



How Can We Accelerate Progress In Neurofibromatosis Research?

*Strategic Planning to Set Future
Directions*

How Can We Accelerate NF Research Progress? *Strategic Planning to Set Future Directions*

Since the identification of the NF1 and NF2 genes in the early 1990's, NF research has made major strides. Today, we have a good understanding of the underlying biology of NF, and have identified some of the major drug targets for the disorder. We have NF cell and animal models, vital for the preclinical testing of candidate drugs. And finally, NF clinical trials are starting to take shape.

The Children's Tumor Foundation has played a key role in driving this progress. We have awarded over \$22M in research grants since 1978, supporting innovative new ideas & focusing on bringing early-career scientist into NF research. Our investment has paid off by establishing a community of NF researchers who have successfully secured over \$200M government funding in the past 10 years alone.

However, obstacles still remain along the path to finding & implementing effective drug treatments for NF. What are these obstacles? How can we surmount them?

What must we - the Children's Tumor Foundation, as well as the NF community at large - do next to accelerate progress toward finding effective NF therapies?

In 2006 we addressed these questions.

First we developed the 'NF Research Landscape' - a review of grant funding for NF research over the past ten years, how it has been spent, and what it has accomplished; and an assessment of where we stand today along the path to finding treatments for NF.

We then convened a strategic planning forum of NF experts, advisors from other foundations, NIH and DOD, and members of the pharmaceutical industry. Their mandate was to identify the obstacles: areas of NF research that, if given attention & funding, could significantly accelerate the field.

A summary of the NF Research Landscape and the recommendations arising from the strategic planning process are presented below.

These recommendations will guide the future direction of the Foundation's research programs, and we hope will help inform future NF research funding by federal agencies & private funding sources.

The NF Research Landscape: Tracking the Progress We Have Made

What is the NF Research Landscape?

The NF Research Landscape is a high-level review of the past ten years of NF research funding, how it has been spent and what it has accomplished; and an assessment of where the NF research field is today along the path of finding drug treatments for NF.

Why Does The NF Research Landscape Focus on Funding Between 1996-2005?

During this ten-year period an unprecedented amount of money was spent on NF research due to the Department of Defense Congressionally Directed Medical Research Program NF Research Program (NFRP), which began in 1996, providing potentially maximum impact on NF research progress.

What Funding Sources Are Represented in The NF Research Landscape?

National Institutes of Health (NIH), NFRP and Children's Tumor Foundation, the three major funders of NF research, are included. For future updates of the Landscape we hope to include other agencies & institutes that have funded NF research (e.g. NF Inc., American Cancer Society, international funding sources and the pharmaceutical & biotechnology industry). Figures presented for NIH and NFRP reflect publicly available information on grants funded as of March 2006.

NIH and NFRP data was derived from public grants abstract listings (<http://cdmrp.army.mil>, <http://crisp.cit.nih.gov/> and other public sources).

For NIH, we captured only extramural funding (i.e. grants to researchers outside the NIH itself; this does not include research funding spent within the NIH itself).

For all grant programs, only dollars actually committed to research grants were included, not e.g. costs of scientific meeting grants or program administration costs.

How Much In Total Was Spent on NF Research 1996 - 2005?

Over \$217M was spent on NF research: Over \$120M by NFRP; over \$93M by NIH; and over \$4M by Children's Tumor Foundation.

These figures reflect publicly available information on grants funded as of March 2006. They do not include meeting support or program administration. As a result they appear to conflict with previously advertised research program budgets notably \$155.3M the commonly advertise figure for NFRP funds for the period 1996 - 2005.

How Much Was Spent on NF1, NF2 and Schwannomatosis Research?

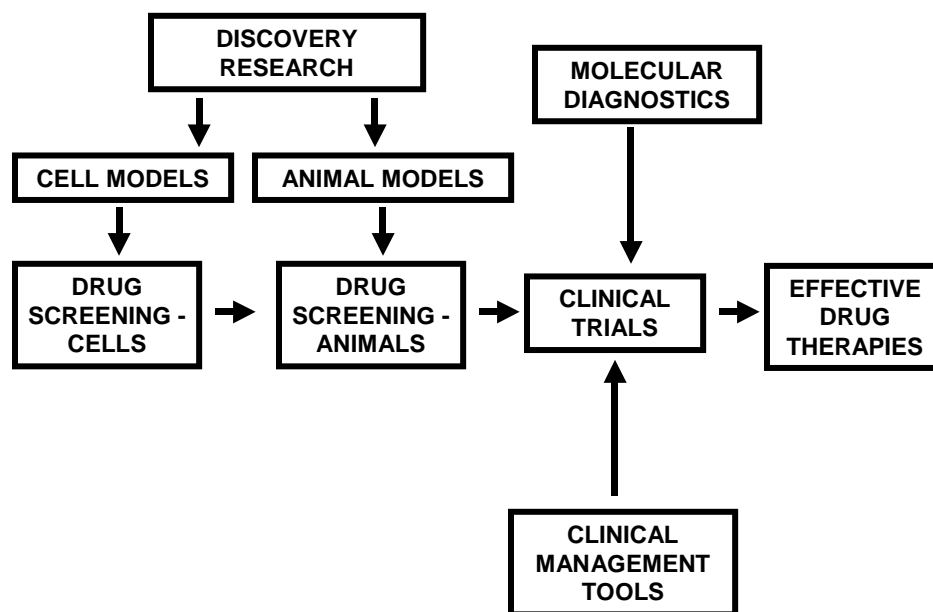
Of the \$217M total spent on NF research 1996 - 2005, over \$123M was spent on NF1; over \$72M on NF2; over \$19M on research relevant to both NF1 and NF2; and over \$2M on Schwannomatosis. The NF2 figure is particularly striking. Considering that NF2 accounts for only 10% of NF patients, and that the NF2 research community itself is quite small, it is very impressive that they have secured over one-third of all NF research funds spent in the past ten years. The fact that the Schwannomatosis figure is small reflects the fact that this is an underdeveloped area, in which the genetics have not yet been unraveled and has few researchers as yet focused on it.

What Type of Research Has Been Funded?

Figure 1 shows the 'bench to bedside' progress of research, from basic 'discovery', to developing cell & animal models, to preclinical testing of drugs, to clinical trials. Each grant was categorized & apportioned into boxes on this chart, and funds attached to that box accordingly. Where projects fit into multiple boxes, funds were shared.

'Bench to Bedside' breakouts are discussed separately below for Children's Tumor Foundation, NFRP and NIH, with some comment on how these funds were allocated.

Figure 1: Mapping the NF Research Landscape



What Research Has Children's Tumor Foundation Supported?

The Children's Tumor Foundation has had a constant vision: attract talented investigators to NF research; support innovative research; and foster collaboration.

The Foundation has spent over \$4M on research awards in the past ten years. Two-thirds of this went to the Young Investigator Awards (YIA) program, the Foundation's cornerstone grant mechanism for 25 years and a proven effective vehicle for attracting young scientists into an NF career.

The Foundation has also funded various contract awards - *ad hoc* grants to invigorate areas of NF research that are promising and cutting-edge, but may need seed funding to generate the preliminary data required to secure larger federal grants from NIH or NFRP. For example, in 2004 the Foundation made a significant contract award investment to develop volumetric tumor imaging analysis - a groundbreaking technology that would not have been developed without Foundation support. It is

already being used to monitor tumor growth in patients with all forms of NF, and will shortly be piloted for use in NF clinical trials.

Two-thirds of the Foundation's total research funding went to **'discovery research'**; **20%** to development of **clinical management tools** (notably the volumetric analysis technology described above); and the remainder to animal model development and drug screening. This is not surprising based on the fact that most funding has gone to the YIA program, which tends to be almost exclusively focused on discovery research.

Two-thirds of Foundation funding has gone to **NF1 research**, and just under **one-third** to **NF2 research**. With rare exceptions - such as the targeted Schwannomatosis Award - Foundation programs are open to both NF1 and NF2 researchers. The discrepancy in funding between NF1 and NF2 reflects the fact that **the Foundation typically receives many more applications focused on NF1 research than NF2 research**.

5% of funding has gone to Schwannomatosis research. As this is an underdeveloped area of research, we have received almost no Schwannomatosis applications for YIA or contract awards, and this spending is largely due a special award in 2005 targeted to invigorate the Schwannomatosis field.

What Research Has NFRP Supported?

Launched in 1996, by 2001 NFRP had become the **largest single source of NF research funds in the world**, providing over \$120M in the past ten years. NFRP offers grants via **various funding mechanisms** ranging from pilot research grants to multi-lab consortia. NFRP has succeeded by constantly **monitoring & responding** to NF research progress. An **advisory panel** that includes NF researchers as well as representatives from federal agencies and NF non-profits including the Children's Tumor Foundation, each year **tailors the program** to meet the current needs of researchers. Examples of this tailoring have included special calls for development of NF preclinical models; an NF2 natural history consortium; and most recently, an NF1 clinical trials consortium.

Two-thirds of NFRP funding went to **discovery research**, with most of the remainder to development of **preclinical animal models**. Minimal funds were spent on drug screening and on clinical management tools & diagnostics.

In a pattern similar to the Children's Tumor Foundation spending, just under **two-thirds** of NFRP funding went to **NF1 research**, and just over **one-third** went to **NF2 research**. Only **1%** went to **Schwannomatosis research**.

An interesting observation on NFRP allocations is that over the past 10 years, there has been a **clear progression from 'bench to bedside'** with progressively less funding going to discovery research. For example, although overall, less than 5% was spent on clinical trials, in 2005 a major commitment was made in this area.

NFRP has been a successful program, **responding to progress in NF research and establishing the framework of a 'bench to bedside' research pipeline**. However, an issue of central importance is the anticipated future demise of NFRP funding.

What Research Has NIH Supported?

NIH is not one single funding entity, but an array of **over 30 institutes** each focused on specific disease areas. Individual institutes provide research grants via standard funding mechanisms, ranging from postdoctoral awards to large multi-lab consortia.

In the past ten years, NIH has committed over \$90M to NF research, with **two-thirds** going to **discovery research**. Of the remaining funds, almost half went to **animal model development**, and one-third to developing **clinical management tools**. Minimal

funds were committed to clinical diagnostics development and to drug screening or clinical trials. **Half** of research funds have gone to **NF1** research, and **one-third** to **NF2** research, with a further **20%** going to research of relevance to **NF1 and NF2**. Less than **1%** of funding went to **Schwannomatosis**.

Ten individual institutes at NIH have funded this NF research. This speaks to the array of tissues & organ systems in the body that are affected by NF. **Two thirds** of NIH NF funding came from **National Institute of Neurological Disorders and Stroke (NINDS)**, the principal NIH neuroscience research institute. **National Cancer Institute** came in a significantly lower second, supporting only around **18%** of all NF research. Additional funding institutes included **National Heart Lung & Blood Institute (NHLBI)**, **National Eye Institute (NEI)** and **National Institute for Child Health & Development (NICHD)**.

Future Recommendations For NIH Funding of NF Research

The **\$90M +** spent by NIH on NF research in the past ten years is a significant amount of money. However its impact has been reduced by the fact that unlike NFRP, it has not been spent in a planned global fashion, but by ten individual institutes.

Anecdotally we have learned that NF researchers typically establish a relationship with one institute early in their career and continue to apply to that institute for funding, where their applications are in competition with many other disorders.

A common criticism of NIH is that **individual institutes do not readily communicate with each other**. This is a critical issue for NF research since the disorder impacts on so many different tissues & organ systems, disseminating our research community across a large number of institutes. **To date there have been no set-aside funds at NIH for NF research and no NIH-wide NF research agenda.**

However, NIH institutes have in the past **co-funded and set aside dollars for targeted awards** for disorders other than NF. This is often done in collaboration with - and due to the lobbying efforts of - non-profit agencies like the **Children's Tumor Foundation**. Looking ahead, an obvious charge for the **Children's Tumor Foundation** is to **educate individual NIH institutes on past NF spending patterns, and to encourage and facilitate collaboration** between institutes to support NF targeted awards.

What is the Current Status of NF Drug Screening & Clinical Trials?

Past NF clinical trials have focused on **chemotherapy drugs**, which - other than the clear concerns about side effects - are not ideal treatments for many NF tumors. Chemotherapeutics are used to treat tumors because they disable rapidly dividing cells, but many NF tumors - e.g. **NF1 plexiform neurofibromas** and **NF2 vestibular schwannomas** - are benign and slow dividing, so may not respond to chemotherapy.

Fortunately, **our understanding of NF drug targets has grown significantly** in the past few years, and in fact the signaling pathways that go awry in NF are common to other tumors & disorders. This is good news, as many drugs already in clinical trials for other disorders could be candidate NF drugs. Indeed, a small number of these are currently in - or entering - **clinical trials for NF**, with others are in preclinical screening.

NF clinical trials themselves pose problems. History has demonstrated pharmaceutical companies are not necessarily enthusiastic about **providing drugs** for trials, so pills (& placebos) must either be formulated or purchased, requiring time & money.

Due to the array of manifestations associated with NF - benign & malignant tumors, bone deformities, learning disabilities - **recruiting enough patients** for an individual

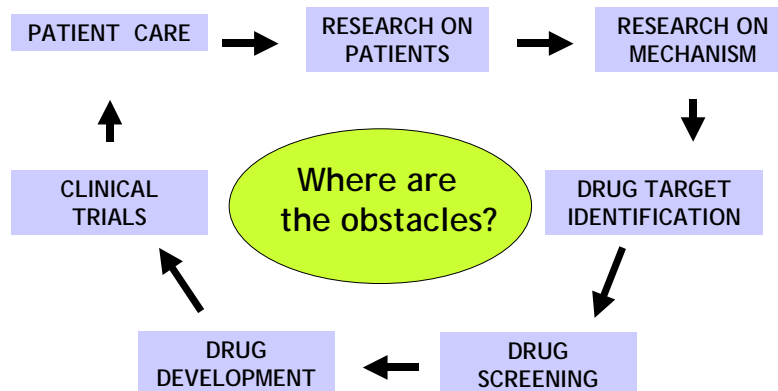
trial can be near impossible for most clinical centers. This is the key reason that the NFRP NF Clinical Trials Consortium is such a powerful resource: for the first time, ten clinical centers are working together to recruit patients and conduct NF trials. The first NFRP Consortium trials are anticipated to begin in early 2007.

The pharmaceutical & biotechnology industry has little interest in NF as a target disorder. This could be due to lack of information on the resources available from the NF community for drug screening & clinical trials. Children's Tumor Foundation is working to educate & engage industry in NF with the Drug Discovery Initiative, especially in encouraging industry to make candidate drugs available for NF preclinical screening and, looking ahead, clinical trials. In addition the company NexGenix is solely focused on NF as a target disorder, and should in the future help to increase attention to the area.

Strategic Planning: Planning & Priorities for the Future of NF Research

Armed with what we had learned from the NF Research Landscape, in August 2006 Children's Tumor Foundation hosted a strategic planning meeting of invited experts & advisors. Their mandate was to identify the obstacles - areas of NF research that, if given attention & funding, could accelerate the identification of effective NF therapies, and improve the lives of those living with NF today. The strategic planning process worked off of the model presented in *Figure 2*: the paradigm that NF clinical care & drug discovery are not only interdependent but a continuum in which each requires the other for success.

Figure 2: Patient care & research are interdependent



The process resulted in FIVE recommended priorities for NF research:

- Preclinical Screening of Candidate NF Drugs
- Establish a National NF Clinic Network
- Establish an NF Tissue Repository
- Identify New NF Biomarkers
- Support NF Clinical Trials

These recommendations will guide the future directions of the Children's Tumor Foundation research programs, and are intended to inform the NF research funding community a whole.

Each priority is discussed below, considering cost & currently available resources. The Children's Tumor Foundation is catalyzing each priority area as outlined.

Priority: Preclinical Screening of Candidate NF Drugs

Why is this a priority? Testing potential therapies in NF model systems will greatly enhance the probability of success in finding new clinical therapeutics.

Strategies for implementation: These are outlined in *Figure 3*.

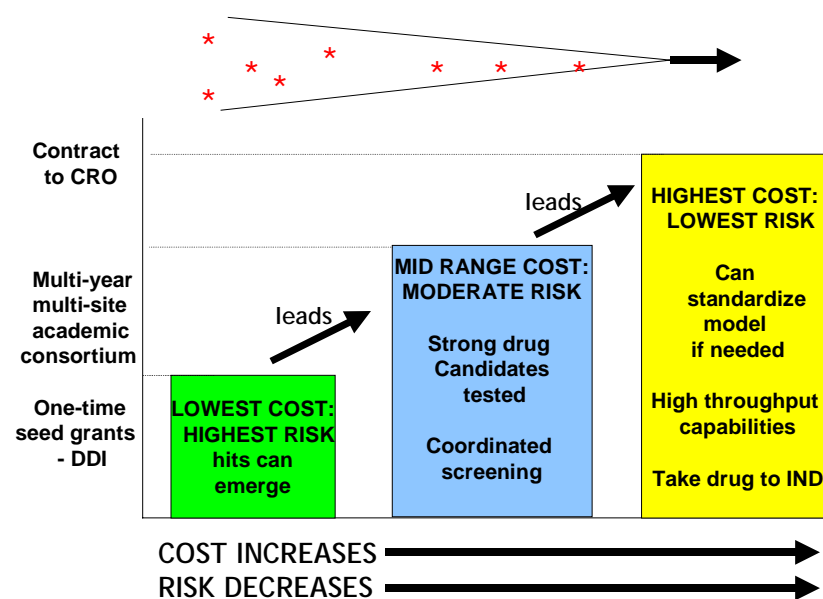
If **limited funding** is available, seed grants can allow researchers to test potential NF therapeutics in cells or animal models, generating preliminary data that will provide support for grant applications to other agencies.

With more substantial funds, a **Preclinical Screening Consortium** will allow multiple laboratories to screen drugs in parallel in mouse models of different NF complications (bone, tumors, learning disabilities), a highly informative approach.

If **unlimited funding** were available, a **Contract Research Organization (CRO)** could conduct all drug screening. The most expensive but also potentially the most efficient approach, a CRO can screen drugs rapidly and also prepare the data required for Investigational New Drugs (IND) to be approved by the Food & Drug Administration (FDA) in order to enter clinical trials.

What Children's Tumor Foundation Is Doing: In 2006 Children's Tumor Foundation launched the **Drug Discovery Initiative Awards**, seed grants for preclinical drug screening. Through the **Drug Discovery Initiative Toolbox**, an online listing of resources for NF preclinical drug screening, the Foundation will help ensure access to existing animal models for all researchers, and foster relationships with the pharmaceutical industry to facilitate access to drugs and compounds.

Figure 3: Preclinical Drug Screening Options



Priority: Establish A National NF Clinic Network

Why is this a priority? A national NF Clinical Network will ensure optimal clinical care for all persons in the United States living with NF, and connect NF physicians & clinics with each other. This network also has the capability of integrating care with research to identify & test future drug therapies, by providing a base of patients for future NF clinical trials and patient samples for research use.

Children's Tumor Foundation is uniquely placed to establish and oversee this Network and will move ahead with leading the implementation of this in 2007.

Strategies for implementation: This is outlined in *Figure 4*. Over the next 5 years:

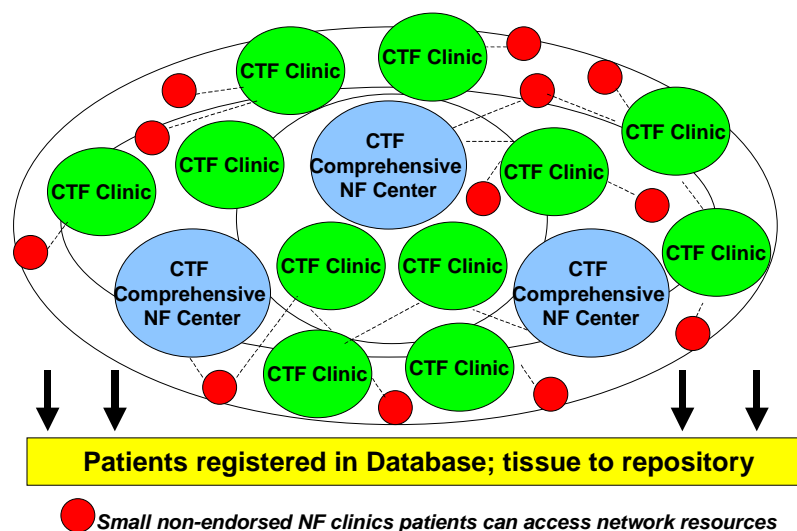
Step 1 - Clinic Endorsement: The Children's Tumor Foundation has written guidelines that define a national standard of NF clinical care in the United States. Beginning in Spring 2007, the Foundation will offer NF Clinics that meet these guidelines the opportunity of Foundation endorsement. Those clinics not ready for endorsement will be encouraged to participate in the Network and access the resources therein.

Step 2 - NF Clinic Coordinator & Incentive Funding: Endorsed NF Clinics can compete in their state or region for up to \$50,000 per year to support salary for an NF Clinic Coordinator. For clinics that do not secure coordinator funding, incentive funding will be available to ensure network participate in particular entering patients in the NF Database, the Foundation's NF patient registry.

Step 3 - Comprehensive NF Center: As the Network becomes established, select NF Clinics that represent clinical & research leadership and have the ability to serve the Network at a regional and national level will be endorsed Comprehensive NF Centers.

What Children's Tumor Foundation Is Doing: See above - the Foundation is leading the formation of NF Clinic Network.

Figure 4: A National NF Clinic Network



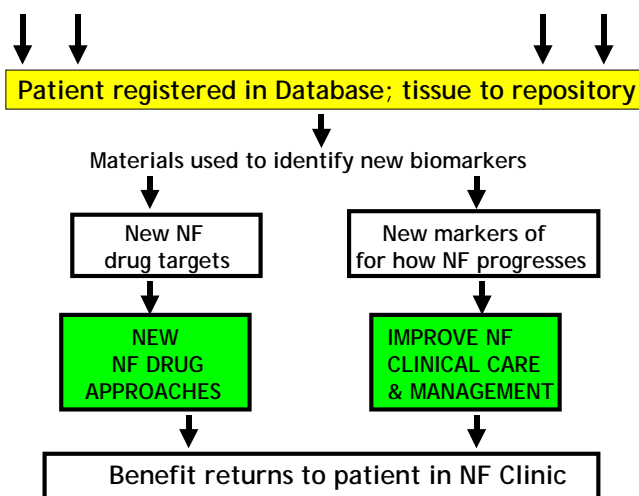
Priority: Establish an NF Biological Materials Repository

Why is this a Priority? Study of biological materials (blood, tissue samples) from NF patients can help us understand how NF progresses and thereby **improve NF clinical care & management**; and can also help to **identify new drug targets**. A central repository will facilitate management & distribution of samples. This repository could operate in conjunction with the NF Clinical Network. Companion 'linked' patient data submitted to NF Database would make samples highly valuable for clinical research. Utilization of the repository is outlined in *Figure 5*.

Strategies for implementation: A dedicated repository for NF tissue can be contracted but will be an expensive undertaking. A full service repository will establish protocols for material collection, storage & distribution; make cell lines from submitted tissues; and keep a detailed database of samples, a vital sharing tool.

What Children's Tumor Foundation Is Doing: Prohibitive cost renders this priority currently outside the capability of Children's Tumor Foundation to solely support. However, many individual researchers have in-house collections of cell lines, tissue samples etc. and are willing to share them. The Foundation is currently tracking these down for inclusion in the DDI Toolbox listings (see above) - resulting in what will be a **virtual repository**. Thus, we can begin to collate what is available today though we do not yet have all of the funding required for an independent repository.

Figure 5: Utilizing an NF Tissue Repository



Priority: Facilitate Identification of Biomarkers

Why is this a Priority? Biomarkers are indicators of the status of NF in a person, and may be radiological, physiological, genetic or biochemical. Biomarkers can help better monitor NF progression, and can help identify new & unique drug treatments for NF. The role of biomarkers is outlined in *Figure 5*.

Strategies for implementation: Biomarker identification could be funded by individual research grants or via a collaborative research consortium. Significant levels of grant funding will be required. This program can grow incrementally in response to funding.

What Children's Tumor Foundation Is Doing: Support of biomarker identification is discovery research and is accommodated by our existing Young Investigator Award program.

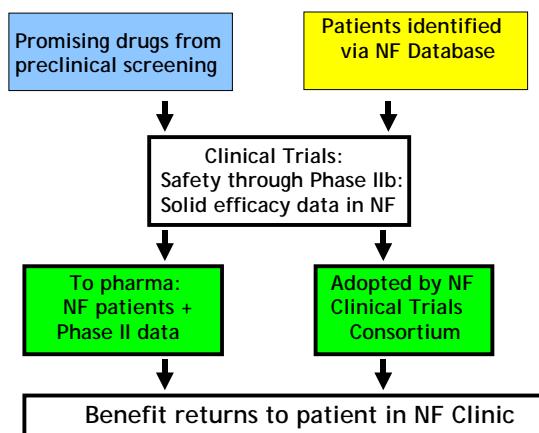
Priority: Support Clinical Trials

Why is this a Priority? As more candidate NF therapies emerge from preclinical screening, the need for NF clinical trials funding will inevitably increase. Implementation of clinical trials is outlined in *Figure 6*.

Strategies for implementation: The NFRP NF Clinical Trials Consortium is structured to do multi-center large-scale trials. Where there is likely to be a growing need, however, is funding for small-scale pilot (small patient numbers, Phase 1 (safety)-early Phase II (efficacy)) clinical trials. These initial trials will provide the necessary data to justify proceeding with larger scale trials within the context of the Consortium, or potentially via industry or other support.

What Children's Tumor Foundation Is Doing: Currently, the Foundation does not support clinical trials. However, we will closely monitor progress in this area, and must keep in mind the potential that in the future we may need to develop a funding mechanism to support this.

Figure 6: Moving from preclinical studies to clinical trials



Strategic Planning Meeting Charge & Participants: August 18-20, 2006

The Strategic planning meeting was convened August 18th - 20th, 2006 in New York City & was attended by members of the Children's Tumor Foundation Medical Advisory Committee & Board of Directors, & by select guests from other Foundations & from industry.

Over 3 days the group considered the questions:

- What areas of NF research need further development to help us more rapidly identify therapies for NF and improve the lives of those living with NF?
- What new funding mechanisms are needed to facilitate this?

The recommendations & priorities presented in this document are a summation of the consensus reached by the group in attendance.

Attendees & Foundation Affiliations¹

Scientific & Medical Advisors

Gareth Evans, MD, University of Manchester

James Gusella, Ph.D., Massachusetts General Hospital (BOD; MAC; RAB)

David Gutmann, MD, Ph.D., Washington University (Co-Chair, CCAB, MAC, RAB; Chair, DDI Review Group)

Bruce Korf, MD, Ph.D., University of Alabama (Chair, MAC; BOD; RAB; CCAB)

Frank McCormick, Ph.D., University of California, San Francisco (MAC; RAB; DDI Review Group)

Roger Packer, MD, Children's National Medical Center

David Viskochil, University of Utah (Chair, CCAB; BOD; RAB)

Board of Directors

Mrs. Suzanne C. Earle (Chairwoman, Board of Directors; MAC)

Richard Horvitz (BOD, MAC)

Jason Pontin (BOD, MAC)

Carolyn Setlow (BOD)

Tara Skirzenski (BOD)

Edward Stern, Esq. (MAC)

Industry

Jay Gibbs, Ph.D., AstraZeneca (RAB, DDI Review Group)

Celeste Richardson, Ph.D., Novartis Institutes for Biomedical Research

Funding Agencies & Foundations

Naba Bora, Ph.D., CDMRP NFP, Department of Defense

Beth Orlando, Ph.D. CDMRP NFP, Department of Defense

Robert Finklestein, Ph.D., NINDS, NIH

Cynthia Joyce, Ph.D., Spinal Muscular Atrophy Foundation

Concepcion (Marie) Nierras, Ph.D., Juvenile Diabetes Research Foundation

Karen Peluso, NF Inc.

¹ Foundation affiliations: BOD = Board of Directors; MAC = Medical Affairs Committee; CCAB = Clinical Care Advisory Board; RAB = Research Advisory Board; DDI Review Group = flagship Drug Discovery Initiative Review Group Fall 2006