SUMMARY REPORT

Overview

On March 29, 2019, the non-profit organization NF2 BioSolutions hosted a first-of-its-kind consortium focused on gene therapy (GT) strategies for the rare genetic disorder Neurofibromatosis Type 2 (NF2). The one-day interactive meeting which was held at the SAP America office in Boston, MA, USA was attended by a diverse group of key researchers and clinicians in NF2, as well as gene therapy experts from both academia and industry. The forty-five attendees of the expert meeting included 11 NF2 researchers, 12 NF2 clinicians, 10 gene therapy researchers, and 6 biotech executives from all over the US and the UK.

The meeting was carried out in a participatory workshop format wherein attendees were grouped into five teams, each comprised of representatives from every expert group. Four brainstorming exercises were prepared for the consortium which were completed by each team in parallel, after which a general discussion amongst all attendees was held for each exercise. The four group exercises focused on:

1. *Existing gene therapy strategies and their applicability on NF2*
2. *Challenges in gene therapy and NF2 research*
3. *Deriving the needs from the challenges in gene therapy and NF2 research*
4. *Developing the process to bring gene therapy for NF2 to the patients*

This report summarizes the top outcomes derived from the consortium and highlights the key points that the focus groups established for each exercise. The immediate steps to be undertaken towards developing the ideas gathered from this expert meeting will also be discussed.

In appendix A is the attendees list and appendix B is the agenda.

DISCLAIMER: This summary report is a compilation of notes and video transcriptions of oral presentations during the consortium. Some information may have been inadvertently missed or misinterpreted during the process.

GENE THERAPY APPROACH: Suicide gene therapy vs. Gene replacement therapy vs Gene knockdown and replacement combination approach

I. Suicide gene therapy

- This approach is also known as a cytotoxic (toxic to cells) approach because it kills tumor cells.
- Refers to the specific introduction of a gene that triggers cell death in tumor cells while sparing healthy nearby cells.
- In theory, this approach could resolve existing NF2 tumors and potentially allow for an endogenous repair mechanism to occur, according to Dr. Brenner.

- ***Challenges***:
  - Several key gene candidates involved in cell death pathways have been identified, but have yet to be exhaustively tested in animal models for safety and efficacy

- The possibility exists that the tumors might regrow if the suicide vector is not able to trigger cell death in all tumor cells.
- If the goal is to inhibit the growth of existing tumors, it will be difficult to determine the minimum percentage of cells to target to effectively halt tumor growth.
- Schwannomas tend to grow back after surgical removal vs meningiomas, i.e. are more aggressive; will they respond similarly to suicide GT approach?

- ***Derived needs***:
  - Need to evaluate if all clinical variations can be targeted by a single cytotoxic GT approach
  - Need to determine if a single dose, wherein not all tumor cells might be targeted for cell death, is enough to achieve the desired therapeutic outcome
    - This will be dictated by the meaning of "therapeutic outcome". If the outcome is to shrink a tumor drastically impacting quality of life, a single intra-tumoral delivery could suffice. However, repeated treatments could be an issue in the NF2 population.

II. Gene replacement therapy

- Refers to providing a functional copy of the defective NF2 gene that is mutated or inactivated in a patient with the aim of rescuing the disease phenotype it confers

- ***Challenges***:
  - Some concerns exist about a possible dominant negative effect of NF2 mutations have been raised, i.e. if they act antagonistically to the inherent or GT-introduced normal copy of the NF2 gene, which will counteract a simple gene replacement therapy approach.
  - Some believe that the overexpressed NF2 gene might form heterodimers with the mutant protein from the mutated allele and then get degraded.
  - Overexpression of Merlin has the possibility to be dangerous either to neighboring cells or elsewhere in the body.
  - If the goal is disease prevention by inhibiting the growth of new tumors we need to determine the percentage of cells (transduction efficiency) needed. Ideally we would want to hit every cell lacking a functional copy of Merlin which will involve all of the patient's cells, at least in germline NF2 cases.
    - Currently, there are no known gene therapy technologies that can accomplish this aim in a living human. Currently, IVF genetic testing and/or gene editing of the embryo could approximate this goal. In addition, AAV is a non-integrating vector, which means that it will be quickly diluted in any dividing cell.

- ***Derived needs***:
  - Need better understanding of the diverse phenotypic variations of tumors in NF2 patients
    - Germline cases have heterozygous NF2 mutations in all cells (one healthy allele, one mutated allele).
    - Mosaic cases have only a percentage of cells harboring heterozygous NF2 mutations
  - Tumors are thought to result after loss of heterozygosity (LOH) when a second mutation event occurs that inactivates the wild type (normal) NF2 alleleNeed to determine if Merlin overexpression is toxic to non-targeted cells *in vivo*
  - Need to determine if Merlin re-expression rescues the phenotype of tumor cells regardless of mutation type
  - Need to confirm if overexpressed Merlin can be shared to neighboring cells (i.e. cross-correction) or not
  - Need to determine if the endogenous mutated copy of Merlin interferes with intended gene therapy effects or not

- Need better understanding of which types of NF2 gene mutations (if any) might be susceptible to the suspected degradation phenomenon

III. Gene knockdown + gene replacement combination approach

- Refers to the use of small RNAs to silence the mutated gene that confers disease, at the same time providing a functional copy of the defective gene that produces normal copies of the encoded protein
- Theoretically, this addresses the challenge of whether existing NF2 mutations have a dominant negative effect in the cell

- ***Challenges***:
  - How do we ensure that the normal copy of Merlin remains after gene knockdown?
  - How do we ensure that the mutated copy of Merlin is knocked down in the target cells?
  - How do we design a vector that will enable us to carry out this combination approach? Single vector or two separate vectors for knockdown and gene replacement?

- ***Derived needs***:
  - Need to determine if Merlin overexpression is toxic to non-targeted cells in vivo
  - Need to determine if Merlin re-expression rescues the phenotype of tumor cells regardless of mutation type
  - Need to devise a knockdown strategy that ensures that functional copies of the NF2 gene remains in the cell, especially in combination with NF2 gene replacement

GENE THERAPY DESIGN: Viral vector selection, delivery strategy, and production

I. Viral Vector Selection

- A vector refers to the carrier, usually a modified virus, that is genetically engineered to deliver the therapeutic gene to target cells for GT.
- The use of non-viral vectors (i.e. liposomes, etc.) were not generally considered and discussed during the consortium.
- AAV was the clear choice when considering a choice of viral vectors for a number of reasons, including high efficiency, long-term stability, low immunogenicity (toxicity), low genotoxicity, safety, existing manufacturing expertise, and the increasing number of IND applications that utilize it.

- ***Challenges***:
  - Questions were raised about which AAV serotype might be best suited to target schwannomas and other NF2 tumor types (AAV1, AAV9, etc?)
  - No single vector design to target all types of NF2 tumors at once due to cell-specificity of promoter, unless we want to do a combination approach to target all tumor types

- ***Derived needs***:
  - Need to identify/test if currently available AAV serotypes (i.e. AAV1, AAV9, or AAVh10) are suitable to use for selected NF2 gene therapy approach
    - AAV9 can be used to generate a new drug without concern about ownership of the IP since use of AAV9 can be purchased
  - If not, need to determine if construction of a custom new vector specific for our goals is warranted
  - Need to identify relevant promoter/s for therapeutic gene expression
    - Consider specificity of expression in target cell types (i.e. VS only, schwannomas in general, meningiomas only, or all NF2 tumor types)
    - Consider extent of gene expression driven by promoter and determine the need for regulation

        - Consider consequences if promoter is active in a particular cell type (i.e. Schwann lineage cells), especially for suicide gene approach, if it will kill both tumor cells and healthy cells

II. Vector Delivery

- Refers to methods for administration of the vector containing the therapeutic genetic material to animal models, and eventually, in patients for gene therapy.

- ***Challenges***:
    - Since NF2 tumors are for the most part considered solid tumors, how can we ensure penetrance if delivered systemically and not intra-tumor?
    - Delivery method will also depend on outcome/approach, i.e. direct injection will be more favorable for killing tumors by suicide gene approach, vs intravenous or intrathecal route for systemic delivery in an effort to stop tumor growth throughout the body.
    - Most NF2-related tumors are in hard-to-access anatomical locations (i.e. brain and spine).
    - Safety and efficacy of intravenous vs the more invasive intraventricular/intrathecal delivery or direct tumor injection is yet unestablished for NF2 tumors.
    - Injection of viral vector into the cerebrospinal fluid (CSF) fluid may be a better route of access to certain tumors but is yet untested in NF2.
    - Intra-arterial (IA) delivery might also be considered; however, the clinical experience with IA delivery of chemotherapy drugs for brain tumors has shown little or no improvement over intravenous (IV) delivery.

- ***Derived needs***:
    - Need to assess which delivery method will be least invasive while at the same time be the most effective to access NF2 tumors for gene therapy
    - Need to optimize dosage escalation and transduction efficiency of vector in target cell types/animal models
        - Determine what percentage of transduced cells are necessary to demonstrate efficacy
        - Determine toxicity of vector
        - Determine biodistribution
    - Need to design assays to measure successful expression of functional Merlin in target cells

III. Vector Production

- Refers to the manufacturing methods for gene therapy vectors from small early clinical studies to larger trials

- ***Challenges***:
    - Facilities and laboratory expertise for vector production
    - Effective titer for tumor treatment still needs to be tested and determined especially for NHP models

- ***Derived needs***:
    - Need to consider scale of manufacturing and large scale production protocols of selected vector
        - Purification method
        - Functional titer
        - Batch size
        - Quality control
    - Need to identify collaborator laboratories that have expertise in generating, testing, and optimizing gene vector constructs

<u>GENE THERAPY MODELS</u>: Cell models and Animal models for NF2 gene therapy

I. Cell models

- Refers to relevant established cell lines with a genetic profile that accurately phenocopies NF2-related tumor cell types.

- ***<u>Challenges</u>***:
  - How do we model the relevant mutation types detected in NF2 patient tumors?
    - There are some Schwannoma cell lines established from patient-derived tumors.
    - Can we develop a panel of iPS cells derived from patient cells?
    - Will an iPSC model help predict which patients respond to different therapeutic strategies?
    - Will a single NF2 hit on the iPSC translate to the disease phenotype?
  - Cell division rates are very slow in NF tumors.
    - Will the NF2 schwannoma cell lines be sufficient models for proof-of-concept studies?
    - How can we design a gene therapy approach targeting dividing cells, if we are to use an AAV vector, since it does not integrate into the cell genome and will be diluted in dividing cells?

- ***<u>Derived needs</u>***:
  - Need to evaluate the feasibility of creating iPS cell lines as a way of creating patient-derived Schwann cells to address some of the questions about NF2 gene variation *in vitro*
  - Need to derive cell models that can recapitulate NF2 tumor cell properties and can be used to test vector efficacy

II. Animal models

- A useful preclinical animal model of human disease requires broad physiological relevance at both genotypic and phenotypic levels.
  - Animal models of human disease should harbor mutations homologous to NF2 gene mutations documented in NF2 patients.
  - Moreover, this genetic perturbation should occur in cell types and gene doses similar to the hypothetical human tumor cell of origin.
  - These tissue-specific genetic mutations should induce tumors that share histological and biological characteristics with the corresponding human tumors.
- For NF2, this could be an ectopic tumor model (like those from Brenner or Giovannini labs) or genetically engineered mice (from the Clapp lab).

- ***<u>Challenges</u>***:
  - In existing models, schwannomas are incompletely penetrant (only occurring in about one-third of mice) and, generally, arise only late in life. Furthermore, vestibular schwannomas have not been observed in most existing murine models of NF2.
  - The utility of Clapp's mice since has been questioned since these are Cre-Lox animals that have lineage specific knockouts, so it is not clear if this would be considered an accurate model for gene augmentation of a human autosomal dominant condition.
  - The choice of the model might depend on the strategic design of vector; i.e, for a suicide gene therapy approach, any tumor models might be useful. However, for gene replacement (alone or with gene silencing), a better representation of an autosomal dominant mutant mouse might be necessary.
  - Safety, dose tolerance, and bio-distribution might best be studied in a (wild type) non-human primate since the immune system of lesser animals is not as representative of the human system.

        - However, the immune system of rats has, in a number of cases, served as a predictive model of safety and biodistribution. Their immune system does appear to respond.
    - NHP animal models take years to develop and will need a tremendous amount of resources to develop from scratch.
    - There are regulatory hurdles that will require the use of an NF2 model; most importantly to test the efficacy of the drug.
    - Efficacy and safety trials could be performed in existing mouse models. The use of larger animals for safety and dosing is not required by the FDA per se, and can be done only in some cases where companies are more concerned about trying to "de-risk" the failure of their programs prior to clinical trial.

- ***Derived needs***:
    - Need to determine if current existing mouse and NHP models for NF2 are sufficient, or if new ones need to be developed
    - Need to identify NHP models for efficacy, safety/toxicity, biodistribution
    - Need to evaluate if non-primate large mammals that can also spontaneously develop schwannomas and meningiomas (i.e. dogs) can also be used
    - Need to identify optimal delivery method especially for large animal models
        - Systemic delivery vs individual tumor injection will depend on desired therapeutic outcome
        - Consider that peripheral tumors are different from CNS tumors in terms of anatomical location, composition
    - Need to evaluate immune response to vector treatment
        - Consider immunosuppressants to prevent antibody response and potentially allow for repeated treatment
        - Has anyone discarded and/or looked at the question of whether the immune system of NF2 patients plays a role in keeping NF2 tumors (genesis and/or progression) in check?
        - What could be the untoward effects of suppressing NF2 patient's immune system for a significant period of time?
        - Has this been studied in models or is there clinical data?

MOVING TOWARDS THE CLINIC: Biomarker Identification and Clinical Trial Design

I. Biomarkers

- Refers to a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (NIH definition).
- Refers to any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease (WHO definition).

- ***Challenges***:
    - Identification may prove difficult given the clinical heterogeneity of symptoms
    - There is currently no known blood-borne NF2 biomarker that can be monitored
    - Some literature points to CSF samples as a possible source of biomarkers for NF2, but research it is not clear how significant the correlation between disease severity and the composition of the CSF is.

- ***Derived needs***:
    - Need to identify and test molecular markers that might be more helpful in evaluating efficacy of GT vs MRI imaging
        - Some participants think imaging is enough and superior to molecular markers
        - Can perform oncogenic analysis of ~100 tumors for <$100k

        - CSF samples can also be analyzed for potential biomarkers for <$100k
    - Need to perform a metabolic study to identify potential NF2 biomarkers
    - Need to gather natural history data to evaluate potentially measurable characteristics/symptoms to serve as disease indicators
    - Consider that Merlin is not usually secreted by either normal or tumor cells
        - Can we use tumor Merlin levels detected by Western blot to monitor disease progression?
        - Are there less invasive ways of determining Merlin expression in NF2 patients?
        - Is this a practical aspect to measure, vs performing routine MRI scanning?
    - Consider practicality/invasiveness vs MRI imaging, a serum biomarker would be ideal

II. Clinical Trial Design

- Refers to any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

- ***Challenges***:
    - Tumor shrinkage is not enough for FDA approval of a trial or a therapy.
        - Must show functional improvement vs placebo controls
    - Patient population is relatively small but widespread.
    - Diverse phenotypic variations of tumors in NF2 patients
    - Ultimately it will be important to choose definable endpoints for the trial design.
    - Consider that since gene therapy is "permanent", Phase 1 can become Phase 2

- ***Derived needs***:
    - Need to build a consolidated NF2 patient registry to account age group, gender, and genetic background
    - Need to involve patients in trial design
    - Need to determine if patients can participate in multiple trials
        - Can design a trial with small cohort of carefully-selected patients
        - Need to design Phase 1 carefully
    - Need to increase scientific/medical literacy of patient population
    - Consider combination therapy with surgery/small molecule drugs in conjunction with GT
    - Prioritize existing treatment tools and determine where gene therapy would fit
    - Consider endpoint measures to determine therapeutic efficacy
        - Tumor reduction/prevention ▮ Challenge: cell division rates are very slow in NF tumors
        - Improvement of quality of life
        - Need to identify *NF2*/Merlin assays and/or biomarkers to measure these
        - Need to identify duration of study to determine GT efficacy (again considering that NF2 tumors are slow-growing)

MAKING THE WHEELS TURN: Financing and Collaboration

I. Financing

- ***Challenges***:
    - Donor funding will be the primary source during the early stages.
    - Early research success will be crucial in securing funding for any further trials.
    - NIH funding may become helpful during the basic science phase but may be difficult to secure.
    - Not likely to receive significant venture capital funding until later in clinical trials.
    - Several proof-of-concept studies need to be done to attract investors.

- ***Derived needs***:
  - Need to engage more ambassadors and volunteers to organize fundraising events
  - Need concerted effort to maximize donor engagement during events
  - Need to identify research grants we can apply to
  - Think about the need to start a company or get an industry partner
  - Need to evaluate if efficacy and toxicity studies can be done simultaneously to maximize funding
  - NBS could fund several proof of concept studies and use them to solicit large scale investment by VC firms in trials. No need to own any IP

II. Collaboration

- ***Challenges***:
  - Consider aligning with other foundations for specific targeted focus, or
  - Taking NBS as a more specific and focused group for NF2 and move towards spinning off a company and having the goal of joining with a Venture Capitalist.

- ***Derived needs***:
  - NBS needs to play a central role in cultivating relationships with various stakeholders in the process of finding a cure
  - Relationships with patients and rare disease community
    - Need to prioritize patient engagement and building the NF2 global community
  - Relationships with clinical and nonclinical researchers
    - Both need to learn from each other and build off the work others are doing
  - Relationships with the FDA, NIH, and other government entities
    - Need to involve FDA early on and often in the pipeline
  - Relationships with industry
    - Venture capital and other private industry funding might be difficult to get until Stage I clinical trials are underway, unless a particularly exciting or novel research approach is identified

Future Directions For NF2 Gene Therapy

- **Plan of Action**
- ***$3 million (~2yrs)***
  - *POC, Dose Ranging, Minimum Effective Dose (MED), Maximum Tolerated Dose (MTD), (Pharmacokinetics etc.)*
  - *Vector: AAV9, AAV rh 10, other novel vector*
    - *IV or IT*
  - *Animal model testing*
    - *GEM Mouse*
    - *Xenotransplant*
- **$3 million (~1.5 yrs)**
  - *Somewhere there needs to be a Natural History Pre-Study*
  - *Safety*
    - *NHP or NF2 Mouse*
- **$15 million**
  - *Clinical Trial*
    - *Sporadic Vestibular Schwannoma and Sporadic Meningiomas*
    - *3-5 dose cohorts*
    - *dose escalation inclusion ≥ 20% tumor growth over 1 yr or Genetic confirmation of NF2 mutation*
    - *3-5 sites 15+ patients*

        - *Outcomes measures*
            - *MRI tumor volume*
            - *Stabilize or tumor regression*
            - *Audiogram*
- ***<u>Create a patient registry</u>***

Appendix A:
Attendees List

Akeola LLC

Dione Kobayashi, PhD
President
Drug development for orphan disease patients.

Apic Bio

Scott Loiler, PhD
Chief Technology Officer
Development of Adeno-associated virus (AAV)
vectors from research scale to GMP production.

Coda Biotherapeutics

Orion Keifer, MD, PhD
Senior Director, Research
Small and large animal model translational gene therapy research.

Genscript

Sasidhar Murikinati, PhD
Associate Product Manager
Immunohistochemistry, in situ hybridization and immuno assays in detecting biomarkers, viral infections and cancers.

Georgetown University

Chunling Yi, PhD
Assistant Professor of Oncology
Hippo-Yap pathway in Neurofibromatosis Type 2.

House Clinic, Los Angeles

Derald E, Brackmann, MD
House Neurotologist
Auditory Brainstem Implant, Neurofibromatosis Type 2, Acoustic Neuromas, Skull Base Tumors.

Gautam Mehta, MD
House Neurosurgical Associate
Neurofibromatosis, von Hippel-Lindau disease, Skull base tumors (schwannomas, meningiomas, pituitary tumors).

William H. Slattery III, MD
House Neurotologist
Treatment and Management of Neurofibromatosis Type II, Treatment of Acoustic Neuromas, Facial Nerve Paralysis.

Lacerta Therapeutics

Darin Falk, PhD
Program Director
AAV, gene therapy, neuromuscular disease, muscular dystrophy, central nervous system and skeletal muscle disorders

Edgardo Rodriguez-Lebron, PhD
Chief Scientific Officer
AAV as CNS gene delivery vector, neurodegenerative processes, gene therapy.

Massachusetts Eye and Ear

Konstantina Stankovic, MD, PhD, FACS
Director, Division of Otology and Neurotology
Associate Professor of Otolaryngology
Mechanisms of vestibular schwannoma (acoustic neuroma)-induced hearing loss. Treatment of vestibular schwannomas (VS). Human and animal models of VS.

Duane (Brad) B. Welling, MD, PhD
Chief Otolaryngology Massachusetts Eye and Ear
Chief Otolaryngology Massachusetts General Hospital
Diseases of the ear and lateral cranial base. Cochlear implants, auditory brainstem implants, facial paralysis and deafness related to NF2. Research efforts primarily focus on NF2-associated vestibular schwannomas.

Massachusetts General Hospital

Gary J. Brenner, MD, PhD
Director, MGH Pain Medicine Fellowship
Animal models and gene therapy for neurofibromatosis, treatment of Schwann-cell derived nerve sheath tumors.

James Gusella, PhD
Professor of Neurogenetics
Neurofibromatosis Type 2, Schwannomas, Meningiomas, Merlin Replacement , Neurofibromin, Tumor Suppressor Genes.

Justin Jordan, MD, PhD
Clinical Director, Pappas Center for Neuro-Oncology
Nervous System Tumors, Neurofibromatosis Type 1 & 2, Schwannomatosis, Genetics of tumor development.

Scott Plotkin, MD
Neurologist, Neuro Oncologist
Professor, Neurology, Harvard Medical School
Director, Neurofibromatosis Clinic at MGH
Neurofibromatosis, Primary brain tumors, Brain and spinal cord tumors, Pediatric Neurology.

Samuel D. Rabkin, PhD
Professor of Neurosciences, Neurosurgery
Applications of HSV vectors for cancer therapy and gene delivery to cells of the nervous system.

Vijaya Ramesh, PhD
Professor, Neurology
Pathophysiology of Neurofibromatosis 2, Tuberous Sclerosis Complex, NF2 in human arachnoidal and meningioma cells.

MPM Capital

Mitch Finer, PhD **CANCELLED**
Executive Partner
Drug development utilizing the novel platforms of cell and gene therapy, cancer immunotherapy and regenerative medicine.

Nationwide Children's Hospital

Long-Sheng Chang, PhD
Principal Investigator, Center for Childhood Cancer and Blood Diseases
Nervous System Tumors, Transgenic and gene knockout approaches to Neurofibromatosis type 2, cell culture and animal models for NF2-associated schwannomas and meningiomas.

Shibi Likhite, PhD
Post-Doctoral Scientist, Meyer Lab
Gene Replacement Therapy, Spinal Muscular Atrophy Type 1.

New York University

Kaleb Yohay, MD
NF2 BioSolutions Professional Advisory Board
Pediatric Neurology, Neurology
Neurofibromatosis, brain tumor, spinal cord tumor, acoustic neuroma, malignant schwannoma, spinal neurofibromas.

Plymouth University Peninsula School of Medicine and Dentistry, United Kingdom

Oliver Hanemann, MD PhD, FRCP
Director, Institute for Translational and Stratified Medicine
Neuromuscular disease, neuro oncology.

RDMD

Onno Faber
NF2 BioSolutions Professional Advisory Board
Founder of RDMD
RDMD generates regulatory-grade clinical and molecular data for rare diseases in a central repository.

Scripps Research

Joseph Kissil, PhD
NF2 BioSolutions Advisory board
Professor in the Department of Molecular Medicine
Dr Kissil's lab works on understanding the molecular basis of NF2 and developing advanced tools and models to assess therapeutics.

University of Manchester, United Kingdom

Gareth Evans, MD, FRCP
Professor in Medical Genetics and Cancer Epidemiology
Neurofibromatosis Types 1 & 2, inherited breast and ovarian cancer, inherited tumor predispositions.

University of Texas MD Anderson Cancer Center

Filippo Giancotti, MD, PhD
Professor
NF2/Merlin, Metastatic dormancy and reactivation, integrin signaling, cancer stem cells, epithelial-to-mesenchymal transition.

Third Rock Ventures

Phil Reilly, MD, JD
Venture Partner
Rare Genetic Diseases Treatment Development, Author "Orphan: The Quest to Save Children with Rare Genetic Disorders".

UCLA Health

Marco Giovannini, MD, PhD
Director, Neural Tumor Research Laboratory
Neurofibromatosis type 2, Schwannomatosis, Meningiomatosis, Rhabdoid Tumors.

PhiOanh (Leia) NghiemPhu, MD,
Associate Professor, Department of Neurology
Director, Neuro-Oncology Fellowship Program, Neuro-Oncology Clinical Service & NF2 Multidisciplinary Clinic
Neurofibromatosis type 2, individualized molecularly based therapy for brain tumors.

Jeremie Vitte, PhD
Associate Project Scientist
Generation, molecular and histological characterization of mouse and cellular models of Neurofibromatosis Type 2, Schwannomatosis.

UNC School of Medicine

Richard Jude Samulski, PhD **CANCELLED**
Professor of Pharmacology
AAV vector and gene therapy development.

University of Central Florida

Cristina Fernandez-Valle, PhD
Professor
Translational science focused on target and drug discovery for development of Neurofibromatosis Type 2 therapies. Myelin, signal transduction.

University of Massachusetts Medical School

Miguel Sena Esteves, PhD **CANCELLED**
Associate Professor
Gene Therapy, Neurodegenerative Lysosomal Storage diseases, AAV vectors, GBM cells, Ataxia Telangiectasia.

Guangping Gao, PhD
Professor, Director
Inventor of AAV9. Adeno-associated virus vector mediated gene transfer for gene therapy & gene therapy of inherited neurodegenerative Canavan Disease.

Dominic J. Gessler, M.D.
Post-doctoral Associate
Canavan disease, Alexander disease, gene therapy for disorders of the central nervous system, N-acetylaspartate metabolism, brain energy metabolism

Chris Mueller, PhD
Principal Investigator and Associate Professor
Development of gene therapeutic approaches for genetic disorders of the lung, liver and central nervous system.

Dan Wang, PhD,
Instructor
AAV vector development, gene delivery to CNS,
gene therapy for rare diseases,
genome editing.

WuXi NextCODE

Rob Brainin, JD
CEO and Father of a NF2 Child.

WuXi NextCODE is focused on using genomics to identify the underlying biology and advance the scientific understanding of disease and propel the next generation of transformative therapies.

Neurofibromatosis Northeast

Karen Peluso
Executive Director

Children Tumor Foundation

Vidya Browder, PhD
Basic Science Senior Manager

Event Organizer: NF2 BioSolutions

Nicole Henwood, MD
President and CEO
Mother of a NF2 child.

Gilles Atlan
Vice-President
Father of a NF2 child.

Steve Cooke, MD
Director
Father of a NF2 child.

Vito Grasso
Director
Father of a NF2 child.

Jill Velez
Director
Mother of a NF2 child.

John and Linda Manth
Director/Advocate
Mother and Father of a NF2 child.

Aziz Rehman, MD
Scientific Advisory Board

Randy Learish, PhD
Scientific Advisory Board Member
Husband of a NF2 patient.

Krizelle Alcantara, MS

Scientific Advisory Board Member

Nishant Tyagi
Volunteer, Texas Ambassador. Nanotechnology

Howie Owens, ND
Volunteer, Canada Ambassador
Father of a NF2 child.

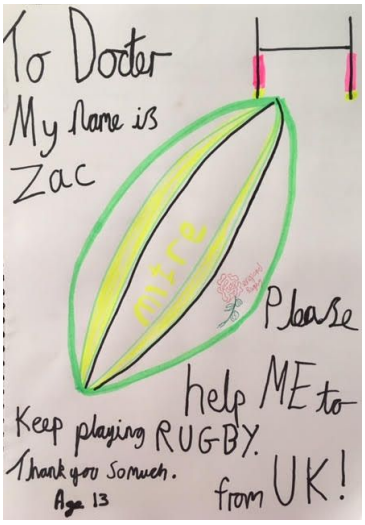
Appendix B:

agenda

Room Setup: groups of 8-9 people, 5 groups, mixed teams based on focus areas and locations (nf2/gene therapy, research/clinic, oncology).
Facilitation style: Design Thinking methodology, post-its/markers/flipcharts/time boxing

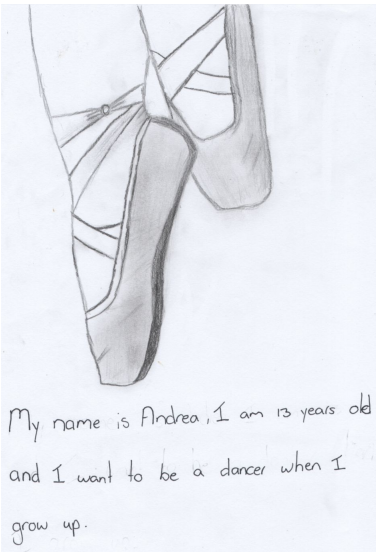
8:30	**Breakfast + Welcoming statement + I need a cure video**	35 min	Dr. Nicole Henwood
9:05	**What is NF2 BioSolutions (What/Why/How) / Agenda**	15 min	Gilles Atlan
9:20	**Two NF2 Live stories** - A face on the mutation. Two dads share their daughter's NF2 journey.	15 min	Rob Brainin John Manth
9:35	**Case study of rare mutation gene therapy successes** How orgs/nonprofits led by advocates did it.	20 min	Dr. Philip Reilly
10:00	**The power of collaboration**	10 min	Onno Faber
10:10	**Gene therapy- Different approaches**	20 min	Dr. Gao
10:20	**BREAK**	10 min	
10:30	**Today, what are the existing gene therapy strategies and how it could apply on NF2-** ○ Group exercises (mostly the gene therapy expert in the teams and explain the strategies) ○ Share between groups	60 min	ALL (coach: Gilles)
11:30	**Today, what are the gene therapy and NF2 research challenges (clinician, researcher, industry perspectives)** ○ Group exercises: Fears/concerns/challenges (in the science, in the lab, in the clinic) ○ Share between groups	60 min	ALL (coach: Gilles)
12:30	**LUNCH**	60 min	
13:30	**Derive need** - what do we need today to overcome the challenges and jumpstart research ○ Group exercises ○ Share between groups	60 min	ALL (coach: Gilles)
14:30	Lessons learned from Duchenne Muscular Dystrophy	15 min	Dr Samulski
14:45	**Imagine the future** - We are in 2025, we found a successful therapy for Nf2, how you did it? What were the steps? The process? How did you collaborate? Patients access?	60 min	ALL (coach: Gilles)

	○ Group exercises ○ Share between groups		
15:45	**BREAK**	15 min	
16:00	**I Like , I wish, I will** - Group exercise Day feedback and determine immediate next steps and who is interested. What did you like about today? What do you wish it would have happened today? What will you do next?	30 min	ALL (coach: Gilles)
17:00	**FINISH**		



United Kingdom

Israel



South Africa

Thank you for helping thousands of kids all over the world
touched by NF2 to live a normal life.