Opportunities for Gene Therapy Development With Novel Engineered AAV Capsids

Presenters

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Presenter disclosures

- Eric Kelsic is a full-time employee and shareholder of Dyno Therapeutics
- Beverly Davidson is on the SAB and/or receives sponsored research from Carbon Biosciences, Homology Medicines, Latus Biosciences, Leal Therapeutics, Moment Bio, Saliogen Thera, Patch Bio, Panorama Medicines, Resilience, Spirovant Sciences, Voyager Therapeutics, Novartis (NBIR), and Roche
- Sharif Tabebordbar is a full-time employee and shareholder of Kate Therapeutics

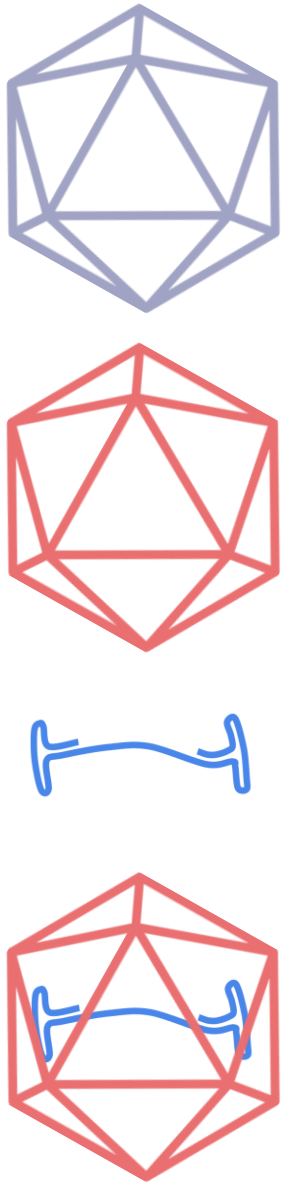
Presentation Outline

1. Definitions and Terminology
2. Background
3. ASGCT Recommendations
4. Theoretical Scenarios to Demonstrate Application of Recommendations
5. Conclusions

Introduction & Background

Definitions and Terminology

- **Natural AAV capsid** - an AAV capsid sequence isolated from a natural sample
- **Engineered AAV capsid** - an AAV capsid with a designed sequence or with modifications made to a natural sequence, for the purpose of improving the potency and safety of a gene therapy
- **Genetic payload** - the DNA genome packaged within a capsid and delivered to target cells
- **Gene Therapy Product** - the combination of a specific AAV capsid with a specific genetic payload sequence



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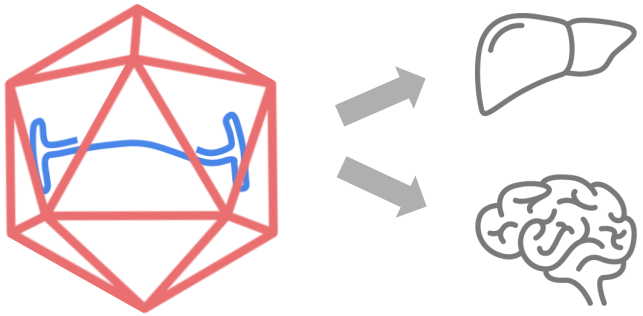
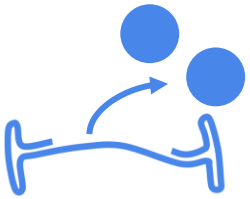
Definitions and Terminology

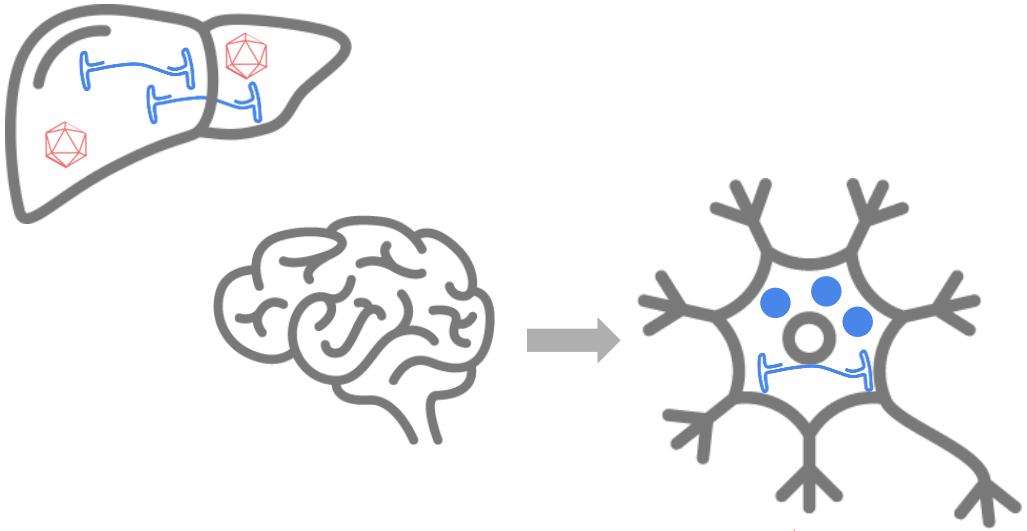
- **Biodistribution** - transport of AAV particles to a cell/organ



- **Transduction** – RNA/protein expression (or other types of functional consequences of the payload) from an AAV gene therapy



- **Off-target delivery** - biodistribution or transduction in cells/organs other than the target cells
- **On-target delivery** - transduction from target cells/organs



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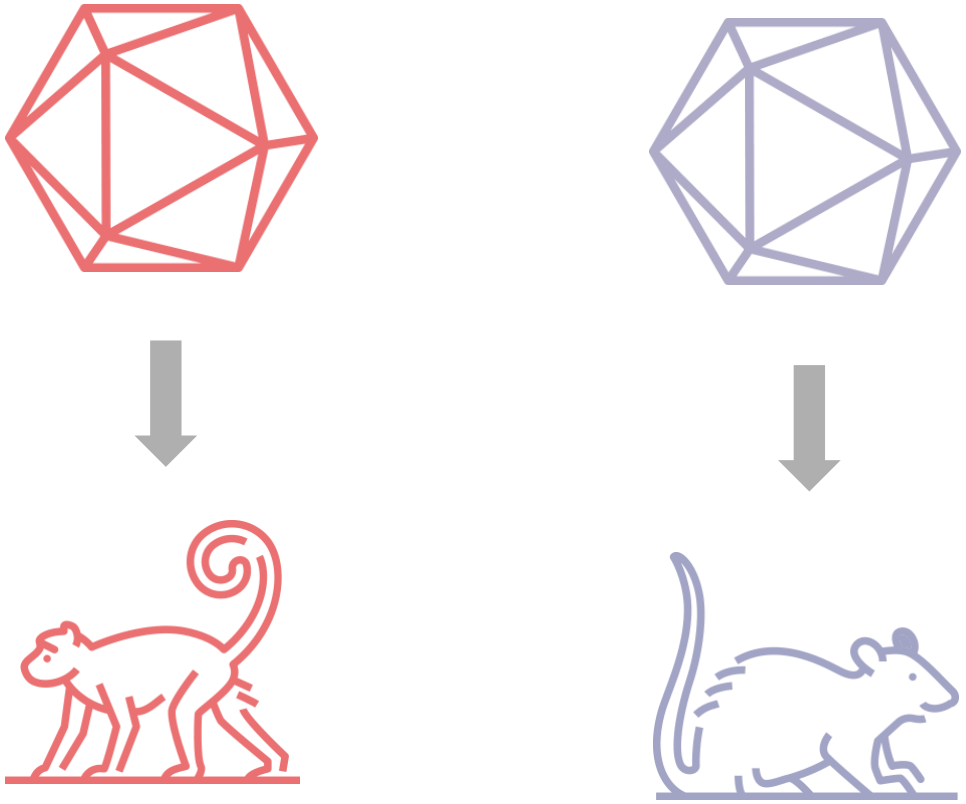
Definitions and Terminology

- **Surrogate capsid** - a capsid which is substituted for the clinical capsid, for example to enable sufficient delivery to target cells of a surrogate animal disease model during pre-clinical studies



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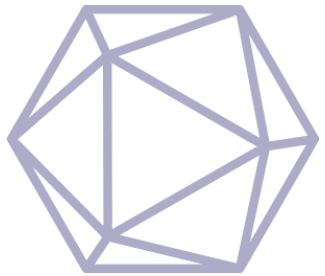
Background

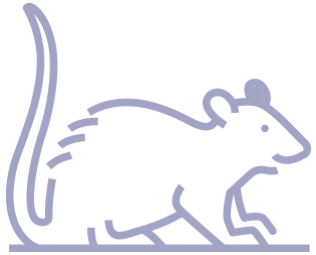
- Novel engineered AAV capsids hold promise to improve the safety and efficacy of gene therapies
  - By reducing biodistribution and transduction to off-target cells/organs, engineered capsids can improve product safety by widening the therapeutic index relative to that of natural AAV capsids
  - By improving the efficiency of payload delivery to target cells/organs, engineered capsids can increase product efficacy and enable successful treatments at lower doses



- Improved protein engineering methods are now yielding engineered AAV capsids with highly improved delivery properties, including 10-100x fold improvement in non-human primate eye, CNS, muscle and other organs (for reference: 2022 ASGCT Annual Meeting abstracts)

Background

- Novel capsids have been shown to exhibit very different delivery properties across animal models (for example between rodents and non-human primates as with AAV9, PHP.B, etc)
- Even a single amino acid change to an AAV capsid can dramatically alter the cell-targeting properties of the gene therapy
- Therefore, novel capsids must be tested in an animal model where there is confidence of translatability to humans
- New science is rapidly improving our understanding of which animal models are most promising for assessing the effectiveness of gene delivery in human patients
- At present, the most trustworthy animal models for assessing translatability of delivery and dose are old world non-human primates



Recommendations

Recommendation – Guidance on Model Systems

With gene therapies comprising both a vector and a genetic payload, the model systems for best assessing vector delivery may differ from the best models for assessing payload efficacy. Along with data to support product safety, **we recommend that FDA provide guidance to sponsors regarding how to separately demonstrate the translatability of capsid efficacy and payload efficacy to humans.**

- We will provide several theoretical scenarios later in this presentation to illustrate potential applications of these recommendations.

Recommendation – Capsid Efficacy

Evidence for capsid efficacy should demonstrate that the capsid is able to deliver its payload to target cells and organs to a sufficient extent to support a conclusion that the Gene Therapy Product will likely result in patient efficacy, assuming payload efficacy. To support the translatability of capsid efficacy to humans, **we recommend that FDA primarily require a sponsor to provide evidence of effective delivery to target cell types in the most scientifically relevant available model** – most recently the greatest confidence has come from data using non-human primates.

- Sponsors may optionally also provide additional support for translatability, but such methods will not be applicable in all cases. Examples of such supplemental support include cross-species in vivo studies, mechanistic conservation of transduction mechanism with human cells and prior human data using the same engineered capsid with other payloads.

Recommendation – Payload Efficacy

Evidence of payload efficacy should demonstrate the effectiveness of the genetic payload component of the gene therapy. Payload efficacy is distinct from capsid efficacy and should be demonstrated in an animal or in vitro cellular model. **We recommend that FDA guide sponsors to demonstrate payload efficacy in the most relevant cellular context.**

- This would enable, for example, assessment of payload efficacy in a mouse disease model, delivered to target cells via a surrogate capsid with delivery properties optimized for target cells in mouse, but where it is not possible to use the same capsid in demonstrating both payload and capsid efficacy due to differences in vector delivery across species. Or a sponsor could provide a package of data including cellular and genetic data (disease severity in heterozygous or chimeric individuals) in the absence of an animal model providing a basis for the prospect of direct benefit in the intended patient population. FDA's perspective on these varied approaches would be valuable.

Recommendation – Product Safety

It is important that the safety of *any* AAV product be evaluated in an animal model showing distribution expected to be representative of what will be observed in patients. This remains true regardless of the capsid novelty, since each unique payload-capsid combination and method of manufacture creates distinct safety implications. Therefore, **we recommend that FDA make no distinction between natural or engineered AAV capsids with regard to required criteria for supporting the safety of AAV gene therapies.**

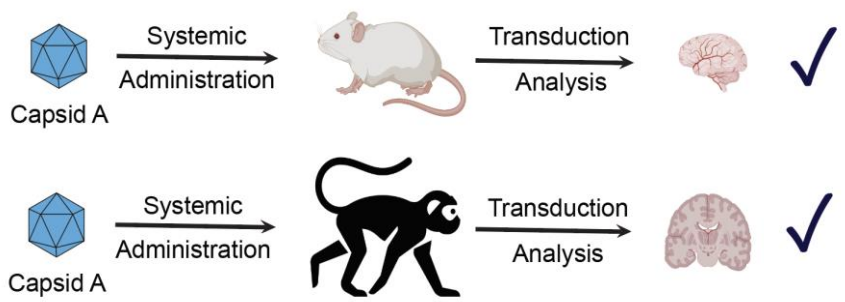
- If FDA were to issue guidance to this end, sponsor methods for assessing AAV gene therapy safety with or without engineered capsids are expected to be very similar, or even identical. In addition to using the most relevant animal model to humans, there should be the potential for leveraging existing safety information known about the AAV capsid being used.

Theoretical Scenarios to Demonstrate Application of Recommendations

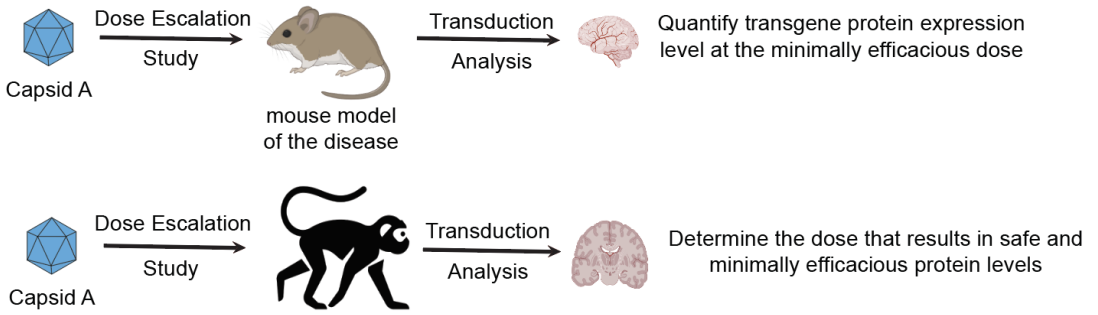
Scenario 1 – Capsid variant transduces the target tissue across species

Capsid A shows capsid efficacy to target tissues/cells in the mouse and non-human primate brain sufficient to support a conclusion that a payload targeted to those tissues/cells is likely to result in efficacy in patients. The sponsor then chooses to proceed with an available and established mouse model of disease, with a safety assessment in non-human primates. A clinical dose range is set based on starting at a dose that results in similar transduction in non-human primates as the minimally efficacious dose level in the mouse model of disease, providing that the safety assessment allows this. Dose escalation is designed to maximize the chance for benefit in humans, to a level that provides a sufficient margin from any safety considerations identified preclinically.

Capsid efficacy



Clinical dose range finding



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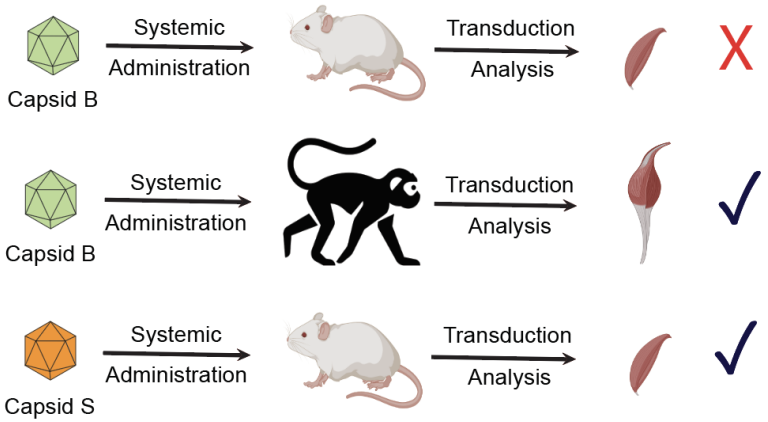
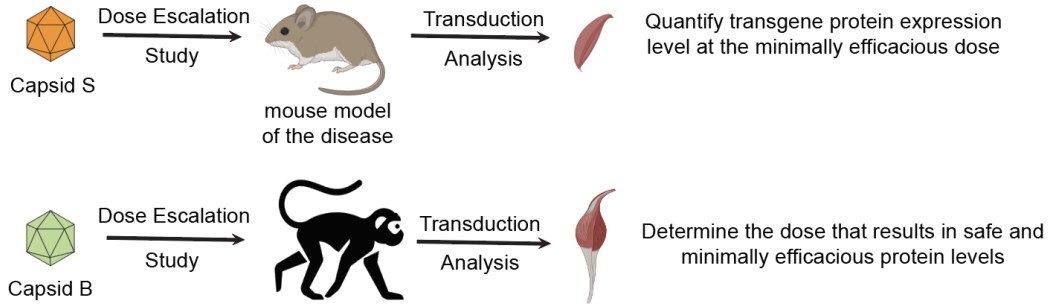
Scenario 2 – Capsid variant transduces the target tissue in NHPs, but not in mice

Capsid B transduces the muscle tissue effectively only in non-human primates. Capsid S (surrogate) effectively transduces mouse muscle and is chosen as a surrogate for Capsid B in an available and established mouse model of disease. Safety assessment is conducted in non-human primates with Capsid B. A clinical dose range is set based on minimal efficacious dose levels identified with Capsid S in the mouse model of disease and the dose required to achieve a similar level of transduction with Capsid B in non-human primates. Selection of clinical dose will also be heavily weighted on sufficient margins from any safety considerations identified in non-human primate studies with Capsid B.

Capsid efficacy



Clinical dose range finding



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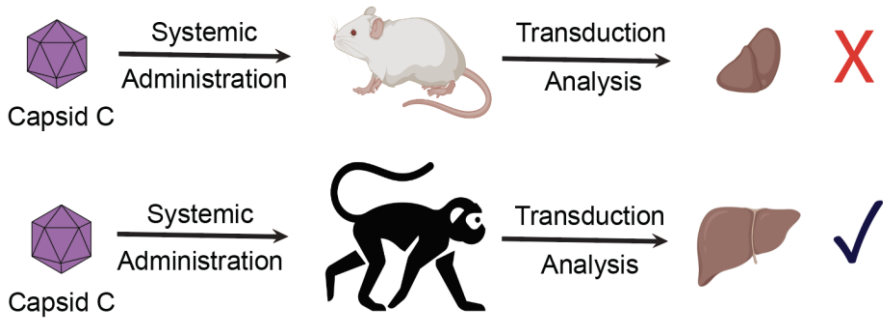
Scenario 3 – Capsid variant transduces the target tissue in NHPs, no disease model available

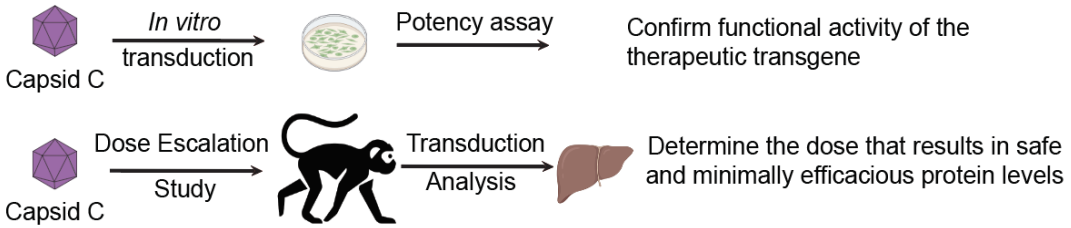
Capsid C only shows capsid efficacy in non-human primates for liver transduction. There is currently no available and/or established animal model of disease. A level of protein production is predicted for sufficient efficacy based on knowledge of the human disease and human genetics (heterozygous or chimeric individuals). Payload efficacy is separately tested in human cells. A clinical dose range is set based in part on levels of protein production measured in non-human primate studies with Capsid C and is heavily weighted on sufficient margins from any safety considerations identified in non-human primate studies with Capsid C.

Capsid efficacy



Clinical dose range finding

Determine minimum efficacious amount of therapeutic transgene based on protein levels in asymptomatic heterozygous or chimera individuals



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Conclusion

Conclusion

- Engineered capsids have the potential to significantly improve the safety and potency of AAV gene therapies.
- Some engineered capsids have different biodistribution and transduction profiles for on-target and off-target tissues across species.
- Capsid efficacy and payload efficacy for AAV gene therapy development candidates that use engineered capsids need to be evaluated separately in the most relevant animal/cellular models.
- Old world non-human primates are the most trustworthy animal models for assessing translatability of delivery and dose to human patients.
- A surrogate capsid can be used for demonstrating payload efficacy in cases that the clinical engineered capsid is not effective in transducing the target tissue/cell types in rodent disease models.
- Safety of AAV gene therapy development candidates that use engineered capsids can be evaluated similarly to those using natural AAV capsids, in an animal model showing distribution expected to be representative of what will be observed in patients.

Acknowledgements

Work group members

- Ben Deverman, PhD, Broad Institute
- Beverly Davidson, PhD, Children’s Hospital of Philadelphia
- Bob Pietrusko, PharmD, Vor BioPharma
- Dirk Grimm, PhD, University of Heidelberg
- Eric Kelsic, PhD, Dyno Therapeutics
- Fatih Ozsolak, PhD, Novartis
- Hiroyuki Nakai, MD, PhD, Oregon Health & Sciences University
- Kathila Altsis, Spark Therapeutics
- Kelly Flagella, PhD, Ultragenyx
- Mathieu Nonnenmacher, PhD, Voyager Therapeutics
- Megan Keiser, PhD, Children’s Hospital of Philadelphia
- Nimi Chhina, JD, PhD, BioMarin
- Peter Ward, PhD, Ultragenyx
- Rob Kaiser, PhD, Castle Creek Biosciences
- Sharif Tabebordbar, PhD, Kate Therapeutics
- Snehal Naik, PhD, Spark Therapeutics
- Tim MacLachlan, PhD, Novartis

Thank you

Appendix/Backup Slides