that blocking cMET with an FDA-approved medication not only enhanced the sensitivity of these cells to radiation, but also independently inhibited tumor cell growth in culture. Taken together, this study provides exciting evidence for both a targeted therapy in schwannomas, as well as a potential drug to sensitize tumors to radiation therapy.

Psychosocial and Cognitive Dysfunction

Nearly 80% of patients with NF1 suffer from some form of psychosocial or cognitive disability, including learning disabilities, attention deficit disorder, or autism-like features. Better understanding cognitive changes in NF1 may translate to major benefits for the military, including potential advances in post-injury cognitive changes in soldiers or in degenerative cognitive diseases in veterans.

- **Dr. Jonathan Payne** (*Murdoch Children's Research Institute, Australia*) is using a special type of MRI, called magnetic resonance spectroscopy (MRS), to safely and non-invasively study the levels of the neurotransmitter GABA in the brains of children with NF1. GABA is a chemical that transmits messages between brain cells, and it has been implicated not only in learning disabilities in NF1, but also in Post-Traumatic Stress Disorder. Development of MRS technology to easily quantify GABA levels in the brain may help us identify people at highest risk of developing learning disorders, PTSD, or other psychosocial disabilities.

Eye Disease

NF1 is associated with abnormal blood vessel development along the retina (in the back of the eye), which may severely impact vision or cause blindness. This mechanism of vision loss may affect many military members and veterans as well, originating from ocular trauma or infections, or even diabetes or macular degeneration. Research involving NF1 eye disease may translate to aiding a much larger pool of military-affiliated individuals.

- **Dr. Brian Stansfield** (*Augusta University*) and colleagues determined that normal expression of VEGF (a protein that has been linked to abnormal blood vessel growth in diseases like diabetic eye disease and wet macular degeneration) has remarkably greater negative effects on mice with NF1 as compared to normal mice. Specifically, in NF1 mice, the presence of VEGF leads to over proliferation and abnormal blood vessel formation. Together, these data suggest that the *NF1* gene is essential for controlling retinal vessel health, and that therapies targeting its interaction between VEGF may offer hope for improving vision in these patients.