State of Research –Board Update March 2023

Melissa Thelen

Research Chair

NR2F1 FOUNDATION

Research Goals

IDENTIFY POTENTIAL TREATMENTS

PREPARE FOR CLINICAL TRIALS AND GRANT FUNDING OPPORTUNITIES

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Clinical Trial Readiness Checklist

- ❑ Understand the mechanism of BBSOAS
- ❑ Mouse Models (representing all mutation/ deletion types broadly)
- ❑ Human Cell Models – iPSC
- ❑ Natural History Data
- ❑ Patient Registry
- ❑ Disease Concept Study
- ❑ Biomarkers/ Biorepository
- ❑ Outcome Measures
- ❑ FDA Interactions

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Balancing Basic Research vs. Translational Research

Basic research is the foundation of medical discovery. Through it, we learn key information about the fundamental biological, molecular, and chemical processes of life.

Translational research is the process of taking a discovery from the laboratory into the clinic, where it can ultimately help people.

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Projects – Past, Present & Future

Project NR2F1

COMBINEDBrain

Scientific Officer

ORCA

RO1 Grant

Strategic Research Meeting

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A Research Advancement Initiative Sponsored by the NR2F1 Foundation

Projects NR2F1

- Outreach to Top 20 Neurology Programs in USA
- Goal : To advance the understanding of current research, treatments effective on neurodevelopmental disorders and advise the NR2F1 Foundation on the best research initiatives for future study and investment.
- Recommendations for innovative research directions that will lead to significant advances in the understanding of this disorder i.e. stem cell therapy, epigenetics, ASOs, identifying biomarkers, etc.

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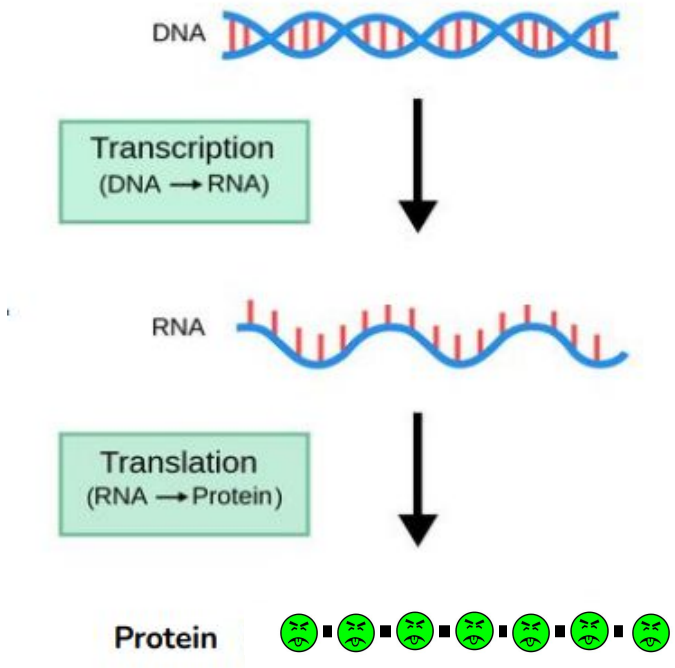
What do we know about NR2F1

- NR2F1 is a gene located on chromosome 5.
- The DNA in chromosomes provide instructions for making RNA for each gene.
  (DNA to RNA: Transcription)
- RNA provides instructions to make a protein.
  (RNA to protein: Translation)
- Each protein has a different function to perform in cells.
- The NR2F1 gene in DNA ultimately describes the NR2F1 protein that will be made.



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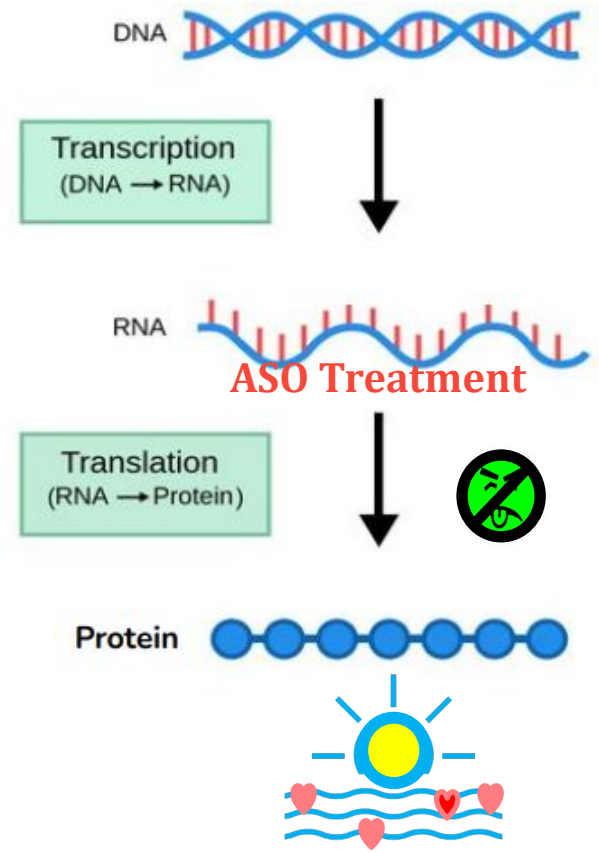
What do we know about NR2F1

- The NR2F1 **protein** is a transcription factor.
  - Transcription factors control other genes.

- NR2F1 acts as an **on/off switch for hundreds of other genes which make hundreds of other proteins.**

- A change in one gene can affect hundreds of other genes.



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COMBINEDBrain

- Mission: Consortium led by patient advocacy foundations, working with the clinicians, researchers and pharmaceutical firms that are developing treatments for the disorders they represent.

- Best Practices from other more mature Patient Advocacy Groups

- Resources
  - Rent a Scientific Officer Program
  - Patient Registry Guidance
  - Intro to Research Teams
  - Programs to Drive Prevalence
  - Connections to Pharma

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Dr. Sarah Poliquin, PhD
Scientific Officer

- Review the BBSOAS literature - Case studies, clinical reviews
- Dig into what is known about BBSOAS that can lead to treatment
- Inventory cell models, mouse models of BBSOAS
- Identify Gaps
  - What resources are available ?
  - How do we answer critical questions and fill the resource gaps?
  - What can we learn from work done in other disorders?

ORCA - Observer-Reported Communication Ability

- Goal is to test if an existing questionnaire can be useful in measuring communication across several neurodevelopmental disorders, including NR2F1. Ideally it will allow us to test the effectiveness of clinical trial interventions and be used to measure communication changes over time in natural history studies.
- We presented the spectrum of communication abilities across BBSOAS to FDA
- 168 subjects – 11 BBSOAS patients/ families enrolled
  - Duke Team interviews parents/ caregivers to understand communication abilities
  - Parents/ Caregivers complete communication survey

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COMBINEDBrain Biorepository

- iPSC lines at a discounted price.
- Donated patient bio samples. These biological samples may include blood, skin biopsies, cerebrospinal fluid, urine, saliva or other tissues which are cataloged and stored at the Infinity Biologix (IBX) facility in New Jersey.
- The COMBINEDBrain Biorepository serves as a centralized location for researchers to easily access bio samples across multiple rare diseases simultaneously. These samples are distributed to researchers and industry upon request, at the lowest possible cost.

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JumpStart - Jackson Lab Mouse Model

NR2F1 Foundation receives $17k Grant

One-time matching grant given by The Orphan Disease Center (ODC) partnering with Jackson Laboratory Rare Disease Translational Center, for the purpose of creating a mouse model for researching BBSOAS.

Existing models for deletion, point mutations in LBD and DBD.

Need a 4th unique mutation for treatment testing

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RO1 Grant Application

In Progress

Extremely competitive grant provided by the National Institute of Health- National Eye Institute for named investigator (Dr. Shah) for a specific project related to their expertise and competencies. (10% of these grants are funded)

$500k over 5 years for international collaboration of BBSOAS experts

Work in progress. Due May 26th to Cincinnati Children's Review Board before for June 6th submission to NEI/NIH.

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Dr. Christian Schaaf

Projects

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Development of Six iPSC Lines

- Funded by NR2F1 Foundation in 2019
  - Induced pluripotent stem cells from BBSOAS patients
  - 3 deletions and 3 mutations
  - Stem cells to share with other researchers/ freeze for future research
- Used for experiments on how mutation affects the viability and function of neurons
  - Does NR2F1 play a role in the cell that we previously did not know about?
  - Does it correlate with structure/ function or both - in neurons based on mutation vs deletion?
  - Is it level of expression downstream, firing pattern of neurons that is different? -What we need is a metric to measure.
- These experiments informed the TRIP BBSOAS current study.

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Translational Research Investigating Phenotypes of BBSOAS

- Foundation funded ($50k) to jump start project (Grant for on-going funding expected July 2023)
- Joint project between Drs. Studer and Schaaf will give us insights into the role of the NR2F1 gene in **brain development**, and its **downstream targets and pathways.**
- Finesse the DBD Mouse Model for long term study/ pre-clinical model
- Study of ALL mouse models in the Schaaf lab!
- **Basis of future therapeutic treatments**

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Potential Antisense Oligonucleotide Treatment

- Antisense therapies are designed to seek out, bind to and destroy a mRNA in a highly specific manner, so that the amount of disease-causing protein is dramatically decreased.
- Antisense therapies can also treat diseases caused by too little protein by increasing the production of the protein, thereby restoring the protein to normal levels.
- Former colleague of Dr. Schaaf from Baylor now works here.

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