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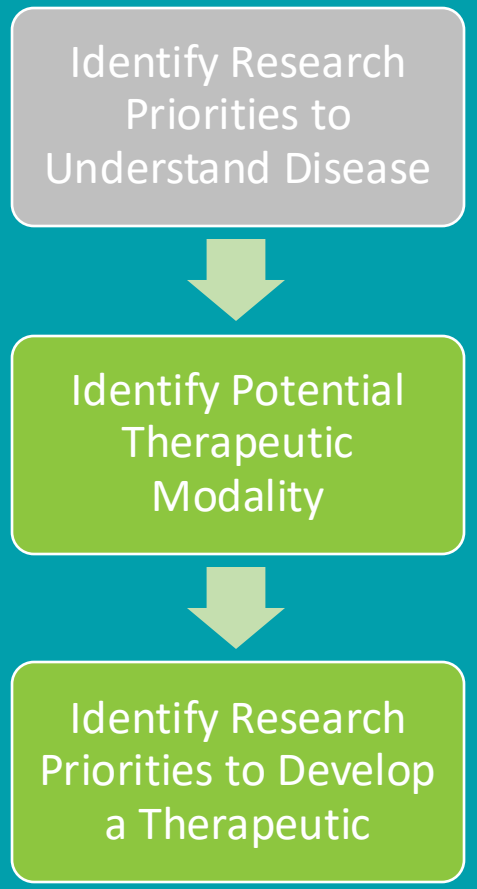
Therapeutic Strategy

Moderated Table Discussion.

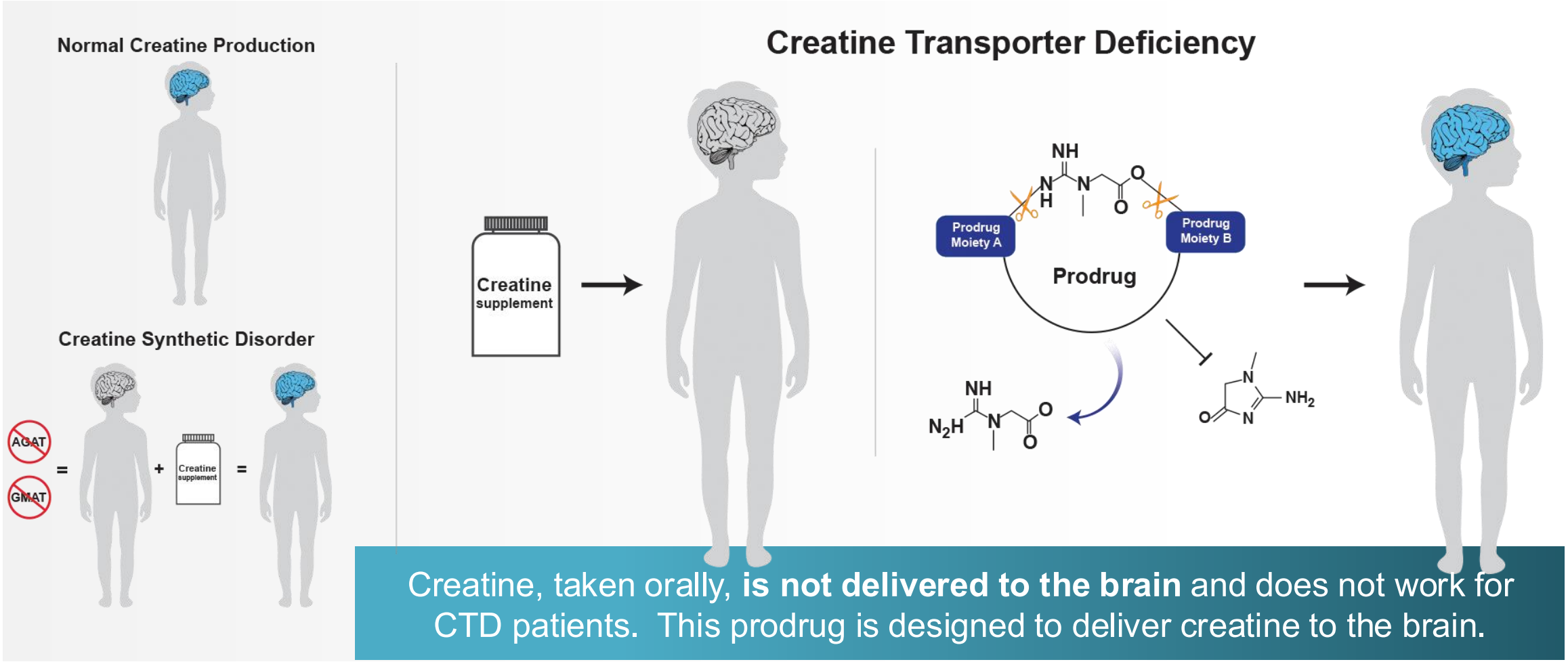


CTD Example; What therapeutic approach should we invest in?

Modality	
Gene Therapy	• Creatine transporter is too large for AAV. A mini-gene has not yet been created, will require further research. • Specifically, which or how many neurons to target is not known. AAV cannot currently deliver to a high percent of neurons
Oligonucleotide	• Can potentially upregulate the creatine transporter in patients with partially-functioning transporters. Will not work on everyone.
Gene Editing	• Diverse panel of mutations leading to CTD. Requires a personalized medicine approach
Small Molecule	• No obvious molecular target • Can deliver to all neurons, likely will be efficacious.
Enzyme replacement & Antibody Therapeutic	• Not applicable – mutation is in a transporter

Creatine Small Molecule Prodrug for Creatine Transporter Deficiency

Deliver creatine as a substrate replacement.



Creatine, taken orally, **is not delivered to the brain** and does not work for CTD patients. This prodrug is designed to deliver creatine to the brain.

Therapeutic Strategy Planning – Which Approach to Invest In?

Define the therapeutic objective (e.g. activate, inhibit, replace)
What modalities can achieve the desired objective?

Modality	Considerations	
Established Modalities (Small Molecule, Enzyme Replacement Therapy, Antibodies)	1. Is what has been clinically and/or preclinically proven for a given modality a potential therapeutic match? 2. What are the limitations of the modality (gene size, tissue target, etc.)? 3. What is the cost of development? Approximate time to a therapeutic? 4. What are the risks associated with the approach?	
Nucleotide Therapeutic		

Therapeutic Strategy Planning – Which Approach to Invest In?

Define the therapeutic objective (e.g. activate, inhibit, replace)
What modalities can achieve the desired objective?

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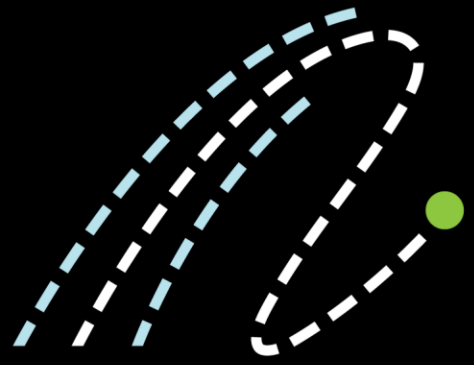
Gene Therapy	1. Is what has been clinically and/or preclinically proven for a given modality a potential therapeutic match? 2. What are the limitations of the modality (gene size, tissue target, etc.)? 3. What is the cost of development? Approximate time to a therapeutic? 4. What are the risks associated with the approach?	
Gene Editing		

Therapeutic Strategy Planning

What research should we fund to progress preferred modality to clinical trials?

Research Questions/Goals *Answers needed to progress to clinical trials*	Scientific Approach



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Thank You