

Toward Therapies for DESSH: Building Foundations and Charting Paths Forward

September 16th, 2026

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Human Development



A roadmap to therapies in DESSH

Basic Research  **Therapeutics Development**  **Clinical Trials**

A roadmap to therapies in DESSH

Basic Research

Define the disorder

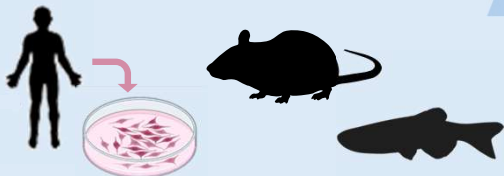
- Physician's studies
- Patient Registry
- Natural History Studies

Identify the gene

- Genome sequencing

Understand the biology

- Determine the function of the WAC gene
- Cellular & molecular effects of gene disruption



Therapeutics Development

Use of indicated & “off-label” interventions in patients

New small molecule drugs

- Drugs screens or rational design

Gene targeted therapies

- Gene replacement with virus
- Gene editing with CRISPR
- AntiSense Oligonucleotides (ASO)
- Protein Replacement

Clinical Trials

Validation/efficacy testing of off-label interventions

New therapies

Phase I

Safety

Phase II

Phase III

Efficacy

FDA approval

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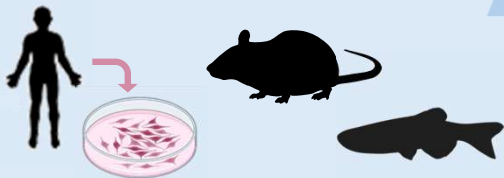
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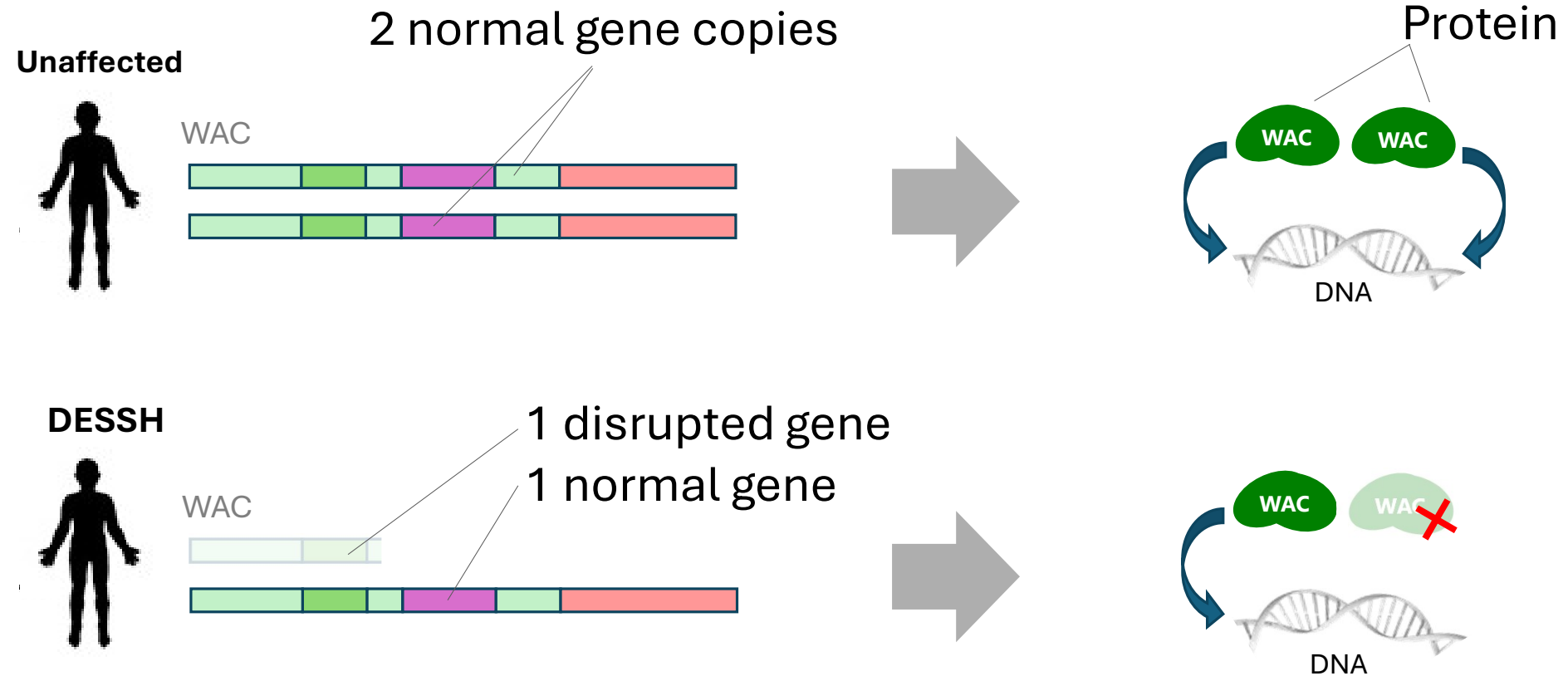
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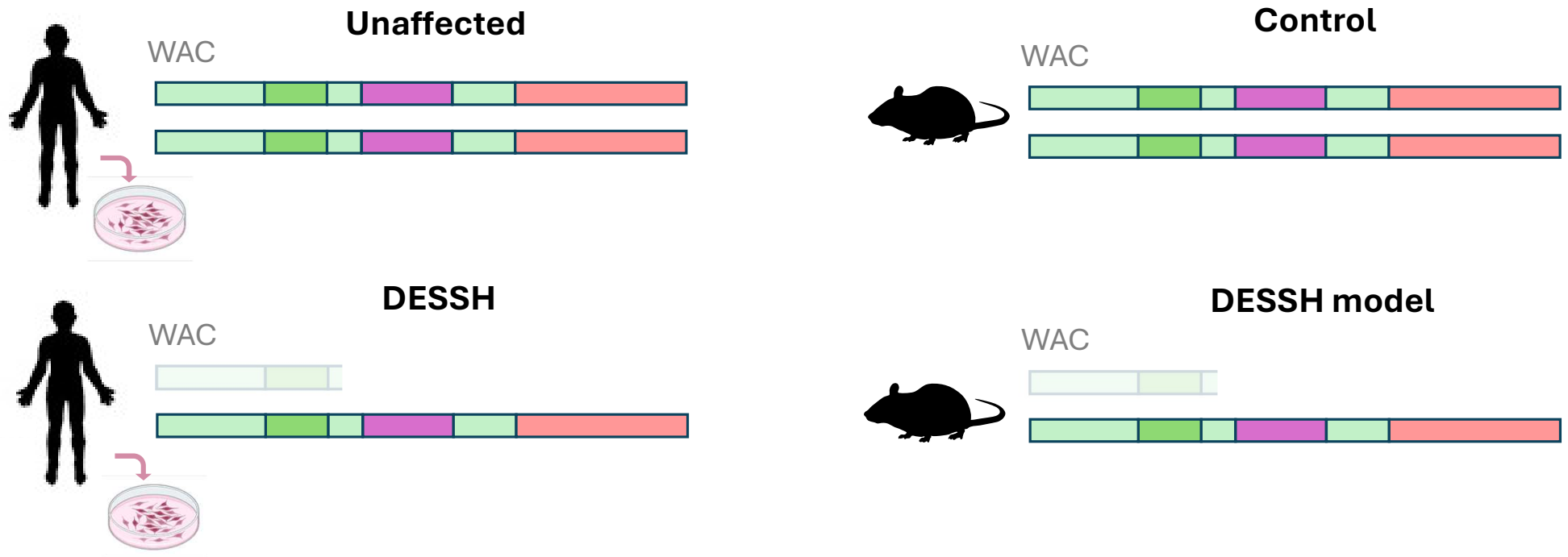
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DESSH results from a variant in one of two copies of the *WAC* gene that disrupts the function of one half of the *WAC* protein

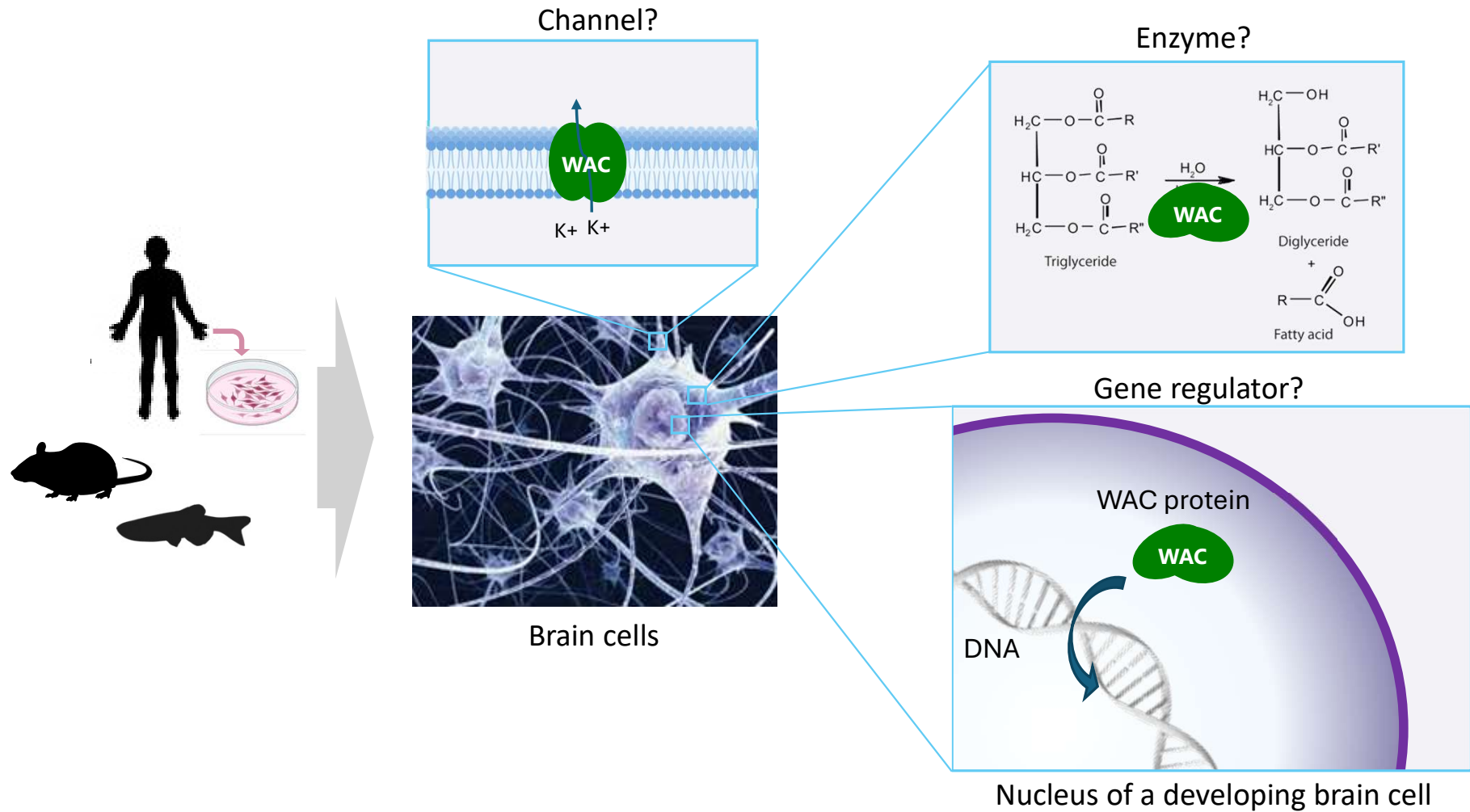


Studying cell lines and animal models of DESSH can help us understand the molecular and cellular underpinnings of the disorder

- The mouse and zebrafish have WAC genes like the human WAC gene and these organism can be studied along side human cells to understand WAC function and DESSH.

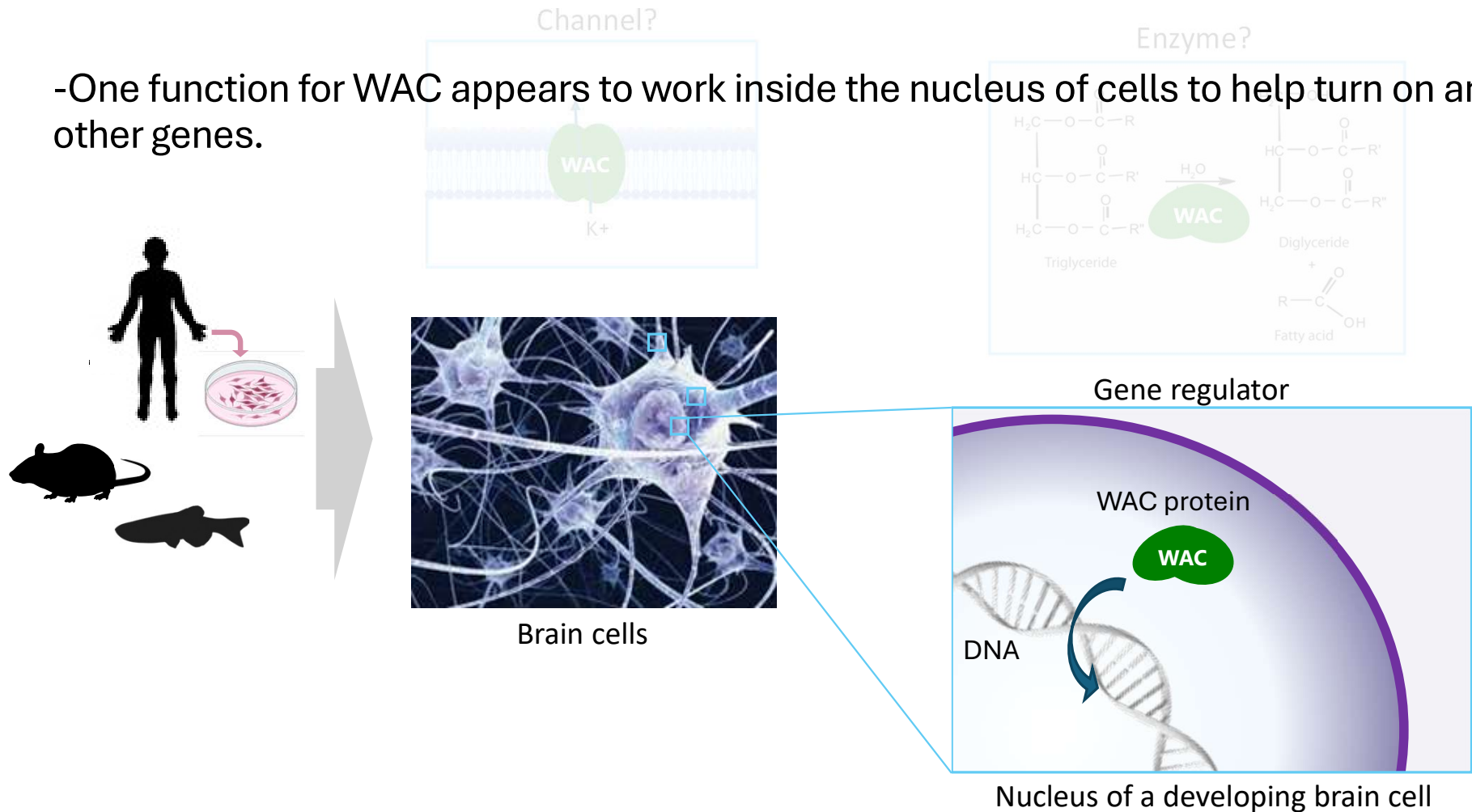


Understanding WAC protein function can guide therapy development



Understanding WAC protein function can guide therapy development

-One function for WAC appears to work inside the nucleus of cells to help turn on and off other genes.



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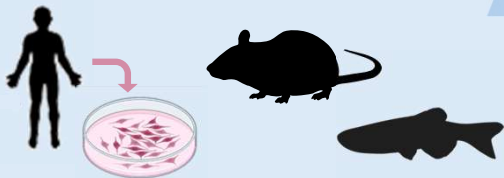
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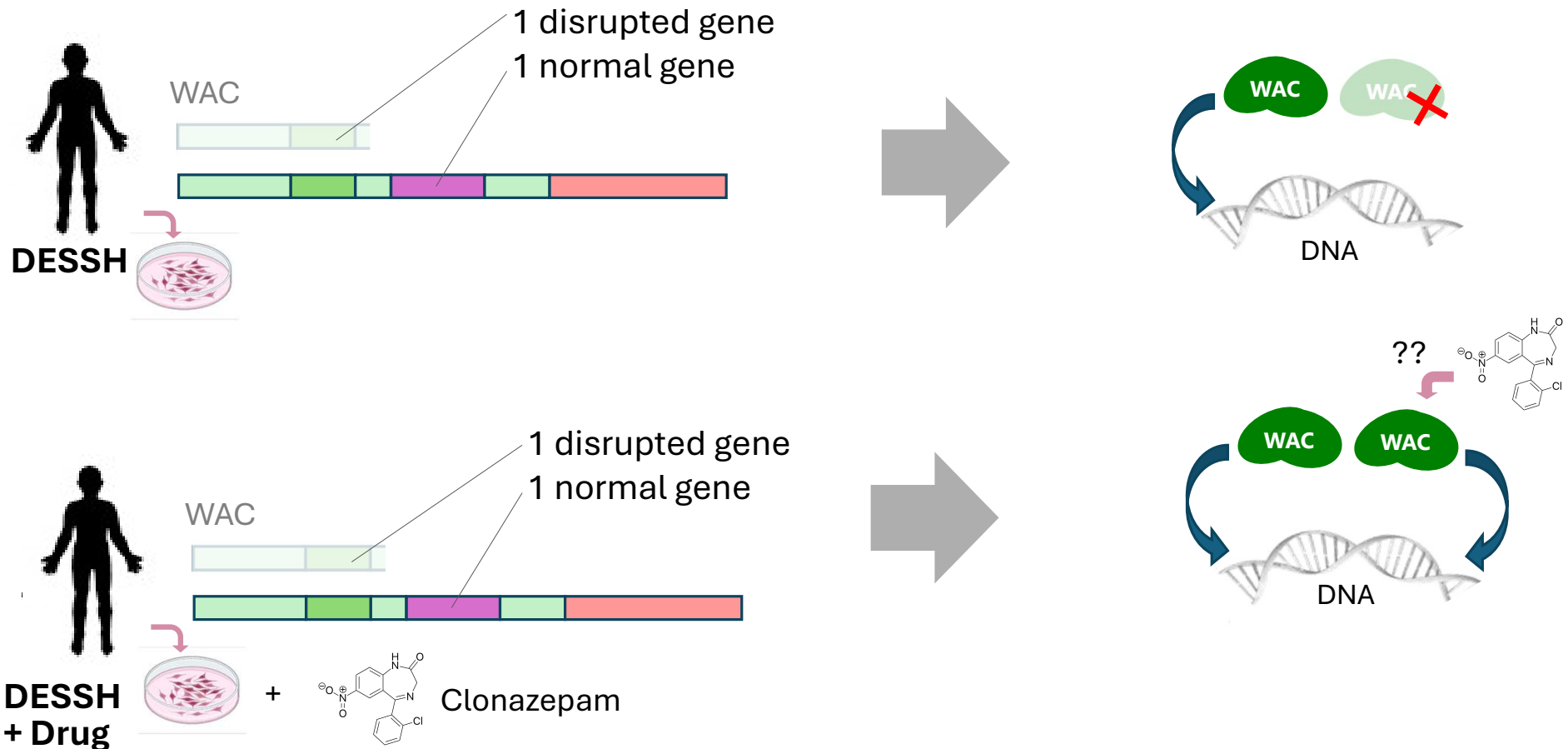
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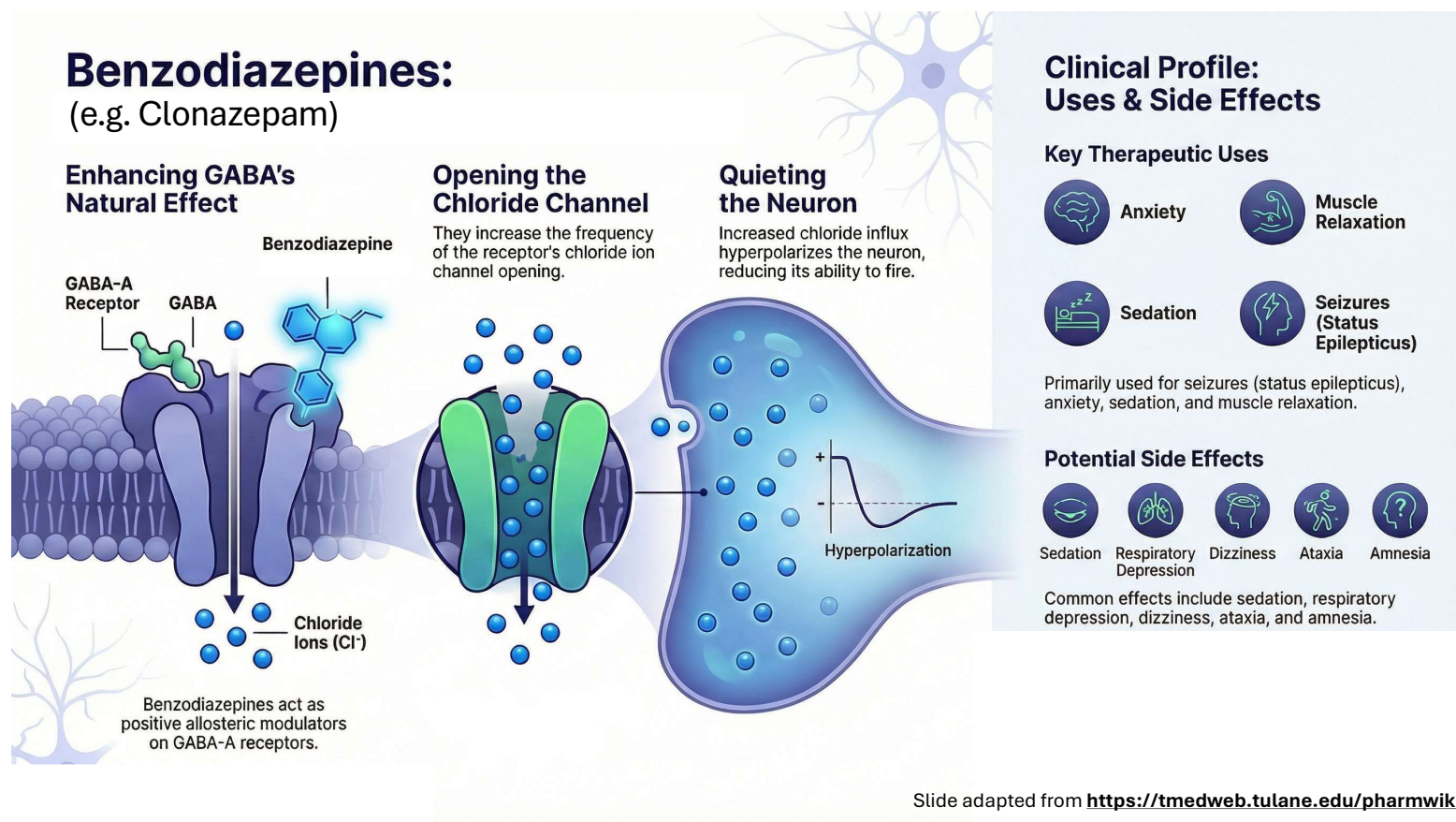
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Drug repurposing: screening for existing drugs that increase the WAC protein as a strategy to find a therapy that can be quickly implemented “off-label”.



Drug repurposing: drugs with relevant “on-target” effects are the best candidates.

-On-target effects may contribute to potential positive effects of clonazepam in DESSH



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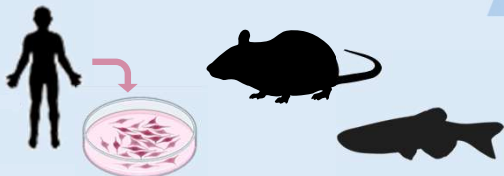
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What is gene therapy? Is it possible for DESSH?

Gene therapy is a technique that uses a gene(s) to treat, prevent or cure a disease or medical disorder. Often, gene therapy works by adding new copies of a gene that is broken, or by replacing a defective or missing gene in a patient's cells with a healthy version of that gene.

<https://www.genome.gov/genetics-glossary>

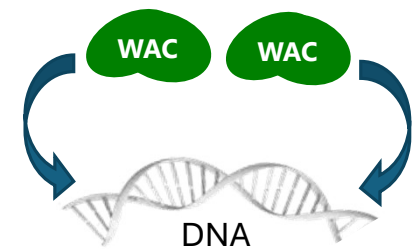
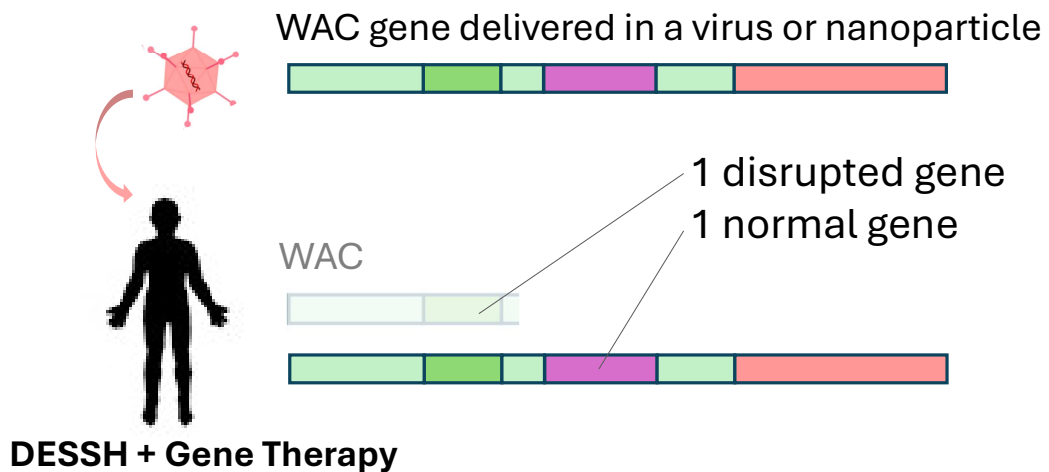
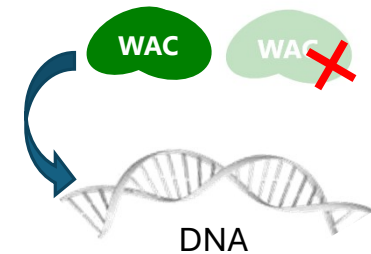
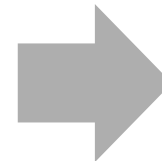
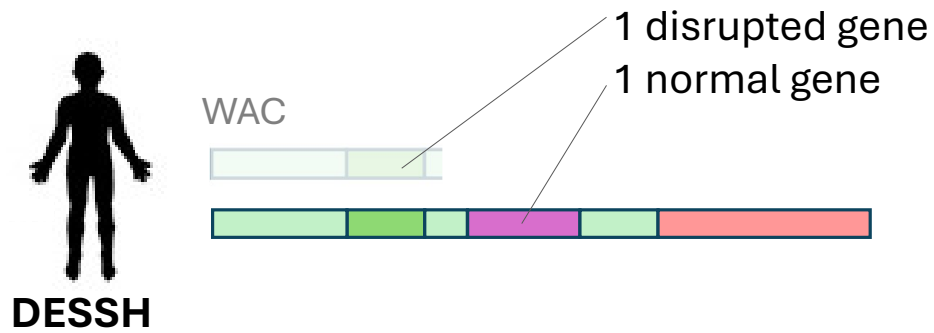
Gene therapy has had some exciting recent success: KJ's story

- Carbamoyl-phosphate synthetase 1 (CPS1) deficiency due to CPS1 gene disruption.
- Liver does not function right, ammonia build up in the blood.
- 50% mortality rate, neurological damage even with current standard of care.
- Gene correction therapy was developed in just months



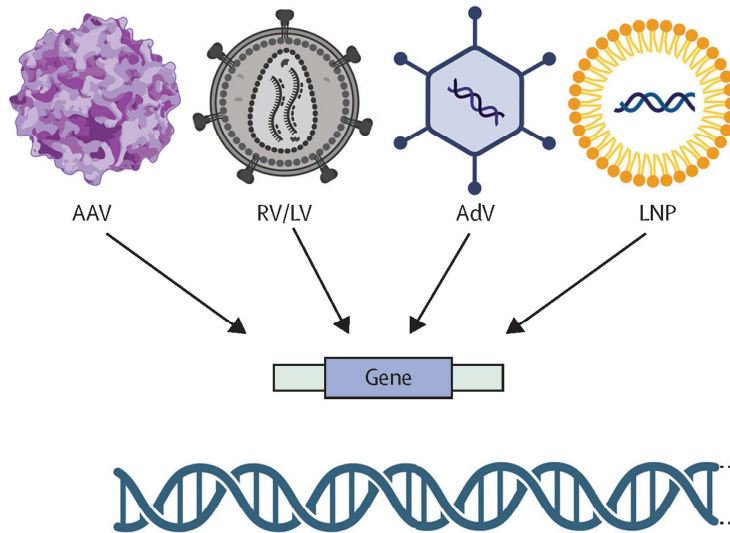
NY Times, 2025

Gene therapy for DESSH could replace the function of the missing copy of WAC



The approach: replacing or correcting the DNA

Gene replacement closest to the clinic



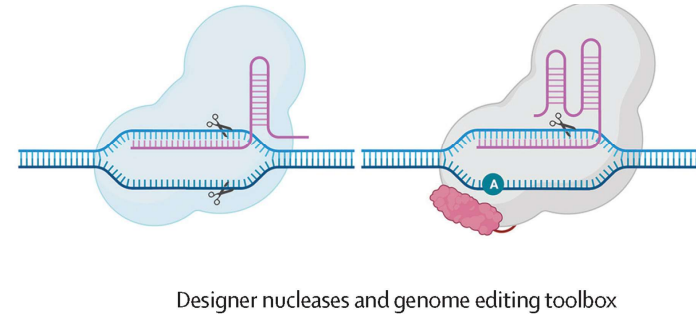
Pros

- Successful clinical experience
- Market authorisations
- Functional cure
- Effective correction
- Optimised delivery route
- Assumed to be long lasting

Cons

- Does not correct underlying genetic defect
- Potential safety issues (genotoxicity)
- Non-physiological gene expression, fine-tuning is needed
- Difficulties with dominant negative mutations
- Immunogenicity

Genome editing not yet proven in the brain



Pros

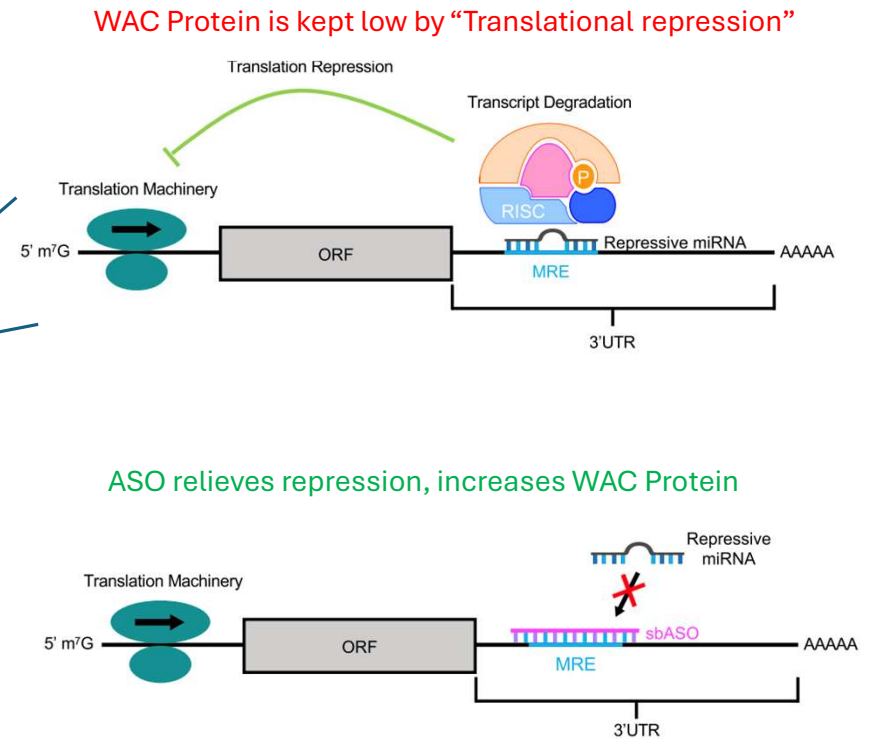
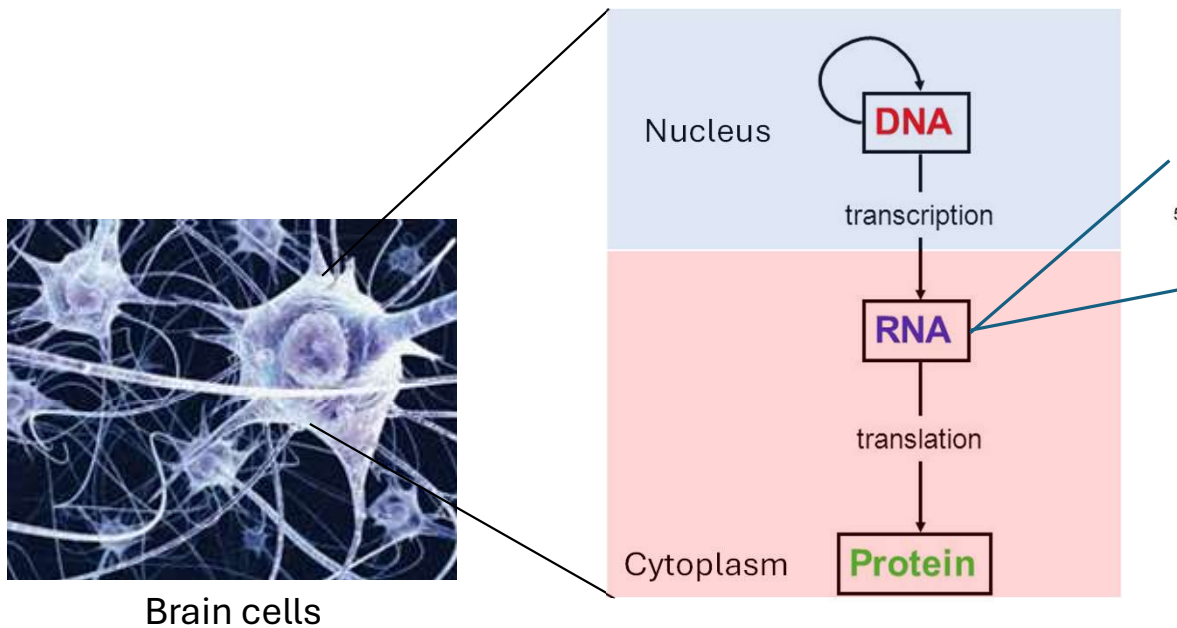
- Can cure underlying genetic defect, including dominant negative mutations
- Easier adaptation for some approaches (CRISPR-Cas9)
- Long-lasting correction

Cons

- Potential ethical dilemmas
- Long-term safety to be demonstrated
- Monitoring is more challenging
- Potential off-target activity and translocations
- Delivery needs optimisation
- Immunogenicity

Schambach et al. *The Lancet* 2024

The approach: creating more protein from the working WAC gene using RNA-targeted antisense oligo nucleotides (ASOs).



Drs. Dougherty, Miller, Gabel, Kroll are starting development at WashU, other labs are also pursuing this.

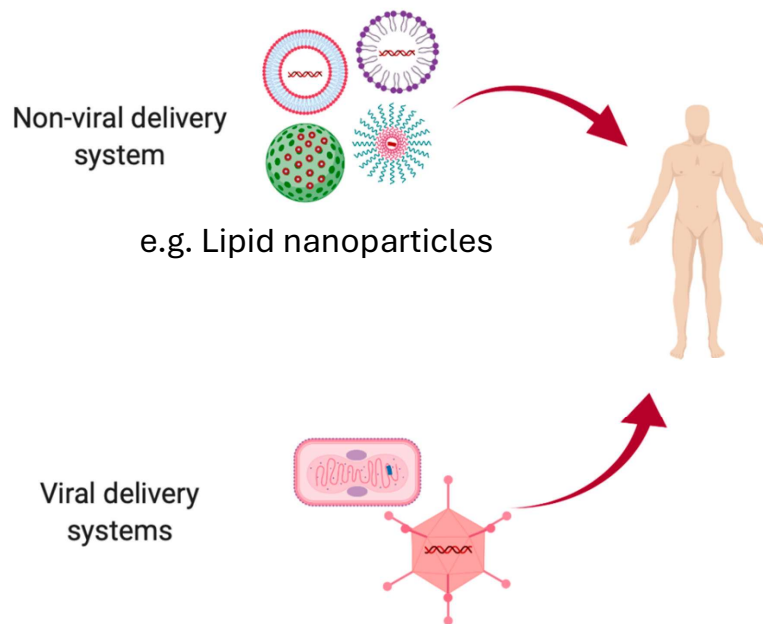
Some graphics from Vanderplow et al. *RNA* 2024

Making gene targeted therapy a reality: hurdles to overcome

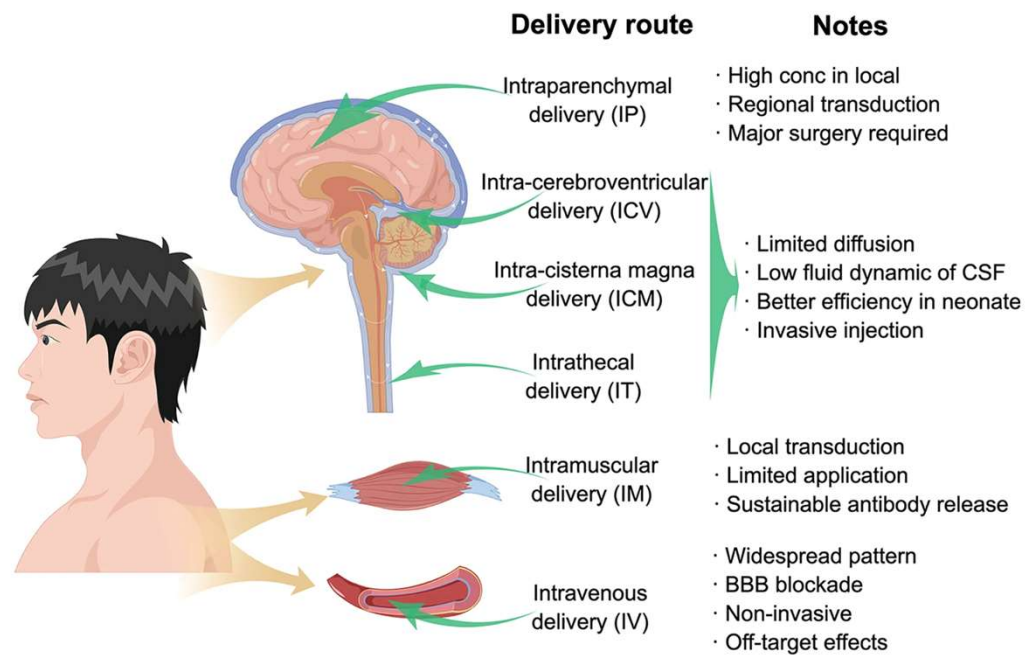
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- Dose: Is the gene “dose sensitive”? i.e. if we deliver too much of it, is that bad?
- Approach: How can we replace gene function in a way that meets timing and dosing constraints?
- Delivery: How do we deliver the therapy to the cells in the body that need it?
- Safety: How do we make sure it is safe?

Delivery: getting enough of the therapy to the right cells

The vector



The route



Safety: the treatment cannot be worse than the disorder

- Gene delivery with virus has risks of severe (sometimes fatal) immune responses.
- Unintended damage to the genome during attempts at gene correction could cause cancer.
- Delivering too much of the gene can have detrimental effects on its own.
- With many current forms of gene therapy you can try it once and only once

For a therapy to go forward, these risks must be mitigated so that potential benefits outweigh the risks from treatment and the normal course of the disorder. This means that gene therapy for the most severe disorders are fast-tracked to the clinic (e.g. KJ).

The challenge

Each of these hurdles (timing, dose, approach, delivery, safety) must be overcome for gene therapy for DESSH to become a reality.

The good news

Multiple labs are tackling these issues

We are not alone: with gene therapy for rare disease, advances for other disorders mean advances for DESSH.

Making gene therapy a reality: hurdles to overcome

DESSH researchers like us can tackle these issues to “de-risk” DESH gene targeted therapy development

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The full weight of federally funded research together with many biopharmaceutical companies are directed at solving these issues to pave the way for therapeutic platforms that can be applied to DESSH

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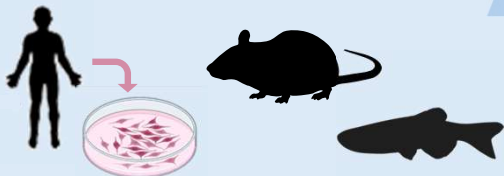
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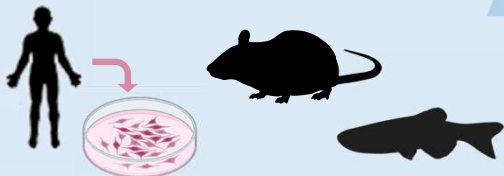
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Research priorities to advance DESSH therapies

Continue to define the disorder, develop biomarkers and outcome measures.

Test available drugs: evaluate efficacy of Clonazepam

Characterize models: continue to define phenotypes (i.e. symptoms) in zebrafish, mouse and human cellular models for measures of therapeutic efficacy.

Identify candidate therapies that are most feasible for DESSH.

- Bioinformatics and AI driven analysis to identify candidate small molecules
- Timing and dose sensitivity studies for small molecules & genetic therapies in animals and human cell

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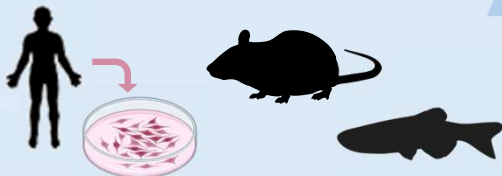
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Patient data gives us “outcome measures” to determine if new therapies are effective.

Your participation here is a critical start but we need to collect more data!

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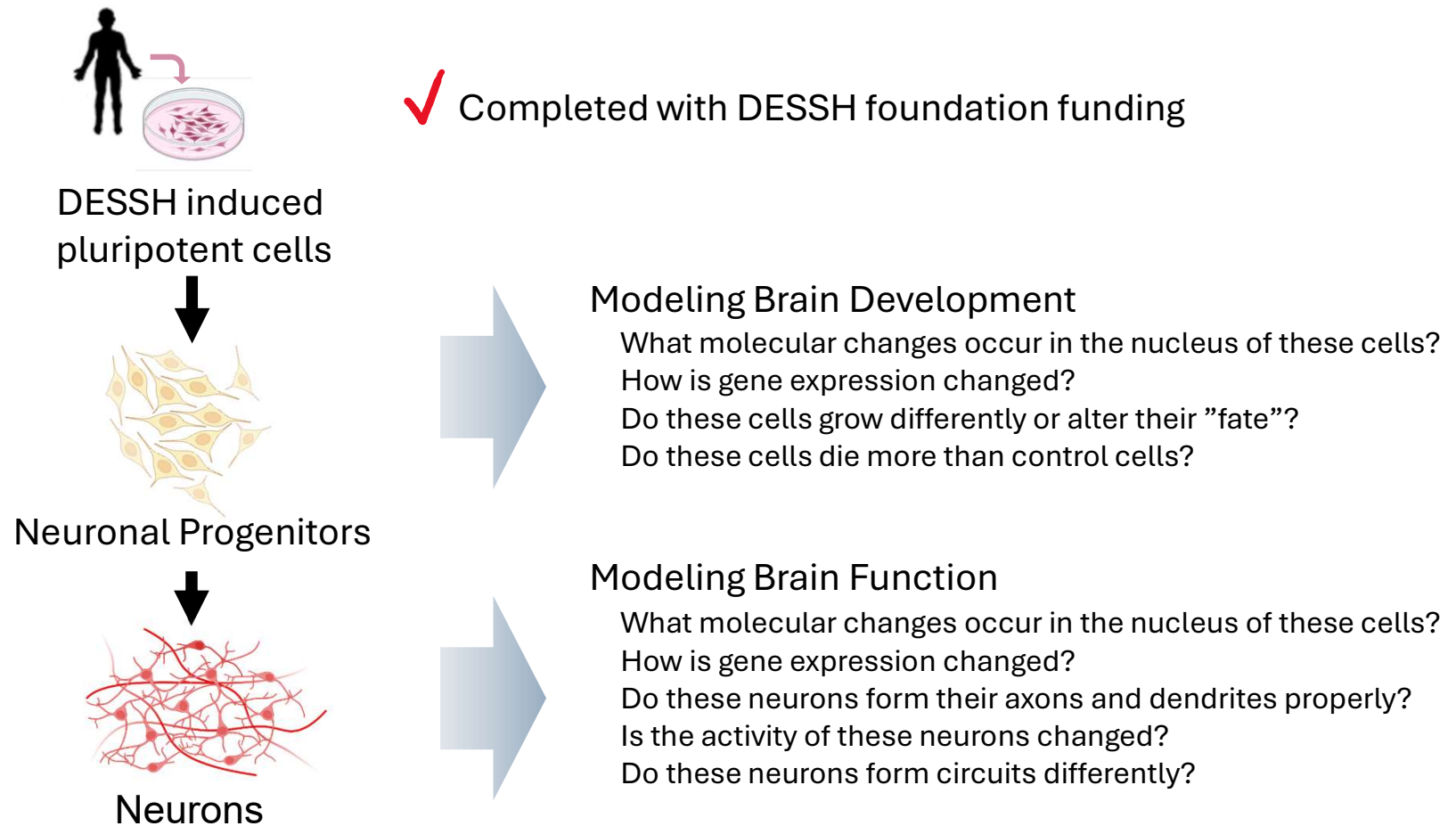
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DESSH iPSCs can be used to identify “symptoms in a dish” that we can use to study the disorder and test therapies.



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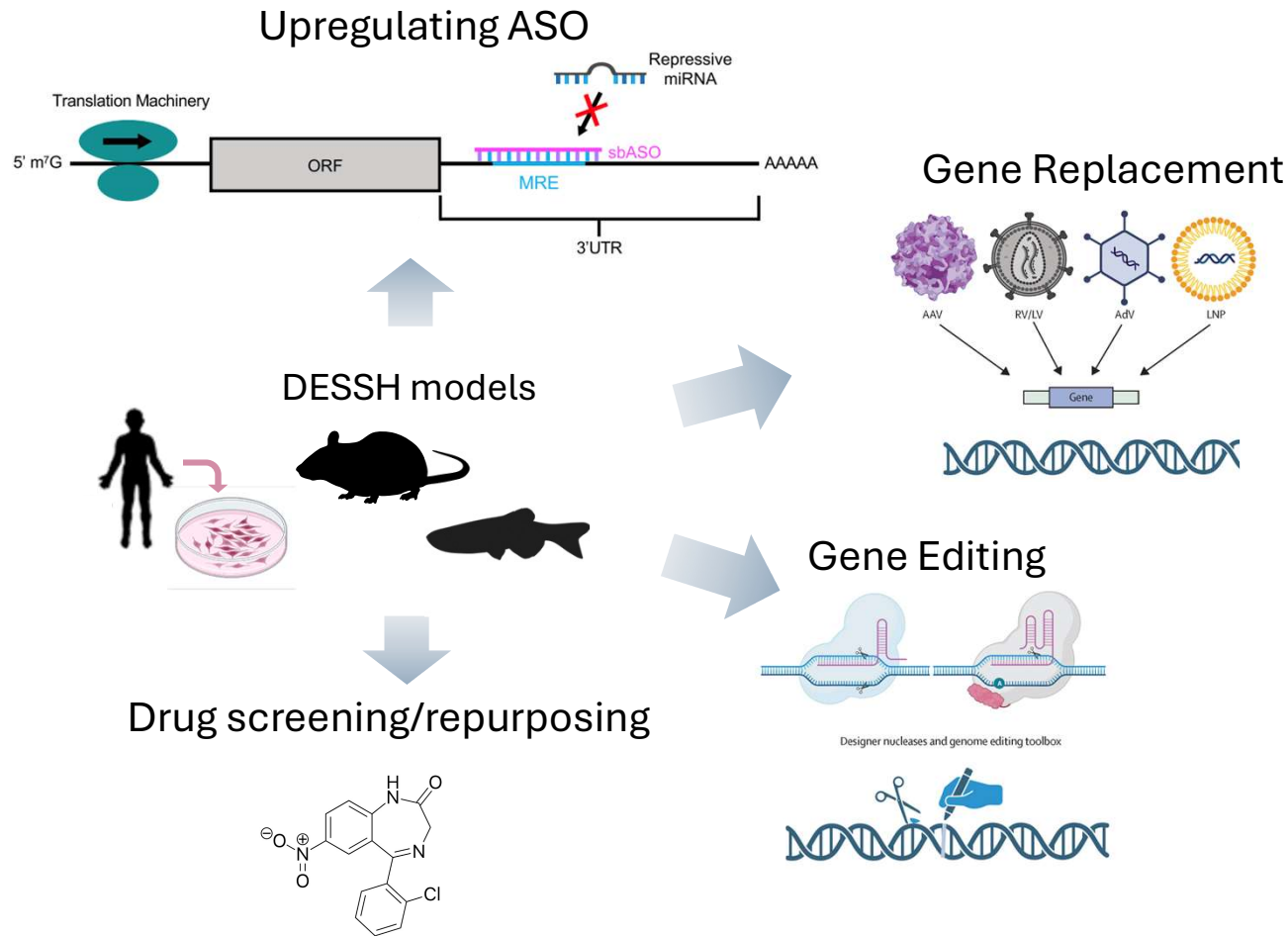
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Exploring therapeutic avenues for DESSH: pre-clinical proof of principle experiments



- Are phenotypes improved?

- Is a specific dose needed?

- What timing is required?

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Challenges and opportunities for rare disease/DESSH therapies

Challenges

- Multi-system disorders-challenging to find small molecule drugs that are disease-modifying.
- Small patient population
 - Can limit biotech/pharma interest
 - Makes clinical trials difficult. “N of 1” studies can be promising but complicated
 - Limited understanding of the disorder, developmental changes, and variation can make it hard to be sure if a treatment is working.

Opportunities

- We know the root cause (WAC gene disruption) and treatments can be designed to address this (e.g. gene targeted therapy)
- Biotech/Pharma and the insurance industry are finding business models that support rare disease therapy development

How can you be involved?

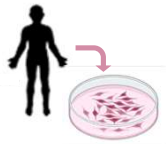
- Participate in research (when possible)
 - Share health data and medical records
 - Provide biospecimens
 - Share your priorities for care
- Be an educated partner
 - Ask questions, share perspective with researchers & clinicians
 - Participate in clinical trials when it is possible for you and your loved ones
 - If you are going to pursue drugs like Clonazepam do what you can to collect data and/or participate in a trial. Report outcomes as clearly and accurately as you can.
- Advocate for research and drug development
 - There is nothing more powerful than the voice of patients and caregivers in raising awareness, fundraising, and driving research

Funding pilot & proof-of-principle studies can have a multiplier effect for DESSH research by launching NIH grants

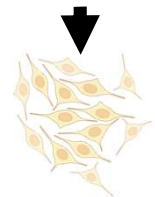
DESSH Foundation

~\$150,000 pilot project

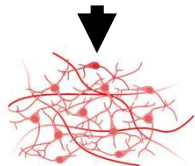
1-2 years



DESSH induced pluripotent cells



Neuronal Progenitors



Neurons

Key Preliminary Results

- Validated cell lines
- Molecular defects defined
- Cellular phenotypes established
- Proof-of-principle gene replacement results
- Candidate small molecules (e.g. Clonazepam)

Large-scale Research

~\$3,500,000 grants



National Institutes of Health



National Institute of Mental Health

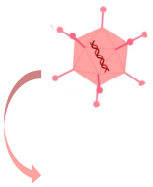


Funding pilot & proof-of-principle studies can attract biotech and pharma interest

DESSH Foundation

~\$250,000 pilot project
~2 years

Gene Replacement



DESSH mouse model

Key De-risking Results

- Circuits and behaviors improve
- Large dosing window
- Late correction possible
- Gene replacement not interfered with by mutated gene

Biotech & Pharma interest



NEUROGENE



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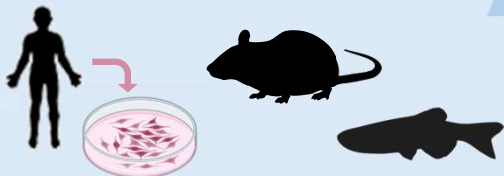
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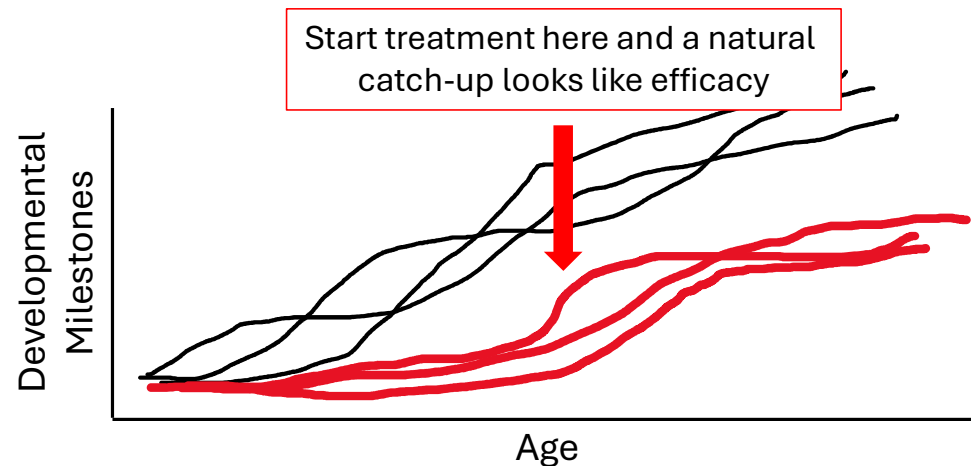
FDA approval

Extra slides beyond this point

The challenge of knowing if a therapy for a developmental disorder is working.

Variability:

- Development happens at different paces for different people.
- Developmental disorders can have delays that are followed by catch-up



Placebo effect:

- most developmental disorders must rely on clinician and care giver impressions to measure efficacy. These measures are susceptible placebo effects.