TheNetworkEdge

The NF Network presents A quarterly research review
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Welcome to the first Neurofibromatosis Network's Science Column, **The Network Edge!** Every three months, The Network Edge will bring you a summary of the latest news from neurofibromatosis (NF) research and clinical trials.

Today, NF research is in a tremendously exciting place, giving hope to those living with NF1, NF2 and schwannomatosis. The Neurofibromatosis Network, through its advocacy efforts as well as by funding its own research, has a central role in ensuring that resources needed to support NF research progress will continue to be available. A number of NF clinical trials are now underway, testing drug treatments for different aspects of NF, from tumor growth to learning disabilities. Meanwhile, early stage 'discovery' research is uncovering knowledge about NF biology, and this information is being used to develop new candidate drug treatments. The result is a 'pipeline' that brings new ideas to the clinic.

What's Inside The Network Edge?

The Network Edge summarizes recent publications from across the NF science and clinical arenas. NF has a highly collaborative international research community, and this is reflected in the The Network Edge, which includes reports from studies in the United States and around the world. This first Science Column opens with a brief reminder of the federal funding that supports most of the NF research in the United States, and of the important role that the Neurofibromatosis Network plays in ensuring this funding continues.

The Network Edge Contents:

1. Impact of the Neurofibromatosis Network on Federal NF Research Funding

The majority of NF research in the United States is funded by two sources: the National Institutes of Health (NIH), and the Congressionally Directed Medical Research Program's Neurofibromatosis Research Program (CDMRP NFRP). In 2011, NIH committed $23M to NF research. The NFRP program began in 1996 and to date has committed $243M to NF research, with $12.8M anticipated for FY12. These funding sources operate in quite different ways. NIH funds projects across

every topic of medical research; NF research applications compete with applications from other areas of research; and since NF causes a range of clinical issues - including benign and malignant tumors of the peripheral nerves and brain, bone abnormalities, learning disabilities and pain - NF funding applications might be submitted to a number of NIH institutes. This decentralizes NIH decision making about NF research funding overall. And NIH does not set aside a specific amount of funding for NF research, so there is no guarantee as to how much NF research will be funded each year.

In contrast to this, the CDMRP NFRP is solely dedicated to funding NF research. Applications to the program receive a scientific review, but the final funding decisions are determined by an Integration Panel. This Panel includes scientific and medical advisors as well as consumer representatives (individuals with NF or their family members). The NF Network's Executive Director, Kim Bischoff, is currently a consumer representative on the Panel.

The Integration Panel takes a 'portfolio' view of research funding. Each year the Panel examines the scientific review recommendations in the context of which areas of NF research are of greatest priority at that time. This portfolio approach mean the NFRP can respond nimbly to support the most pressing areas of NF research. In the past this portfolio approach has led the creation of the first NF Mouse Model Consortium in 2000; and more recently, to the creation of the NF Clinical Trials Consortium in 2006.

What NIH and NFRP have in common is that neither funding source is guaranteed to continue each year. The overall NIH budget is approved annually by Congress; recently this budget has remained flat, making it progressively harder for researchers to secure an NIH grant. And, as noted above, NIH funding for NF research is not set aside. As a result, NF research applications face progressively tougher competition in seeking a grant. Ensuring annual renewal of CDMRP NFRP funding is even more challenging. Each year, a funding request for this - and for other CDMRP disease-focused programs - is included as a line item in the overall Department of Defense budget request to Congress. This request goes through rounds of consideration and review, and during this process, CDMRP is at risk of being reduced or even cut.

The Neurofibromatosis Network's constituents – those with NF, their families and supporters – play a critical role in continuing NIH and CDMRP funding for NF research. This is accomplished through visits with, and letter writing to, Congressional district representatives - to share stories of living with NF; to emphasize the importance of the NIH and CDMRP funding of NF research; and to ask for their Congressman's support for continuation of these programs. The impact of the personal stories of Neurofibromatosis Network constituents on the ongoing success of federal funding for NF research cannot be underestimated.

2. The CDMRP NFRP NF Clinical Trials Consortium Continues and Expands in 2012

In 2006, the CDMRP NFRP established the world's first NF Clinical Trials Consortium (NFCTC). Since most clinical centers see only a modest number of NF patients, it is challenging for one site to recruit enough patients to do a clinical trial, especially for a rare NF feature such as optic pathway glioma. The NFCTC linked 9 clinical centers, providing a collaborative framework so that trial participants could be recruited at multiple sites. The NFCTC accelerates the timeframe to complete a clinical trial and allows for multiple trials to be conducted in parallel, offering greater benefit more rapidly to those living with NF.

During its first 5 years, the NFCTC opened three NF1 clinical trials: Sirolimus for plexiform neurofibromas, Lovastatin for learning disabilities and RAD-001 for low-grade gliomas. In 2011, the CDMRP NFRP recognized the importance of NFCTC by approving its continued funding and expansion for another 5 years. NFCTC now includes 13 member sites and 4 additional collaborating sites, improving geographical coverage for faster recruitment. In addition, the NFCTC has broadened its focus to include clinical trials for NF1, NF2 and schwannomatosis. More information about NFCTC is available at www.nfconsortium.org.

3. NF1 Clinical Trials

A number of clinical trials for NF1 have started over the past few years. Though not all of these will yield positive results, such as tumor shrinkage, it is important that the findings from all trials are reported, because this information can be used to improve the design of future trials. **Kim *et al.*** reported the results of a clinical trial of the drug Sorafenib for the treatment of plexiform neurofibromas in children with NF1. Sorafenib targets a number of molecular pathways that are important in promoting plexiform neurofibroma growth. It has been shown to be safe and effective in children's cancer trials. The NF1 trial enrolled children aged 3 to 18 with NF1-related inoperable plexiform neurofibromas. However, no plexiform shrinkage was seen during drug treatment, and Sorafenib also caused side effects - pain, skin rash and mood alteration. Because of these side effects the drug dose couldn't be increased to see if a greater drug amount would shrink the plexiform tumor. The trial was discontinued. One of the important things learned from this trial was that even if a drug is safe and effective cancer patients at a particular dose, it cannot be assumed that the same dose will be safe and effective in NF1.

One of the most important issues in a clinical trial is defining endpoints that will show whether the treatment worked or not. An example of an endpoint would be a reduction in tumor volume in response to a drug. As the number of NF1 clinical trials grows, more research is focusing on endpoint design. Optic pathway glioma (OPG) tumors can occur in children with NF1; they can be managed with surgery or radiation but usually lead to vision loss. As new drug therapies for OPG emerge, the possibility of preserving vision is a possibility. A report from **Avery et al.** discusses how the measure of visual acuity is being introduced into OPG clinical management. The report reviews different approaches for measuring visual acuity, and proposes a standardized testing protocol that can be used to monitor NF1 patients in the clinic and to detect drug response in OPG clinical trials.

4. NF1 Clinical Management

The question of whether NF1 plexiform neurofibromas will grow significantly during life is unpredictable, and presents one of the most challenging aspects for clinical management of NF1, particularly because these tumors are also at risk of becoming malignant. Two recent publications examined this issue. **Nguyen *et al.*** reviewed the growth of NF1-related internal plexiform neurofibromas in 201 individuals using whole body MRI, cross-referencing tumor burden volume, growth rate and age. In most cases, plexiforms were found to grow slowly or not at all, and in some cases they shrank. The occurrence of new tumors is rare in persons who already have an existing plexiform; and new tumors are rare in adults with no plexiforms. Those most at risk for tumor growth are children who have existing internal plexiforms. A French and American study by **Sbidian *et al.*** aimed to identify a way to predict whether or not a child with NF1 is at risk of developing internal plexiform neurofibromas. The study examined 357 children and found the development of internal plexiforms could be predicted from the child's age, the presence of xanthogranulomas (a type of skin tumor), and the presence of existing subcutaneous and plexiform neurofibromas. Interestingly, this study found that internal neurofibromas developed earlier in females than in males. Together, these two studies highlight the importance of clinical monitoring of children for plexiform neurofibromas.

5. NF2 Clinical Trials

Drug trials for NF2 vestibular schwannomas have made significant progress in the last few years. One of the first and most prominent NF2 trials was of the drug Bevacizumab which prevents new blood vessel formation in tumors by targeting vascular endothelial growth factor A (VEGF-A) and shrinking the tumors. In NF2 trials of Bevacizumab, hearing was restored in some patients; this was first reported in the *New England Journal of Medicine* in 2009. **Plotkin *et al.*** recently presented an update on this trial with an analysis of 31 participants with NF2, ages 12 to 73. Individuals received Bevacizumab for 6 to 41 months. Of the 31 participants, 17 showed tumor shrinkage. 23 participants were evaluated for hearing

changes; 13 showed improvement. On average, these responses were first seen 3 months after drug treatment began. After 1 year of drug, 90% of participants had stable or improved hearing; after 3 years this number was at 61%. After 1 year, 88% of patients had a stable or decreased tumor size; after 3 years this number was at 54%. Overall this report cements Bevacizumab as a promising treatment for NF2 vestibular schwannoma management.

In another NF2 drug trial, **Karajannis *et al.*** report the results of a Phase II trial of Lapatinib, which acts by targeting the epidermal growth factor receptor (EGFR). 21 participants, adults and children, with NF2 related vestibular schwannomas were enrolled in the trial. Between 3 and 12 months of treatment, 17 participants had greater than a 15% decrease in vestibular schwannoma volume. Some participants had a 23% size reduction. 13 participants were evaluated for hearing changes. 4 participants showed improvement; one sustained improvement for more than 9 months. Lapatinib had some minor side effects. Lapatinib may therefore have promise in NF2, and the authors suggest future trials combine it with other drugs such as Bevacizumab.

6. NF2 Clinical Management

Although these drug therapies for NF2 are emerging, surgery is still often the first line of treatment pursued. An Australian review by **Szudek *et al.*** summarizes the latest surgical treatment approaches for NF2-related vestibular schwannomas and other schwannomas, including surgery options and outcomes, including preservation of hearing and facial nerve function.

Meningiomas commonly occur in NF2, but not much is known about the long-term natural history of these tumors. The lack of information about meningiomas has limited the ability of doctors to make decisions on how to treat these them. Aiming to remedy this, the French group of **Goutagny *et al.*** did long term follow up of 74 individuals with NF2 with, collectively, 287 meningiomas (an average of 3 per person). On average, participants were monitored for a little over 9 years. The findings show the value of taking an active treatment approach for new and brain edema-associated meningiomas. They also highlight the need for more clinical trials that are actually focused on NF2 meningiomas as the primary tumor of study, and suggested that these trials should include meningiomas that grow at a rate of 20% or greater per year.

For individuals with NF2 and hearing loss, two devices may help restore communication abilities - the cochlear implant (CI) and the auditory brainstem implant (ABI). A CI is an option in NF2 if the auditory nerve is still functional. If the auditory nerve is no longer functional, such as after surgery, then the ABI is an option. Recent reviews examine these devices.

Carlson *et al.* followed up with 10 people with NF2 between 1 and 8 years after they had received a CI. 9 persons had achieved sound awareness; 6 attained open-set speech recognition; and 7 use the CI daily. The study supported the CI as a favorable option for NF2. The United States and Italy based group of **Colletti *et al.*** and France based **Vincent** examined the use of the ABI in NF2. Over 500 persons worldwide with NF2 now have an ABI. The ABI electrode array is a small paddle placed on the cochlear nucleus of the brainstem. Each electrode activates a variety of neuron (nerve cell) types. The ABI gives different patients different levels of sound and speech comprehension, and usually better lip reading, and is a good option for individuals with NF2 who have lost auditory nerve function.

7. NF1 Learning Disabilities

Around two-thirds of individuals with NF1 have some sort of learning disability. Clinical trials to treat these are underway. It has been challenging for researchers to figure out good measures for trial response, but these measures - known as trial endpoints - are critical to show whether or not a drug is working. Some important work about NF1 learning disabilities came from studying mice who were tested for their ability to navigate a water maze and memorize the position of – and later find - a safety platform in the water. This maze tests an aspect of brain function called visuospatial learning. Mice with

NF1 learning disabilities can't master the water maze, but their performance was improved by taking the drug Lovastatin which has since progressed into clinical trials of children with NF1 learning disabilities. **Payne, Barton *et al.*** report that they have developed a computerized equivalent of the mouse water maze as a test that can be given to children with NF1 learning disabilities. The test reveals that like the mice, children with NF1 also have visuospatial learning deficits. This test can now be used in clinical trials of drugs to treat NF1 learning disabilities, to look for improvements.

Children with NF1 often have attention deficit disorder (ADD) or attention deficit and hyperactivity disorder (ADHD) but it is not known if this affects the intellectual abilities of the child. A series of recent papers investigates this issue.

In a German study, **Lidzba *et al.*** studied 114 children with NF1 and either ADD or ADHD and found that they fared worse than the general population in intellectual assessment. This suggests that ADD/ADHD can have a negative impact on the intellectual development of children with NF1. From the same German group, **Mautner *et al.*** conducted a quality of life survey comparing adults with NF1 and ADHD, with adults who have ADHD but not NF1. This study showed that the ADHD group with NF1 is more emotionally unstable than the group with ADHD but not NF1. Participants with both NF1 and ADHD reported significantly lower overall 'life satisfaction' taking into account general health, self-satisfaction, sexuality, and family. Two reports from an Australian group also investigate this. **Pride *et al.*** compare three populations of children: those with NF1, those with NF1 and ADHD, and an unaffected population, and look at academic ability and predictors of underachievement. The study finds that inattention and academic underachievement are characteristic in NF1, and that ADHD and NF1 together further burden some aspects of learning. Interestingly, **Payne, Arnold *et al.*** found that in the children with both ADHD and NF1, executive function – i.e. working memory and the ability for planning - is not any worse than in children with just NF1. Finally, a British study from **Lehtonen *et al.*** conducted a survey of available information on behavior and attention deficits in children with NF1, drawn from existing publications. The results of the survey showed that intelligence, academic skills, visuospatial skills, social competence, and attention can be impaired in children with NF1. Less clear was the information available on deficits in memory, motor functioning, language, and executive functions. Together these studies offer a useful window into understanding the further impact of attention deficit on individuals with NF1, but suggest this is an area that needs further study and collaboration.

Emotion and anxiety in NF is the topic of a study by **D. Wang *et al.*** who examined emotional functions in 248 people with NF1, NF2 or schwannomatosis. The study found that NF causes increased depression, anxiety and perceived stress, and lower self-esteem, than in the general population. There was no difference in these measures between NF1, NF2 or schwannomatosis. However, the data was not correlated with the severity of the NF in the individual.

Understanding these and other complex issues that surround NF1 learning disabilities is something that will clearly benefit from collaboration. In this vein, **Acosta *et al.*** provide an update on The Learning Disabilities Network *(LeaDNet),* a consortium of researchers and clinicians established in 2006 to focus on to understand the biology of, and to figure out how best to treat, NF1 learning disabilities. The LeaDNet group has continued to expand and now includes researchers and physicians working across a broad range of genetic disorders such as autism, which also cause learning disabilities. The goal is to share knowledge across disciplines and to advance the development of rational biological treatment strategies that will help not only those affected by NF1 learning disabilities, but also those affected by a range of other conditions.

8. NF1 Bony Abnormalities

Bone abnormalities affect as many as 25% of individuals with NF1. Over the past few years, a number of studies have shed light on the biology of these bone abnormalities and begun to translate new findings into clinical treatments. **Schnabel *et al.*** previously showed that adults with NF1 have a reduced overall bone density and greater incidence of deficiency of a Vitamin D derivative. In a new study the group reports on a clinical trial to test the effects of Vitamin D(3) on bone mineral density in persons with NF1 and a Vitamin D(3) deficiency. Patients were analyzed after 1 year and after 2 years of treatment. The study showed that Vitamin D(3) supplementation improved bone mineral density in NF1 after 1 year, with further improved after 2 years. The Finnish group of **Heervä *et al.*** report on a study using their Patient Registry of 460 NF1 patients to examine bone fracture risk among this population. The study showed that NF1 is associated with an increased age-dependent fracture risk compared to the general population. Particularly at risk are those with NF1 who are under 17 and over 41 years of age. This study demonstrates the importance of and need for preventative treatments that will offset the risk of bone fractures in individuals with NF1.

9. Schwannomatosis Update

The rarest form of neurofibromatosis is schwannomatosis, and this is still not well understood. The first diagnostic guidelines for schwannomatosis were published in 2005, and the first candidate gene, SMARCB1, was linked to schwannomatosis in 2007. Since it is so rare, most physicians see only a very small number of cases, and accurate diagnosis is still challenging. **Merker *et al.*** present a review of the variety of schwannomatosis presentations seen in 87 patients at Massachusetts General Hospital over a 16 year period. 89% of persons presented with peripheral schwannomas; and 74% presented with spinal schwannomas. The presence of intracranial tumors was quite rare. 46% of persons presented with pain that was not associated with a tumor mass. 68% of persons presented with chronic and persistent pain that was not alleviated by surgery or medical management. This review provides further guidance as to the array of physical symptoms and features that might be expected with a clinical presentation of schwannomatosis.

10. Increased Breast Cancer Risk in NF1

It is well known that individuals with NF1 can develop a range of nerve tumors, but there is also an increasing body of evidence to suggest that women with NF1 are also at increased risk of developing breast cancer. Two recently published studies and a commentary address this issue. **X. Wang *et al.*** examined the records of 76 women with NF1 and compared them to women in the general population. The study found that there is a statistically significant increased incidence of breast cancer in the women with NF1. In particular there is an increased incidence of early onset breast cancer (women under age 50). In another study of 126 women with NF1, **Madanikia *et al.*** found more than a four-fold increased risk of breast cancer than in the general population.

A commentary by **Evans** looked at these two studies and put them in context with previous United Kingdom studies that suggest women with NF1 and under the age of 50 are at a five-fold increased risk of breast cancer. Together, these findings suggest that breast cancer screening guidelines should be evaluated and emphasized for women with NF1. They should be viewed as a potentially high-risk group for breast cancer. Dr Evans emphasizes the need for resources that will support earlier commencement of breast cancer screening in women with NF1, and for vigilance on the part of physicians to be aware of this increased risk among their female NF1 patients. He also highlighted the need to conduct large scale multisite studies to further verify and further understand this increased risk.

11. Other Clinical Features of NF1

Individuals with NF1 are at risk of developing disorders of the blood vessels, or vasculopathies, but these are not widely discussed or well studies. **Kaas *et al.*** examined brain and peripheral scans from 80 children with NF1 seen over a 10 year period. 14 of these children were found to have vasculopathy - 2 with peripheral vasculopathy and 12 with brain vasculopathy. This study highlighted the prevalence of vasculopathy and emphasized that it should be considered as part of NF1 management.

Children with NF1 often have hypotonia (low muscle tone). Based on a correlation analysis, **Wessel *et al.*** report that the presence of hypotonia might predict that the child is also likely to develop an NF1-related brain tumor. **Stevenson *et al.*** looked at hand grip strength in a group of persons with either NF1 or related genetic conditions including Noonan syndrome and Costello syndrome. Hand grip strength was found to be impaired in these persons compared to the general population.

Soucy *et al.* examined whether children with NF1 are shorter than the general population. 170 individuals with NF1 were examined, and it was confirmed that the NF1 group was overall shorter.

The French group **Pasmant *et al.*** addressed the question of whether we can link a person's genotype (their genetic alterations) to their phenotype (their physical appearance). This would be extremely helpful in NF1 where a variety of physical manifestations can occur: if phenotype could be mapped back to the genotype, it might be possible in the future to predict the progression that someone's NF1 will take during their life. However this area of research is still in its early stages and is confounded by the many individual variations seen in persons with NF1. The report emphasized the importance of genetic elements called modifier genes, and even potentially the impact of environmental factors, in contributing to the clinical progression of NF1.

12. What's New in NF1 Biology and Drug Targets?

NF1 features such as tumors will develop in a person because of genetic changes that occur inside cells. These genetic changes lead to altered molecular signaling inside the cells, and this in turn will cause a tumor to form, or lead to learning disabilities, or cause bony abnormalities to occur. Figuring out the molecular signals that have been altered is important because each signal is a link in the chain that might also be targeted by drugs that will stop tumor growth or correct learning disabilities. A few recent publications present the case for specific signals as possible drug targets in NF1.

Impaired NF1 gene function causes the signal heat shock factor 1 (HSF1) to be expressed. **Dai *et al.*** suggest that HSF1 has a role in promoting the growth of malignant peripheral nerve sheath tumors (MPNSTs), tumors which affect an estimated 10% of persons with NF1 and are very difficult to manage clinically. Dai's study showed that HSF1 keeps tumor cells grown in the dish alive, and that HSF1 is prominently expressed in human MPNST tumor samples. **S.J. Lee *et al.*** show that impairment of NF1 gene function in MPNST cells also increases expression of another cell signal, Bcl-xL. This signal appears to make MPNST cells drug resistant, because when Bcl-xL is inactivated in these cells, the cells become sensitive to the anticancer drug doxorubicin. It is suggested that Bcl-xL might contribute to the change that occurs when a benign plexiform neurofibroma tumor becomes a malignant MPNST; and that inactivating Bcl-xL in tumors might therefore be a useful companion to an anticancer drug treatment strategy in NF1 MPNST.

Keng *et al.* developed a mouse model where NF1 gene function is impaired and the function of another tumor related gene, PTEN, is also impaired. Highly aggressive MPNSTs form in these mice. The cooperation of these genes may have a role where NF1 benign plexiform tumors progress rapidly to highly malignant MPNSTs. **Patel *et al.*** identified a role for another cell signal, Aurora Kinase A, in promoting MPNST growth. The Aurora Kinase A inhibitor, MLN8237, was able to shrink MPNST tumors implanted into mice, and to increasing the survival of the mice. Aurora Kinase inhibitor may therefore be worth pursuing as a treatment for MPNSTs.

An intriguing area of study is the question of whether cells that give rise to NF tumors are actually specified very early in life in the embryo. If this is the case, it could help with early detection and

treatment of tumors. **D.Y. Lee *et al.*** examined the origins of optic pathway gliomas using a mouse model of NF1 tumors, and show that these tumors originate from a stem cell in the third ventricle of the brain.

The NF1 tumor 'microenvironment' refers to the cells and materials that comprise the structure and composition of a tumor, and the molecular signals that are sent from cell to cell. This Indianapolis-based group of **Yang *et al.*** has successfully harnessed their knowledge of the NF1 tumor microenvironment to advance the progress of the drug Imatinib into Phase II clinical trials for NF1 plexiform neurofibromas, and they present a review of what is known about the microenvironment.

Over the past few years, new mouse models of NF1 learning disabilities have proved helpful in studies of this area. **Kallarackal *et al.*** examined one of these mouse models to see whether changes in small-conductance calcium-activated potassium channels (SK channels) might have a role in causing the NF1 learning disabilities. The group treated the NF1 learning disabilities mouse model with a drug apamin, which blocks the SK channels, and found these mice to perform better in the water maze after a few days of drug treatment. It is thought that the drug is modulating long term potentiation, a brain function that is critical during learning, and which is compromised in NF1. These studies may open a new avenue to explore for the development of drugs for NF1 learning disabilities.

Finally, new biology findings are reported not just from mice but from very different models of NF1. Zebrafish make terrific models for studying the underlying genetics of disease because these fish can be bred quickly and the fish itself is transparent so the internal organs such as nerves can easily be examined. **Shin *et al.*** use zebrafish to study the effects of completely inactivating the NF1 gene. Without the active NF1 gene these fish will not live beyond the larval (embryonic) stage but studying these larvae shows extensive effects on the development of the nervous system, learning behavior and skin pigmentation lesions. As they can be bred rapidly and in large numbers, fruit flies (drosophila) are also widely used to study genetics, including NF1 genetics. **Rohrbough *et al.*** reported from a fly study that a secreted signaling molecule Jelly Belly (Jeb) activates Anaplastic Lymphoma Kinase (Alk), a receptor tyrosine kinase, and that this may have a role in controlling cognitive dysfunction in NF.

13. What's New in NF2 Biology and Drug Targets?

Schwannoma tumors are seen in both NF2 and schwannomatosis, and these tumors originate from cells of the nervous system called Schwann cells. Schwannomas grow because the NF2 gene has become inactive in Schwann cells, causing these cells to multiply uncontrollably. A consequence of NF2 gene inactivation is that the cell signal Rac1 becomes hyper-activated. But is Rac-1 a direct cause of tumor growth? To test this idea, **Manchanda *et al.*** created a mouse model in which two different genes were inactivated in Schwann cells - Rac1 and another gene, Prkar1, which creates part of the cell signal Protein Kinase A and will promote tumor growth when activated. Loss of Rac1 activity in these mice reduced tumor formation, which would be expected; but surprisingly, loss of Rac-1 also caused increased expression of the Nf2 protein. Conversely, activating Rac1 expression decreased Nf2 protein expression. This is important because it puts forth the idea that Rac-1 and Nf2 have a two-way regulatory relationship. Further studies of the mouse model showed that the Rac-1/Nf2 relationship might further be regulated by Protein Kinase A. This study puts forward new signaling interactions that might be future NF2 drug targets.

Ammoun *et al.* explored the molecular signals that promote vestibular schwannoma growth using a model of human NF2 tumor tissue grown in a dish. The group found that cell signals insulin-like growth factor-I (IGF-I)-mediates cell proliferation and cell-matrix adhesion; c-Jun N-terminal kinases mediate increased proliferation; and AKT mediates cell survival. These findings open up new candidate drug targets. Finally, **Morrow *et al.*** present an updated review of the biology of the NF2 protein, merlin.

14. Legius Syndrome Update

In 2007, a Belgian group identified a new NF1 like syndrome that was termed Legius Syndrome after its pioneer, Dr. Eric Legius. Legius Syndrome presents clinically like a mild form of NF1, with its principal features being café-au-lait spots and mild learning disabilities. Its underlying cause is a mutation of another tumor suppressor gene, SPRED1, rather than the NF1 gene. Since its identification, Legius Syndrome has been of significant interest to clinicians and families alike because it has a less unpredictable outlook than NF1. **Stowe *et al.*** recently showed that Legius Syndrome and NF1 have shown that the NF1 protein interacts with Spred1 protein and is necessary for Spred1 to function. This finding helps to understand the overlapping features of NF1 and Legius syndrome.

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