MILITARY BENEFIT

DEPARTMENT OF DEFENSE
NeurofibromatosisResearchProgram

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 have yielded findings that could have a broad impact for those with NF, as well as the military.

- Bone Repair
- Muscle Weakness
- Pain Management
- Psychosocial Disabilities
- Vascular Disease and Wound Healing

- **Neurofibromatosis (NF) is a devastating genetic disorder that causes multiple clinical problems.** This includes nerve and brain tumors; disfiguring skin growths; inability to heal after bone fracture, which may ultimately require amputation; psychosocial issues; unmanageable chronic pain; deafness; blindness; cardiovascular defects; muscle weakness; and paralysis.
- **Anyone can be affected by NF.** There are three forms of NF - NF1, NF2 and schwannomatosis. Together these affect 1:3000 people. Half of NF cases will be inherited but half will occur randomly. This means that anyone, and any family, may be affected by NF.
- **NF research can benefit the military as a model for advancing treatments for cancer, bone healing, nerve regeneration, brain injury and other conditions.** NF gene mutations can pop up in diseased tissues in people who don't have NF. This includes lung, liver and brain tumors, leukemia, and secondary radiation-induced tumors. And both breast cancer and leukemia are examples of cancers that have an increased incidence in people with NF and in military personnel. Drugs that restore the NF signaling pathway are being developed to treat the manifestations of NF, but may also help improve repair of damaged bone, nerve paralysis and injured blood vessels, which could have application in treatment of war injury.
- **The Department of Defense fills a special role by providing peer-reviewed funding for innovative and rewarding medical research through the Congressionally Directed Medical Research Programs (CDMRP).** The well-executed and efficient programs within the CDMRP, including the Neurofibromatosis Research Program (NFRP), demonstrate the government's responsible stewardship of taxpayer dollars.
- **NFRP grants do not duplicate or supplant National Institutes of Health (NIH) research efforts, but rather enhance and compliment NIH efforts.** Research grants are awarded to researchers in every state in the country through a competitive two-tier review process.

Bone Repair

Around a third of people with NF1 have abnormal skeletal growth; this can lead to long bone fractures that can't heal properly and may need limb amputation. NF1 also causes low bone mineral density, weakening bones and further increasing fracture risk. NF1 bone research is a fast-moving field and is yielding new information about how we can increase bone strength and improve bone repair. The nature of military activity increases the risk of fracture and osteoarthritis. Therefore new findings for the prevention and treatment of bone injury would be valuable to the military.

- **Dr. Feng-Chun Yang** *(Indiana University)* has studied mesenchymal cells, a precursor cell type that generates new bone cells. When the *NF1* gene is not working in mesenchymal cells, they are less able to form mature bone cells. Normal behavior can be restored if mesenchymal cells are treated with drugs that target the cell signals PI3-K and MAPK. This is an important finding that identifies PI3-K and MAPK as good candidate drug targets for ensuring that new bone-making cells can be generated as would be important in fracture healing.
- **Dr. Florent Elefteriou** *(Baylor College of Medicine)* is testing a new treatment for promoting bone fracture repair called C-type Natriuretic Peptide (CNP). He is testing CNP in mice with depleted *Nf1* gene function in their bones. Lack of functional Nf1 gene causes these mice to have a tendency toward bone breakage after which they are unable to heal normally. Dr. Elefteriou hopes that CNP will promote this healing. CNP comes from a class of drug already FDA-approved for children, so if it facilitates bone healing in mice it could potentially move rapidly into clinical trials for both children and adults.

Psychosocial Disabilities

Two thirds of people with NF1 have some form of psychosocial disability. Though originally classed as learning disabilities, research has broadened our understanding of this area and revealed common threads between NF1 learning disabilities, autism spectrum disorder and other psychosocial disabilities. As we learn more from the NF population about psychosocial function, we should be able to shed light on this area for the benefit of the military both in terms of cognitive training and in treatment following return from military action

- **Dr. Maria Acosta** *(Children's National Medical Center)* is conducting a clinical trial to test the use of computerized training (CogMedRM) in conjunction with the drug methylphenidate to promote thinking and learning abilities in young people with NF1. If successful, CogMedRM may be used at home or elsewhere by children and adults, potentially as a training tool for improvement of cognition in the warfighter.
- **Dr. Kathryn North** *(Murdoch Children's Research Institute, Australia)* is studying and mapping out the features of autism spectrum disorder as they appear and develop in young children with NF1, from toddlers to adolescents, comparing the findings to children from the general population with autism spectrum disorder but not NF1. This is the first time this has been done thoroughly and it should yield some new insights into whether autism in NF1 is different than in the general population, informing our broader understanding of the nature of autism and how it may be clinically managed and treated.

Muscle Weakness

Children with NF1 have inherent low muscle tone and muscle weakness which impacts quality of life and development into adulthood. This research opens up a new area of NF research and has potential broader application for recovery from military injuries in particular restoring optimal muscle function.

- **Dr. Aaron Schindeler** *(Children's Hospital at Westmead, Australia)* is part of a group that has pioneered study of muscle weakness in NF1 using both mouse models and human studies. It used to be thought that people with NF1 had muscle weakness due to tumors pressing on nerves or other indirect causes, but it is now clear these weaknesses are due to *NF1* gene defects directly in the muscle cells. Clinical studies have now shown this affects muscle metabolism, gait, physical and social interactions, etc. and can be recognized from infancy.
- **Dr. Yuan Zhu** *(Children's National Medical Center)* studied how motor function (communication between brain signals and muscles) might be disrupted in people with NF1. Dr. Zhu genetically engineered mice in which the *Nf1* gene is disrupted during embryonic development of the section of the brain that controls motor function. After *Nf1* gene mutation motor function was impaired. This is the first finding to report a biological basis – cerebellar signaling - for motor function deficits in NF1.

Pain Management

Severe and unmanageable pain can occur in NF, particularly in schwannomatosis, and significantly impacts quality of life. Chronic pain, and how to treat it effectively, is one of the most poorly understood areas of medicine, but has very high relevance to those in the military recovering from service-related injuries. NF research has shown there are similarities between the type of pain that occurs in NF and phantom limb pain which can occur following amputation in the warfighter. Research is advancing to identify new ways to target pain effectively with the right drugs or therapies.

- **Dr. Larry Sherman** *(Oregon Health & Science University, Oregon)* has developed and is now studying mice that are genetically engineered to have the pain that people with schwannomatosis have. The mice are hypersensitive to pain stimuli and this allows Dr. Sherman to study pain biology and test new treatments that may in the future be used in the clinic.

Vascular Disease and Wound Healing

NF1 elevates the risk of vascular disease including aneurysm, stroke and vessel occlusive disease. This can cause premature death, particularly in younger patients. In addition NF1 seems to make small blood vessels around wounds less able to heal. This research will help develop markers for early detection of vascular changes that can predict those at risk of potential forthcoming cardiovascular events as well as developing treatments for this and to increase wound healing capacity which is of great relevance to the warfighter.

- **Dr. Brian Stansfield** *(Georgia State University)* is studying a type of cell called macrophages that have multiple functions in the body including in the vascular system. When there is injury to the vascular system, macrophages are 'recruited' to the wound. However in mice where macrophages are deficient in functional *Nf1* gene, a larger number than normal of macrophages are recruited to the injury. Macrophages promote inflammation, and this impairs healing and promotes the onset of vascular disease. This research has solidified a link between *Nf1* gene activity and vascular disease and identifies macrophages as cells to target during treatment.