Expanding Your Reach: Strategically Growing Your Research

Salvatore La Rosa, Ph.D.
Vice President of Research and Development
Children’s Tumor Foundation

Dan Lavery, Ph.D.
Director, CDKL5 Program of Excellence, Orphan Disease Center at the University of Pennsylvania
Chief Scientific Officer, Loulou Foundation

#PennMedMDBR2018  #GGPennRareSymposium
Expanding Your Reach: Strategically Growing Your Research

Salvatore La Rosa, Ph.D.
Vice President of Research and Development
Children’s Tumor Foundation
Expanding Your Reach: Strategically Growing Your Research

Salvatore La Rosa, PhD
VP Research and Development
slarosa@ctf.org
Disease Focus: NEUROFIBROMATOSIS (NF)

- Family of 3 rare genetic disorders:
  - NF1 – incidence 1/3,000
  - NF2 – incidence 1/25,000 – 30,000
  - Schwannomatosis – incidence est. 1/30,000

In COMMON:
- Benign Tumors growing on the nerves/ pain
- Loss of Function mutations of tumor suppressors
- All genes highly relevant to malignant cancer!
- NF is a lifelong condition – need for chronic treatment
Most urgent medical need

NF1
- Mortality: Malignant transformation/ cancer
- Morbidity:
  - Functional loss due to tumors – vision, movement
  - Pain
  - Cognitive & social challenges

NF2
- Mortality: Brain stem compression – meningioma
- Morbidity:
  - Functional loss due to tumors: hearing, vision, swallowing
  - Neuropathy & Pain

Schwannomatosis
- Mortality: pain killer overdose
- Morbidity: excruciating pain
CTF’s Earlier Strategy (Before 2012)

Research funding only for academia

- Investigator Initiated Awards & Grants
  - Young investigator Award (YIA)
  - Drug Discovery Initiative (DDI)
  - Clinical Research Award (CRA)
- NF Preclinical Consortium Grant

Support for patients

- Clinic network
- Education materials—brochures and flyers
- Educational events—NF Forum and family symposia

Support for researchers

- International NF Conference
2012: commitment for a change

- The Foundation decided to make a change in how it will support NF research
  - **Switch** from supporter to research partner
  - **Build** an experienced internal team of scientists
  - **Drive** the research community towards projects that would help fulfill the organization’s mission
  - **Being proactive** within its research projects (mainly act as project managers)
  - **Facilitate** all non-experimental procedures, so that researchers can focus on research (reagents, procurement, MTAs, negotiations, contracts, …)

*Invest in initiatives that make pharma R&D go FASTER!*
1. Map CTF initiatives to the patient - to - market pipeline.

2. Identify gaps—fund the gaps that hinder the path to the clinic and improve the NF Preclinical Initiatives.

3. Define what makes a foundation unique and build upon that uniqueness.
Challenges in NF (rare disease)

- Patients misdiagnosed
- Patients are treated as ‘victims’
- Lack of knowledge around patient needs
- Tissue is very scarce
- Few researchers work on NF
- Not enough data
- Too few cell and animal models
- Lack of clinical trial sites & validated endpoints
- Funding is limited
- Market unknown
- Pharma/ Biotech not always interested
Expanded project portfolio in 2018

**Patients**
- Support
- Educate
- Clinic Network
- Registry
- Patient engagement

**Basic Research**
- Award grants
- Provide Biobank
- Tumors and tissues
- Build open data hub

**Translational Research**
- Award grants
- & contracts
- Preclinical test platform

**Clinical Research**
- Award grants
- Provide KOL network
- Support trials
  - NF Registry
  - REiNS

**Market**
- Build market model

**TEAM SCIENCE: Synodos Consortia**

Blue Text = NEW
Challenges in NF (rare disease)

• Patients misdiagnosed
• Patients are treated as ‘victims’
• Lack of knowledge around patient needs
• Tissue is very scarce
• **Few researchers work on NF**
• Not enough data
• Too few cell and animal models
• Lack of clinical trial sites & validated endpoints
• **Funding is limited**
• Market unknown
• Pharma/ Biotech not always interested
## CTF Strategy Implementation

<table>
<thead>
<tr>
<th>Few Researchers, not enough Data</th>
<th>Limited funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Build Collaborative Consortia</td>
<td>Collaborate across Funders Strategize together!</td>
</tr>
</tbody>
</table>

- **Synodos (TEAM SCIENCE)**
- **MEK storyboard**
In rare disease, we don’t have the ‘luxury’ to compete
Increase efficiency by breaking down silos!

FROM SEQUENTIAL SILO-BASED TO CROSS-DISCIPLINARY SYNCHRONIZED

- CTF launches the SYNODOS consortia program in 2014.
Synodos Delivered:
- New Drugs for NF2
- First NF1 pig models
- New NF1 Low Grade Glioma targets
- Strategy for Pain in Schwannomatosis
Synodos – A new funding model

• Patients set the topic of research (identify the need)
• Foundation rolls out the RFA describing the problem
• ‘Dream team of very diverse experts’ apply. Both researchers and clinicians are required to be part of the team
• CTF assembles world class review team – will act as scientific advisory committee throughout lifetime of the consortium.
• All raw data is shared immediately in CTF-funded NF data hub (Sage Bionetworks)/ after 12-month embargo data open to all.
• Sage Bionetworks guarantees centralized data integration
• Industry standard project management provided by CTF staff
AIM: identify a screening sequence from cells to animals (to humans) that is predictive of efficacy

- Data openly available at [www.synapse.org/synodosnf2](http://www.synapse.org/synodosnf2)
Today: 5 Synodos Teams

More than 20 institutions and 40 Principal Investigators

- University of Central Florida
- University of North Carolina
- Johns Hopkins University
- Nationwide Children's Hospital
- Indiana University
- National Institute of Health
- National Cancer Institute
- University of Minnesota
- Cincinnati Children's Hospital Medical Center
- University of Iowa
- Sanford School of Medicine
- Exemplar Genetics
- Recombinetics
- UC SF
- The Children's Hospital of Philadelphia
- Johns Hopkins University
- University of Toronto
- German Cancer Research Center
- The University of Manchester
- University of Firenze
- Columbia University

NF1 Low-Grade Glioma
Schwannomatosis Pain
Reaching out to out-of-the-field researchers

Data by Disease

Type of data

www.synapse.org/ctf
REGISTRATION TRIAL: SELUMETINIB

In 70% patients, >20% tumor shrinkage
MEK inhibitors development in NF
Top 5 US funders of NF research

1355 Grants and $782M from 73 different Funders worldwide

(source Dimensions for Funders, search done on March 22, 2018)
103 Grants and $78M in NF-MEK research

Scope of grants and study type

A

Basic Science

B

Translational and clinical science

CTF  CDMRP  NCI  NINDS  CTF/NTAP  NTAP
CTF as a Partner Funder

- All funders came together to code all grants in the same way.
- All funders are complementary and essential in the NF space.
Invest in initiatives that make pharma R&D go FASTER!

- **Patient Registry** to speed up clinical trials.
- **NF Data Portal** to speed up research
- **Preclinical Consortium** to speed up drug testing.
- **Clinical trials consortium** to speed up clinical trials (CDMRP).
- **Key Opinion Leader (KOL) network** to speed up decision-making.
- **NF Clinic Network** to reach out to patients and intervene in their care
- **REiNS** to help to chose endpoints and design clinical trials
Expanding partnerships

Other Foundations
- NF Collective (all US NF Organizations)
- Child Neurology Foundation
- Tuberous Sclerosis Alliance
- LLS

Industry
- Springworks therapeutics
- Vivace therapeutics
- RDMD (patient reciprocity)
Expanding Your Reach: Strategically Growing Your Research

Dan Lavery, Ph.D.

Director, CDKL5 Program of Excellence, Orphan Disease Center at the University of Pennsylvania

Chief Scientific Officer, Loulou Foundation
Expanding Your Reach: Strategically Growing Your Research

Dan Lavery, PhD

Director, CDKL5 Program of Excellence,
Orphan Disease Center
Chief Scientific Officer, Loulou Foundation
CDKL5 deficiency disorder

- Rare, X-linked disorder defined in 2004 by \textit{de novo} loss-of-function mutations in the CDKL5 gene.

- \textbf{Incidence 1 in 40-50,000.} One of the most common causes of genetic epilepsy – yet patients still need to be identified.

- \textbf{Intractable infantile seizures} within the first months after birth.

- \textbf{Severe developmental delay} leading to intellectual disability, along with speech, visual, and motor deficits.

- \textbf{No effective treatment available.} 1 Orphan Drug Designation.
The Loulou Foundation

- **Genesis and Strategy** – Founded in 2015, Loulou Foundation is focused on driving CDKL5 Deficiency Disorder therapeutic development by de-risking at each step
  - Not a patient advocacy group, but works closely with them
- **Multiple approaches to treat CDD** – Treatments (e.g., anti-epileptics) and eventual Cures (e.g., gene therapy)
- **Parallel Objectives to De-Risk:**
  - Funding academic research to answer **basic questions of CDKL5 biology**
  - Engaging and enabling industry early on
  - Breaking down barriers between groups
  - Plugging the gaps – translational toolkit / regulatory engagement
CDKL5: relatively young, small field
CDKL5: relatively young, small field

PubMed citations

- 1998-2003: 0-50 citations
- 2005: 50-100 citations
- 2007: 100-150 citations
- 2009: 150-200 citations
- 2011: 200-250 citations
- 2013: 250-300 citations
- 2015: 300-350 citations
- 2017: 350-400 citations

CDKL5 (blue) and MECP2 (orange) citations over time.
How to expand footprint of CDKL5?

• Funding support for basic and translational research
• Provide critical research reagents to lower barrier of entry
• Create an active CDKL5 community to foster collaboration
  – Academics
  – Industry
  – Other funding institutions like NIH
Academics: Lowering barriers

• Grant support: CDKL5 Program of Excellence pilot grants
  – 1 year, $150,000 grants on topics from basic CDKL5 biology to repurposing to viral-mediated gene therapy
• Directed research: Creation of reagents / models / tools for CDKL5 community
  – Rodent models
  – Patient-derived iPSC lines
  – Antibody reagents
CDKL5 Pilot Grant Program

• Since 2016, LLF has funded research grants via the **CDKL5 Program of Excellence Pilot Grant Program**, directed within the Orphan Disease Center (ODC) at the University of Pennsylvania.

• One year, $150,000 grants for research towards CDKL5 therapeutic development, including addressing **critical basic science questions**
  – *E.g.*, animal and cellular disease models, X chromosome reactivation, biomarker discovery, rational drug repurposing strategies, CDKL5 kinase substrates.

• To date: **31** research projects funded, supporting over **120** researchers
  – Can lead to mainstream NIH funding.
Annual meetings to drive community

CDKL5 Forum:

• Engage academia, patient community, and industry to foster collaboration

• Attract new researchers to the area

• Since its start in 2015, has become the flagship meeting for CDKL5

http://www.louloufoundation.org/
Mouse CDKL5 Protein Expression Atlas

Paul Baxter, Sam Booker, Aiman Kayenaat, Elizabeth Davenport, David Wyllie, Michael Cousin, Giles Hardingham, Peter Kind

University of Edinburgh

Using the sheep polyclonal CDKL5 (mouse) antibody provided by the University of Dundee, we profiled CDKL5 expression in the mouse brain, including a multi-section coronal atlas of CDKL5 immunolocalisation in wildtype male P28 C57BL/6 mice, pseudo-3D rotation and stack reconstructions, and validation of the CDKL5 antibody signal using CDKL5 knock out mouse brains.

Above, antibody validation showing CDKL5 expression in wildtype (left) and CDKL5<sup>−/−</sup> mice (right)

- CDKL5 Atlas, including:
  - High res images of each section and links to the Allen mouse brain atlas for anatomical reference

https://www.cdkl5forum.org/
The Loulou Foundation

2015: First Annual CDKL5 Forum Research congress (London and Boston)
Over 180 participants and a total of 35 companies attended 2017 Forum.

Private non-profit UK foundation

2015

2016

2017

2018

3 editions of the CDKL5 Program of Excellence Pilot Grant Program
A total of 31 separate research projects in 41 labs at 30 leading institutions, enabling the focused research of over 120 scientists.

Currently:
Preparing the field for 5-6 potential clinical trials within the next 2 years.
Launching disease-modifying programs.

Strategic partnership with Penn Medicine Orphan Disease Center and launched the CDKL5 Program of Excellence

www.cdkl5forum.org On-line portal for research collaborations

Establish dialogue with regulators and participate in regulatory meetings

2017: Help launch international alliance of patient organizations

CDKL5 Deficiency Patient Alliance

FDA

*
Expanding Your Reach: Strategically Growing Your Research

- Support academic research through pilot grants
- Create reagents such as animal models and human cell lines for use by the community
- Engage scientific community both in person (CDKL5 Forum) and online (CDKL5forum.org) to foster collaboration
  - This includes other funding agencies such as NIH
• Thank you!