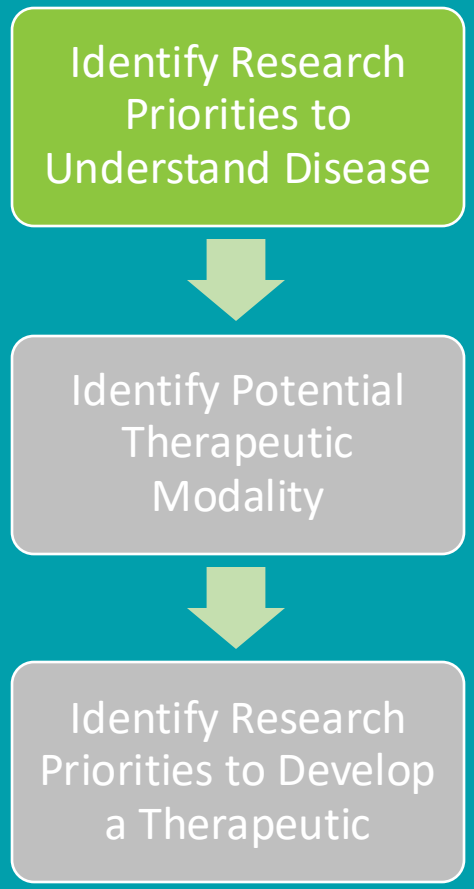
Rare Bootcamp™

Identifying Research Priorities

Moderated Table Discussion.



Current Understanding of the Disease

What is known and what are the gaps?

Considerations
Affected gene(s)/pathway (monogenic/polygenic) • Genetic mechanism/variants (e.g. deletions, mutations, haploinsufficiency, GOF/LOF…) • Prevalence and heterogeneity of clinical presentation
Disease Biology: What is the affected physiological process? • Target tissue and cell type • What specific molecular pathway(s) are affected? • What tools exist to model the disease?
Disease Manifestations: How does the disease manifest? What is the pathology? • How is the pathology currently assessed? • Is it progressive? Is it reversible? • What is the diagnostic journey and what age is common diagnosis? • Are there clinically validated endpoints or biomarkers?

What are the Knowledge Gaps

What basic research (if any) should we fund to understand the disease?

Gaps & Research Goals	Scientific Approach

Example: Creatine Transporter Deficiency – knowns

Affected Gene/Pathway	• X-linked dominant neurodevelopmental disorder caused by mutations in the SLC6A8 gene encoding creatine transporter (CrT) • Prevalence: Limited data; under-diagnosed; ~30K patients • Variable clinical presentation; siblings with the same genotype can have very different severity
Biology	• Loss of CrT function results in insufficient Cr levels in neurons, which rely upon Cr for excess energy reserves due to their high metabolic activity and functional requirements to form and maintain proper connections. • Low neuronal ATP metabolism directly related to creatine (Cr) depletion • Rodent models do not demonstrate a robust pathological phenotype
Disease Manifestations	• Symptoms: Neurological deficits, including autism, delays in speech and language development and general ADHD-like behavioral problems, motor skill delay and random seizures. • High unmet need and no existing therapies. Long diagnostic journey exacerbated by lack of disease modifying therapy results in low patient/HCP awareness/engagement especially among adult population

CTD Example; What are knowledge gaps? (Keep asking why!)

- What is the mechanism by which a lack of creatine affects neuronal function? If via ATP, how does creatine impact ATP metabolism?
- How much creatine is needed in the brain for normal function?
  - Do various aspects of the pathology require different levels of creatine? e.g. speech & language development, motor skills, seizures
  - What brain regions most impact pathology?
- Is the neuronal deficit reversible, can adding creating to a deficient neuron restore function?
- Does this mutation only impact neuronal function? What about other cell types in the brain?
- Are there any impacts of this mutation to peripheral tissues?
- Since it is X-linked, what differences are seen between males and females?
- etc.?

What answers will help you develop a therapeutic?

Who can help answer these questions – what sort of investigator, lab, etc.

How much will it cost? Does finding the answer justify the expense?