

Therapeutic Strategy

Moderated Table Discussion.

Identify Research
Priorities to
Understand Disease



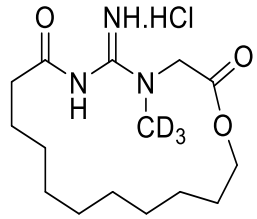
Identify Potential
Therapeutic
Modality



Identify Research
Priorities to Develop
a Therapeutic

Questions to consider during modality presentations

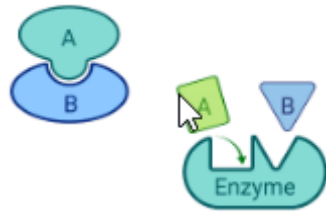
What is a Modality?



Small Molecule



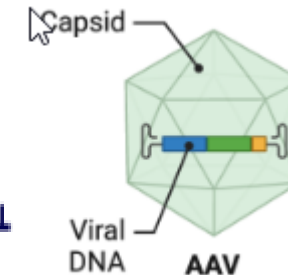
Antibody/ADC



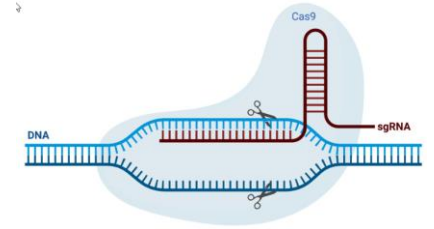
Enzyme/Protein



Nucleotide



Gene Therapy



Gene Editing

1. What has been clinically and/or preclinically proven for a given modality?
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?

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)	<ol style="list-style-type: none"><li data-bbox="445 405 1161 615">1. Is what has been clinically and/or preclinically proven for a given modality a potential therapeutic match?<li data-bbox="445 691 1161 843">2. What are the limitations of the modality (gene size, tissue target, etc.)?	
Nucleotide Therapeutic	<ol style="list-style-type: none"><li data-bbox="445 919 1161 1072">3. What is the cost of development? Approximate time to a therapeutic?<li data-bbox="445 1148 1161 1243">4. What are the risks associated with the approach?	

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	
Gene Therapy	<ol style="list-style-type: none"><li data-bbox="445 401 1154 615">1. Is what has been clinically and/or preclinically proven for a given modality a potential therapeutic match?<li data-bbox="445 686 1123 843">2. What are the limitations of the modality (gene size, tissue target, etc.)?	
Gene Editing	<ol style="list-style-type: none"><li data-bbox="445 915 1072 1072">3. What is the cost of development? Approximate time to a therapeutic?<li data-bbox="445 1143 1085 1243">4. What are the risks associated with the approach?	

Therapeutic Strategy Planning

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

Research Questions/Goals <i>Answers needed to progress to clinical trials</i>	Scientific Approach

CTD Example; What therapeutic approach should we invest in?

Modality	
Gene Therapy	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• Can potentially upregulate the creatine transporter in patients with partially-functioning transporters. Will not work on everyone.
Gene Editing	<ul style="list-style-type: none">• Diverse panel of mutations leading to CTD. Requires a personalized medicine approach
Small Molecule	<ul style="list-style-type: none">• No obvious molecular target• Perhaps can deliver creatine as a substrate replacement. Difficult to engineer a small molecule that will get to the neuron and only then release creatine.• Can deliver to all neurons, likely will be efficacious.
Enzyme replacement & Antibody Therapeutic	<ul style="list-style-type: none">• Not applicable – mutation is in a transporter

Creatine Small Molecule Prodrug for Creatine Transporter Deficiency

