Neurofibromatosis Therapeutic Acceleration Program (NTAP) at Johns Hopkins University

Jaishri Blakeley, MD
Plexiform neurofibroma (pNF)

**NF1**
Neurofibromatosis type 1
1/3000 individuals
100,000 in US

**pNF**
Plexiform neurofibroma
~50% develop multiple nervous system tumors

**MPNST**
Malignant peripheral nerve sheath tumor
~10% transform into aggressive malignant sarcomas

**COMPELLING, URGENT, UNMET MEDICAL NEED**

- Standard of care is surgery, but high rate of recurrence/progression and poor long term benefit
- Extensive regulatory precedent (16 clinical trials in pNF in the last 10 years) → critical knowledge, but still no effective treatments
- **OVERLAP WITH MANY RAS Driven Disorders; Potential For Expansion To Other Larger Market Indications**
About NTAP

Improving treatment options for individuals with plexiform neurofibromas

• Privately funded foundation
  — Philanthropic gift to the Johns Hopkins University School of Medicine
  — Targeted funding of projects across academia and industry worldwide

• Mission
  — Focusing on therapeutics
  — Fostering collaboration
  — Open and timely sharing of results
  — Streamlining the research process
NTAP Collaborative Strategy

Streamlined and Interactive Review of Proposals

Successful and Timely Completion of Milestones Required for Continued Support

Optimal Resource Deployment

Single Focus: Therapeutics for plexiform neurofibroma

Required Data Sharing & Integration of Results

Milestone Based Funding

• Scout for and partner with experts in content areas that address the gaps
• Academic, federal, commercial, pharmaceutical
• Leverage partner investments and knowledge
• Identify discrete gaps in the field

Fill the Gaps on the Therapeutics Pathway

• 2 page “idea” application and budget
• Reviewed within 4 weeks by content experts and NF experts
• Interactive process for revision until final mutually agreeable project plan is achieved

Average times:
- Proposal review: 24d
- PI revision: 39d
- Contract preparation: 35d
- Contract negotiation: 64d
- Time to payment from contract: 18d
- Total application to payment: 6mo

Streamlined and Interactive Review of Proposals

• Required open access, but timeline for release is collaborative
• Balanced intellectual property policies:
  - Investigator interests protected
  - IP protection
  - Rapid data analysis and integration

• Required investigators meetings in person and via “virtual lab meeting”

Investigator Collaboration and Project Integration

• Payments linked to completion of project milestones
• Milestones set by investigators

Successful and Timely Completion of Milestones Required for Continued Support

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NTAP Summit: Script the Critical Path

- NTAP Summit September 2012
  - 38 thinkers from multiple backgrounds across academia, foundations, regulatory bodies and the pharmaceutical industry
  - Conclusions: Incomplete tool box and a lack or coordinated effort
  - Identified priorities:
    - Cell culture model systems
    - Animal models – pre-clinical experimental design harmonized with clinical trial design and vice versa
    - Identification/development of suitable patient-based endpoint measures for clinical efficacy trials
    - Natural/clinical history data
    - Biomarker discovery and development
## Plexiform Neurofibroma Cell Culture Initiative

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<tr>
<th>Need</th>
<th>Cellular models that represent the heterogeneity of the disease to effectively and rapidly evaluate potential therapies and identify new therapeutic pathways</th>
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| Partner | National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH)  
Marc Ferrer; Rajarshi Guha; Craig Thomas; Madhu Lal; Sam Michael; Sita Sittampalam |
| Model | Five international investigative teams funded through a competitive request for proposals:  
- Raymond Mattingly, PhD, WAYNE STATE UNIVERSITY  
- Luis Parada, PhD, UT SOUTHWESTERN  
- Karlyne Reilly, PhD, NCI  
- Eduard Serra, PhD, IMPPC, SPAIN  
- Margaret Wallace, PhD, UNIVERSITY OF FLORIDA  
NTAP supports a full time scientist at NCATS who is developing the assays and optimizing the panel for qHTS (Dannielle Ryman, MS) |
**Plexiform Neurofibroma Cell Culture Initiative**

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<th>Deliverables</th>
<th>Status</th>
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<tr>
<td>• Panel of cellular models of pNF (single cell to 3D co-culture systems, mouse and human)</td>
<td>• 15 cell culture systems optimized and screened using NCATS library of 1912 late-stage drugs</td>
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<td>• qHTS results shared in real time within the consortia, ultimately to be made open access</td>
<td>• Several new targets identified, others validated</td>
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<td>• Computational modeling comparing hits across species, models and screens</td>
<td>• Hits being prioritized for combination and secondary screens</td>
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Access to infrastructure and expertise not feasible for any one person

Advantages of academic experts and industry efficiency

Allows validation of qHTS results across multiple systems

Path in place for GEMM pre-clinical efficacy studies and clinical trials

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## Patient Reported Outcomes

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<th>Need</th>
<th>Validated endpoints for clinical trials to demonstrate meaningful benefit for patients with pNF</th>
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| **Partner** | • Food and Drug Administration Drug Development Tools Qualification Program (DDTQP)  
• Children's Tumor Foundation NF Registry |
| **Model** | • Four science teams with expertise in PRO awarded grants through competitive request for proposals  
• All teams submitted their scientific plan to the DDTQP |
| **Deliverables** | • 5 PRO measures for patients with NF1 and pNF that will be publically accessible for use in clinical trials  
• Detailed psychometric properties for each measure |
The need
Better understanding of the progression and heterogeneity of pNF to define endpoints

Partner
Pediatric Oncology Branch of the NCI

Model
- Prospective natural history study was nearing closure due to budget cuts
  - >130 patients with pNF enrolled
- Funded 1 FTE post-doctoral candidate to analyze and report existing data
- Prospective data supplemented via collaborations with international clinical centers of excellence
- All data in central repository, open access

Deliverables
- Continued enrollment
- Analysis of longitudinal tumor growth rates
- Analysis of radiographic features and clinical manifestations
- Platform for biomarker discovery
The Francis S. Collins Scholar Program

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<th>The need</th>
<th>Clinicians trained in the management of NF1 and the conduct of rigorous NF1-focused clinical translational research</th>
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<tr>
<td>Goal</td>
<td>Build a community of exceptional investigators who are trained in both the clinical care of NF1 patients and the challenges of patient-centered therapeutic development by attracting and retaining the most promising clinician scientists</td>
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<tr>
<td>Partner</td>
<td>Mentors from industry, regulatory, academic and clinical backgrounds</td>
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<tr>
<td>Model</td>
<td>Successful applicants receive full salary support, stipends for research costs, tuition for relevant coursework, mentor stipends, and travel support for two years</td>
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**Biomarker Initiative**

**Key questions**
- How can we know which patients will become symptomatic with pNFs?
- How can we predict which tumors will become malignant?

**New initiative to be launched in 2015**
- Partnered with Innocentive to create an Idea Challenge (small grants to generate ideas, direct strategy)
  - 10 “solutions” awarded prizes
- Prospective biomarker discovery plan now in development, seeking collaborators
Collaborations

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Supporting the Path to Therapies for Patients with Plexiform Neurofibroma

1. Target identification & validation
2. Lead optimization
3. Unbiased screen of compounds against disease representative
4. PK, PD and efficacy in animal models
5. In vivo dosing strategy investigation and companion biomarker discovery
6. Enter clinical studies:
   - IND package
   - Dose finding
   - Learning efficacy trials
7. Confirmatory efficacy trials with imaging and COA measures
8. Regulatory Approval and Coverage based on proof of patient benefit
NTAP Summary

NTAP is directing funds to industry/pharmaceutical companies, academic institutions, and government agencies and orchestrating projects that will have the greatest impact for patients with pNF

- Narrow mission – therapeutics for pNF patients
- Leverage what has already been done or is in process
- Partner wherever the infrastructure and expertise exist
- Understand the needs of all parties and work toward “win-win” situations
- Maintain strict milestones and reporting requirements
- Centralize data, use systems-based analysis
- Be politely disrupting
- Scout for creative ideas and partnerships

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