Gene therapy for rare disease

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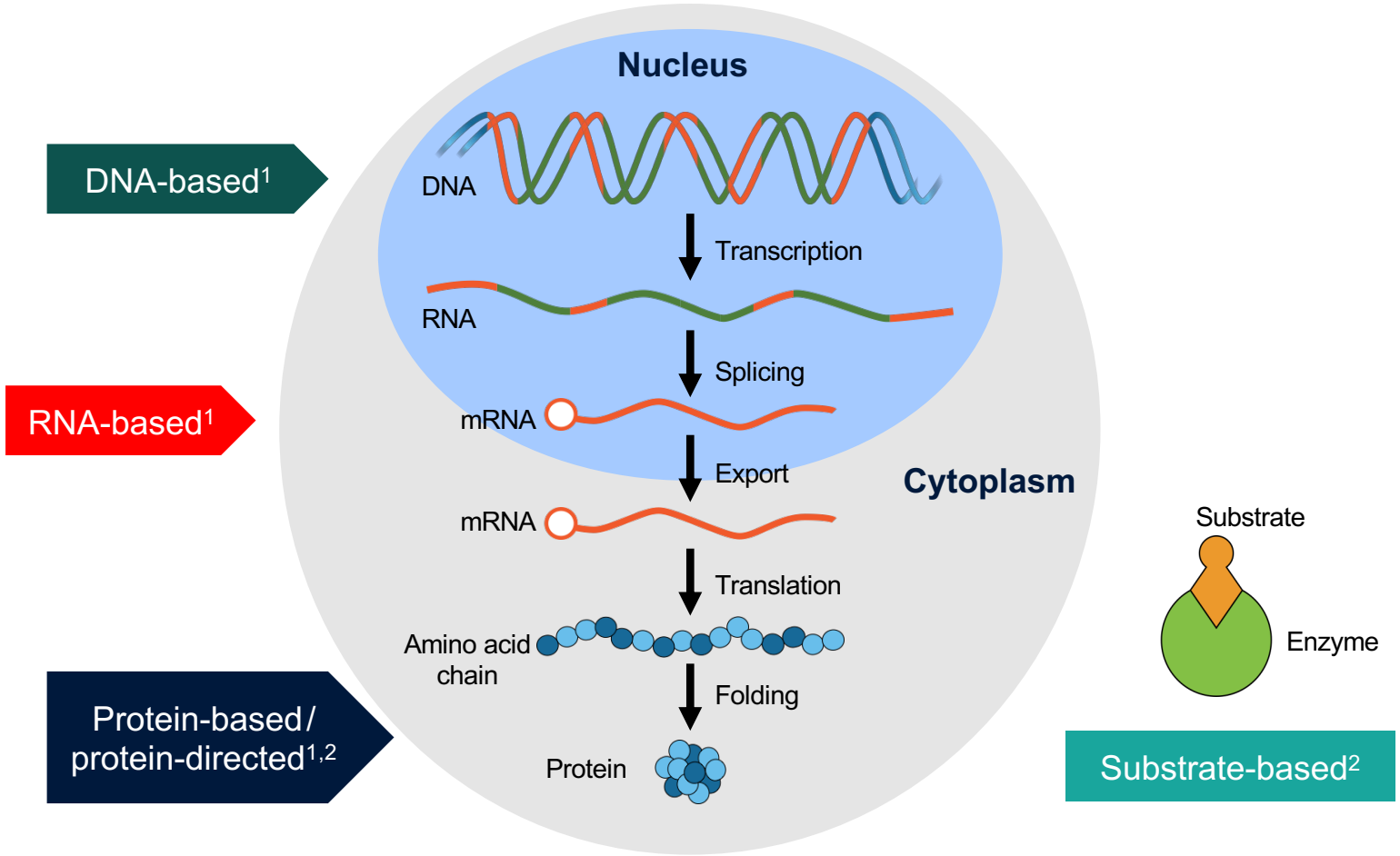
Disclosures relevant to today's talk

- Scientific advisory board, RYR1 Foundation, the Muscular Dystrophy Association, and Muscular Dystrophy Canada
- Site investigator, ASPIRO clinical trial (gene therapy for XLMTM), Astellas
- Sponsored pre clinical research (liver disease in XLMTM), Astellas
- Advisory committee, Gene Therapy Network (Novartis sponsored educational initiative, now inactive)

Genetic Medicine Strategies for Rare Genetic Diseases

Gene Therapy Definition (CADTH):
a set of strategies that modify the expression of an individual's genes or repair abnormal genes involving the administration of a specific nucleic acid (i.e., DNA or RNA) via a viral or non-viral vector



1. Nature Education. Gene-based therapeutic approaches. Available at: https://www.nature.com/scitable/topicpage/gene-based-therapeutic-approaches-3881. Accessed 15 November 2018;
2. Gambello MJ, Li H. *J Genet Genomics* 2018;45(2):61–70.

Key Approaches to Gene Therapy[1]

Gene therapies can be designed for targeted delivery and continuous, long-term activity of therapeutic genetic material[2,3]

	 **Gene transfer**	 **Gene augmentation**	 **Gene inhibition**	 **Gene editing**
Definition	The function of a dysfunctional or missing gene is replaced with a functional transgene	Addition of therapeutic genes that target a specific disease mechanism, often used to supplement a targeted therapy	Silences expression of a mutant gene that codes for a toxic protein or too much protein	The patient's genome is edited to correct a mutant gene that promotes disease, including point mutations or small inversions/deletions
Therapeutic potential	Monogenic diseases	Monogenic, complex, and infectious diseases	Disorders linked to toxic or over-expressed protein	Monogenic diseases and cancers

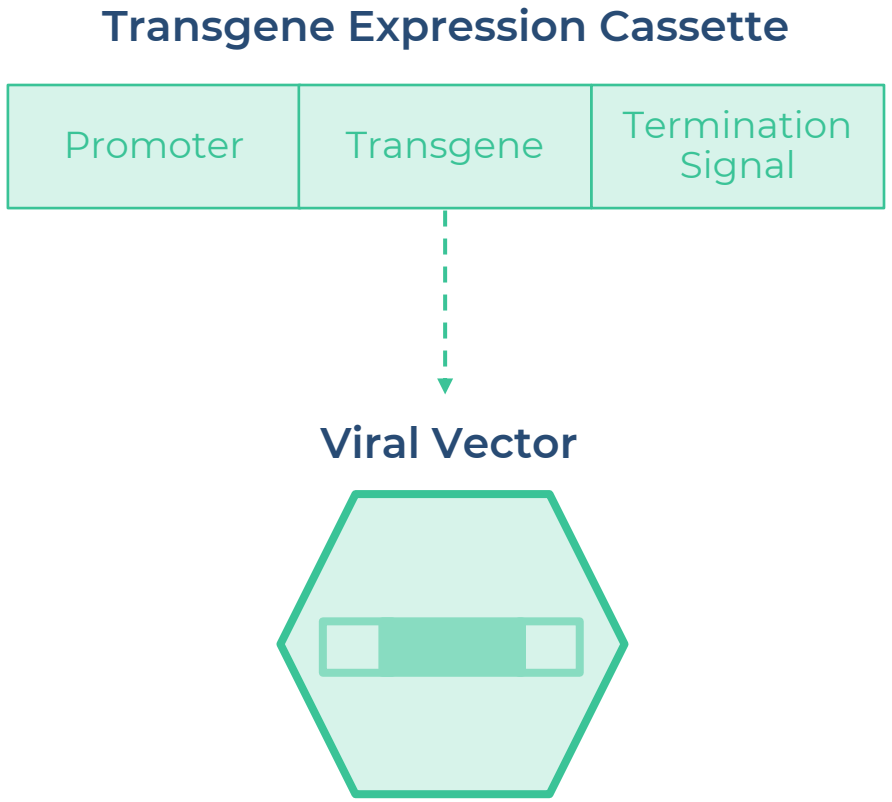
GRT Components

Three key components:

- the **vector**, or vehicle, which is injected into the patient and by which a transgene is delivered to the targeted cells[1]
- the **transgene**, which is a sequence of complementary DNA (cDNA) coding the replacement gene[1]
- the **promoter**, which is the DNA sequence that acts as a "turn on" switch and modulates the expression of the transgene[1]

Also typically includes, either:

- A **termination signal** to end gene transcription[1], or
- **Inverted terminal repeats (ITRs)** at either end of the cassette to allow for synthesis of complementary DNA[2]



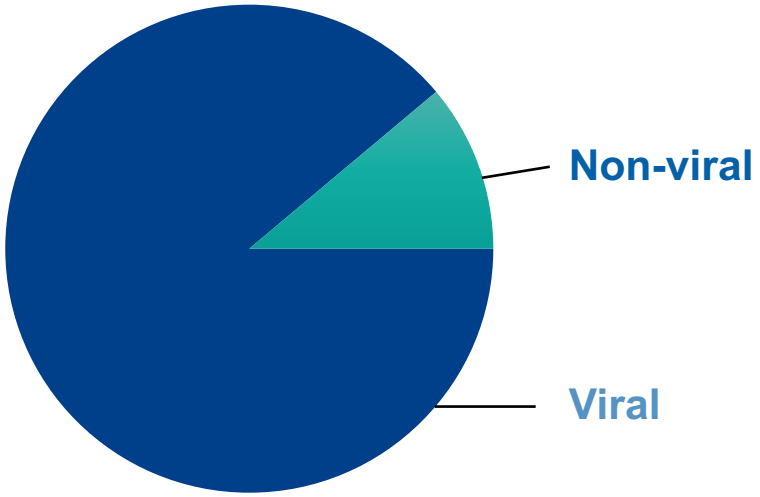
Adapted from Wang D. *Discov Med* 2014;18:67–77.

1. Wang D, et al. Discov Med 2014;18:67–77.
2. Ayuso E, et al. Curr Gene Ther 2010;10:423–436.

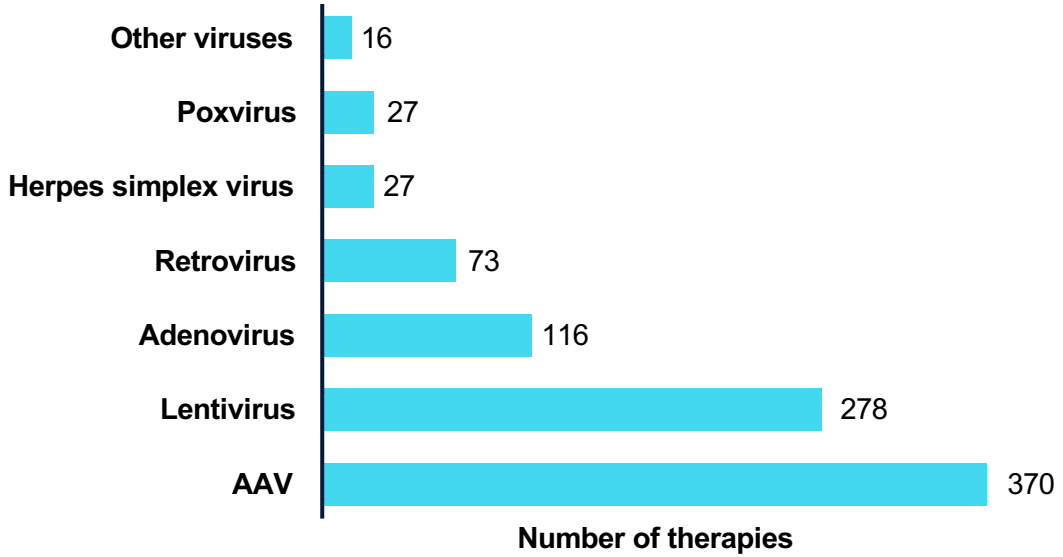
The Majority of Gene Therapies in Development Use AAV Vectors

88% of gene therapies in development use viral vectors, with AAV vectors being the most common

Viral vs Non-viral Gene Delivery



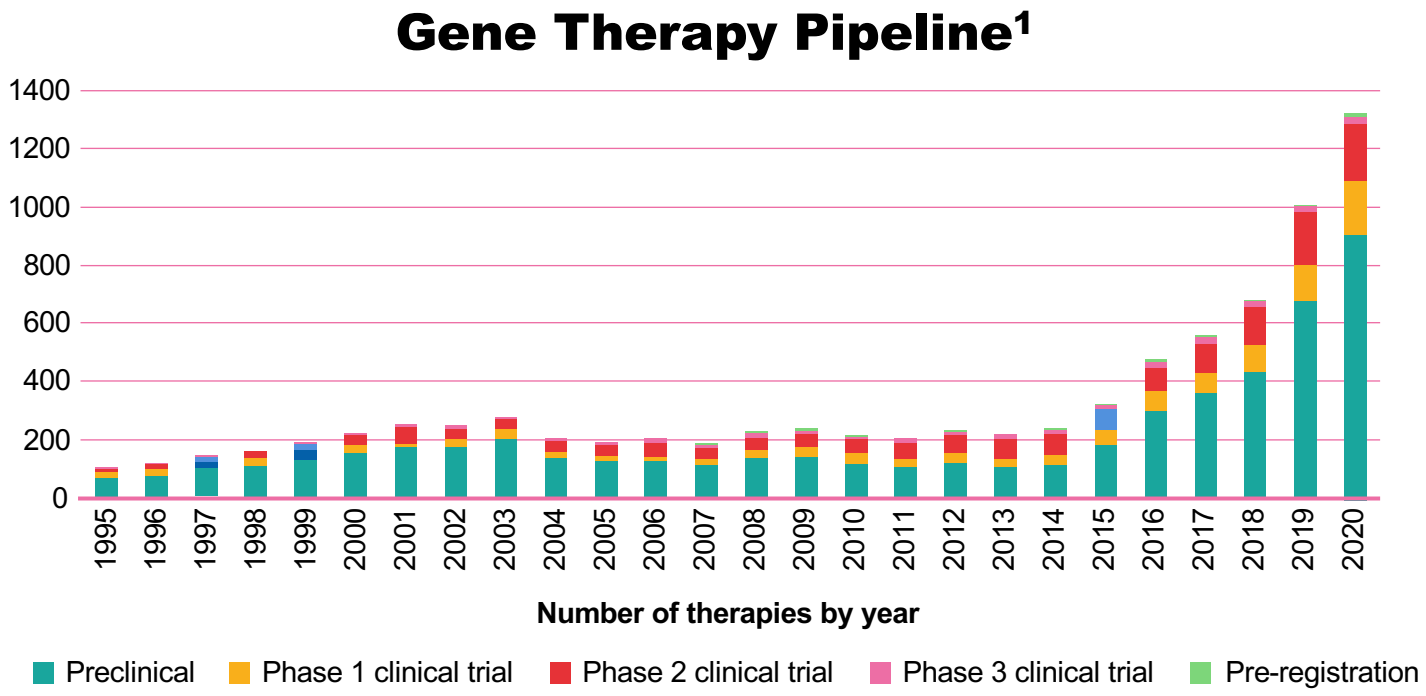
Viral Vectors Used in Pipeline Therapies



AAV, adeno-associated virus.
Figure adapted with permission from American Society of Gene and Cell Therapy.
American Society of Gene and Cell Therapy (April 2021). Accessed September 9, 2021.
https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-q1-2021.aspx

Multiple different AAV serotypes with different tissue distribution

There Has Been a Rapid Growth in the Gene Therapy Landscape in Recent Years



Neurological diseases are the most common non-oncology disease states targeted by gene therapies[1]

The number of gene therapy clinical trials has significantly increased over the last 30 years, with an increasing number of investigational new drug (IND) applications[2,3]

At present, > 2000 studies related to gene therapy listed in clinicaltrials.gov

A Range of AAV-based Gene Therapies for Rare Genetic Diseases Are in Clinical Development

Key: Phase | Viral vectors used | Targeted gene(s)

Giant axonal neuropathy (GAN)[1]

- *Phase 1*
- *AAV9*
- *GAN*

Batten disease[2-4]

- *Phase 1 and 2*
- *AAV9 / AAVrh10 / AAV2*
- *CLN6 / CLN2*

Familial Parkinson's disease[5-7]

- *Phase 1 and 2*
- *AAV2*
- *AADC / GDNF*

Pompe disease[8]

- *Phase 1*
- *AAV9*
- *GAA*

X-linked myotubular myopathy (XL-MTM)[9]

- *Phase 1 and 2*
- *AAV8*
- *MTM*

Duchenne muscular Dystrophy (DMD)[10-12]

- *Phase 1 to 3*
- *AAV9 / AAVrh74*
- *micro-dystrophin*

Spinal muscular atrophy[13-15]

- *Approved*
- *AAV9*
- *SMN1*

Safety and efficacy of gene replacement therapy for X-linked myotubular myopathy (ASPIRO): a multinational, open-label, dose-escalation trial

Perry B Shieh, Nancy L Kuntz, James J Dowling, Wolfgang Müller-Felber, Carsten G Bönnemann, Andreea M Seferian, Laurent Servais, Barbara K Smith, Francesco Muntoni, Astrid Blaschek, A Reghan Foley, Dimah N Saade, Sarah Neuhaus, Lindsay N Alfano, Alan H Beggs, Ana Buj-Bello, Martin K Childers, Tina Duong, Robert J Graham, Minal Jain, Julie Coats, Vicky MacBean, Emma S James, Jun Lee, Fulvio Mavilio, Weston Miller, Fatbardha Varfaj, Michael Murtagh, Cong Han, Mojtaba Noursalehi, Michael W Lawlor, Suyash Prasad, Salvador Rico

Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of *SMN2* (STR1VE): an open-label, single-arm, multicentre, phase 3 trial

John W Day, Richard S Finkel, Claudia A Chiriboga, Anne M Connolly, Thomas O Crawford, Basil T Darras, Susan T Iannaccone, Nancy L Kuntz, Loren D M Peña, Perry B Shieh, Edward C Smith, Jennifer M Kwon, Craig M Zaidman, Meredith Schultz, Douglas E Feltner, Sitra Tauscher-Wisniewski, Haojun Ouyang, Deepa H Chand, Douglas M Sproule, Thomas A Macek, Jerry R Mendell

Approved Gene Therapies

Gene therapies have been approved for the treatment of certain cancers and inherited diseases, including[1–13]:

	Agent	Disease Area	Approval date		
			US (FDA)	EU (EC)	China (NMPA)
***Ex vivo* treatments**	Autologous CD34+ cells encoding the human ADA cDNA sequence*[1,2]	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)	–	May 2016	–
	Tisagenlecleucel†[3–5]	B-cell precursor acute lymphoblastic leukemia; large B-cell lymphoma	August 2017; May 2018	August 2018	–
	Axicabtagene ciloleucel‡[6,7]	Large B-cell lymphoma	October 2017	August 2018	–
	Autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene§[8]	Transfusion-dependent β-thalassemia without β^0/β^0 genotype	–	May 2019	–
***In vivo* treatments#**	Gendicine[9]	Head and neck squamous cell carcinoma	–	–	October 2003
	Voretigene neparvovec-rzyl¶[10,11]	Bi-allelic *RPE65* mutation-associated retinal dystrophy	December 2017	November 2018	–
	Onasemnogene abeparvovec-xioi[12]	Spinal muscular atrophy	May 2019	–	–

*Brand name: Strimvelis®; †Brand name: Kymriah®; ‡Brand name: Yescarta®; §Brand name: Zynteglo™; ¶Brand name: Luxturna™; #Alipogene tiparvovec (brand name: Glybera) was approved by the EC in October 2012 for the treatment of familial lipoprotein lipase deficiency. However, due to extremely limited usage, it is no longer marketed13.
ADA, adenosine deaminase; cDNA, complementary DNA; EC, European Commission; FDA, U.S. Food and Drug Administration; NMPA, National Medical Products Administration (formerly the China Food and Drug Administration); RPE65, retinal pigment epithelium-specific 65 kDa protein.
1. GSK. Press release. May 27, 2016. Available at: https://www.gsk.com/en-gb/media/press-releases/strimvelistm-receives-european-marketing-authorisation-to-treat-very-rare-disease-ada-scid/. Accessed September 12, 2019; 2. European Commission. Strimvelis. Available at: https://ec.europa.eu/health/documents/community-register/html/h1097.htm. Accessed September 12, 2019; 3. U.S. FDA. News release. August 30, 2017. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-b-cell-all-and-tocilizumab-cytokine-release-syndrome. Accessed September 19, 2019; 4. U.S. FDA. News release. May 1, 2018. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm606540.htm. Accessed September 12, 2019; 5. European Commission. Kymriah. Available at: https://ec.europa.eu/health/documents/community-register/html/h1297.htm. Accessed September 12, 2019; 6. U.S. FDA. News release. October 18, 2017. Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm581296.htm. Accessed September 12, 2019; 7. European Commission. Yescarta. Available at: https://ec.europa.eu/health/documents/community-register/html/h1299.htm. Accessed September 12, 2019; 8. European Commission. Zynteglo. Available at: https://ec.europa.eu/health/documents/community-register/html/h1367.htm. Accessed September 12, 2019; 9. BioPharm International. Available at: http://www.biopharminternational.com/genesis-gendicine-story-behind-first-gene-therapy. Accessed September 12, 2019; 10. U.S. FDA. News release. December 18, 2017. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm589467.htm. Accessed September 12, 2019; 11. European Commission. Luxturna. Available at: https://ec.europa.eu/health/documents/community-register/html/h1331.htm. Accessed September 12, 2019; 12. U.S. FDA. News release. May 24, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease. Accessed September 12, 2019; 13. UniQure. Press release. April 20, 2017. Available at: http://uniqure.com/GL_PR_Glybera%20withdrawal_FINAL_PDF.pdf. Accessed September 12, 2019.

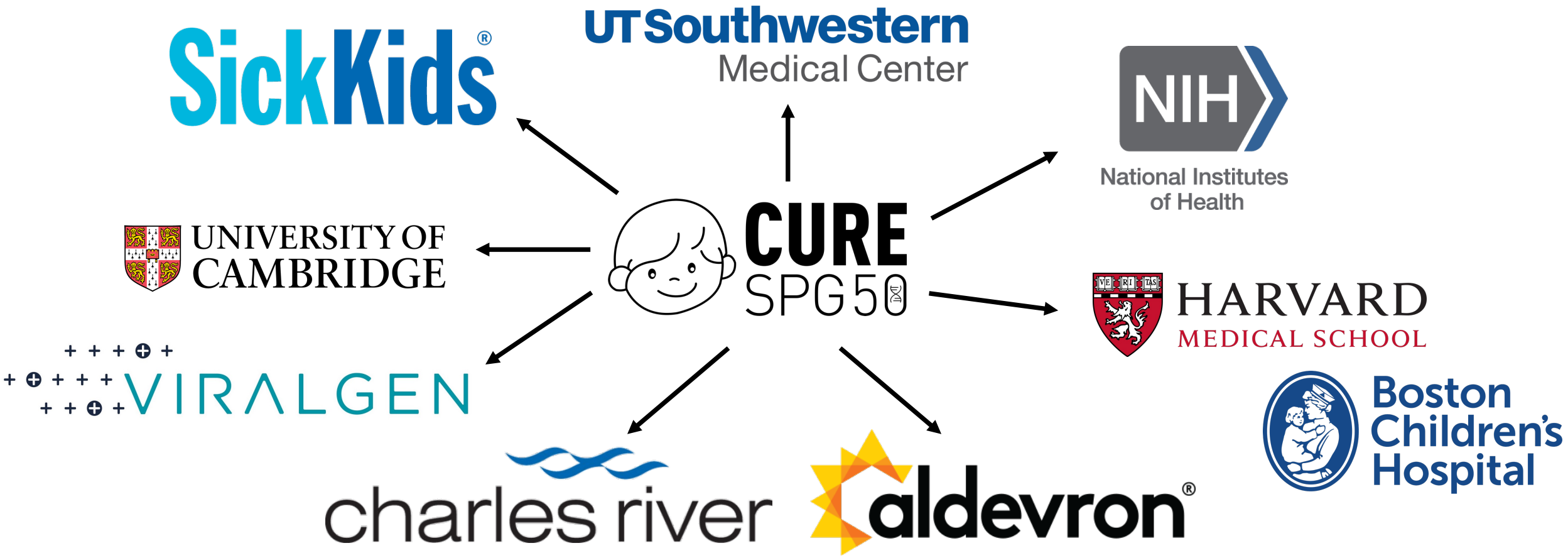
Future directions (and the future is now) part 1

- additional gene therapy programs are in clinical development (we need to ensure that these arrive in Canada)
  - need Canada to be represented in rare disease GT clinical trials
  - need GT approved outside of Canada to be rapidly brought here
- research
  - foster and support pre clinical development (expand group of diseases treated with AAV, new AAVs, new strategies for genes/diseases not treatable with AAV-GT)
- clinical infrastructure
  - develop clinical teams prepared to administer GT and then monitor after treatment
  - important administration and safety consideration related to GT that require specialized care teams
- **many more rare (and particularly ultra rare) diseases could be treated by gene therapy**
  - most are not of commercial interest to pharma
  - how do we move forward with developing gene therapy for all suitable rare diseases?

SPG50 (spastic paraplegia type 50)

- SPG50 is an autosomal recessive disease caused by biallelic pathogenic variants in the *AP4M1* gene
- Patients with SPG50 present in infancy with increased muscle tone and global developmental delay
- SPG50 is a progressive disease that leads to spastic quadriparesis, severe intellectual disability, seizures, and early death
- SPG50 is an ultra-rare disease with ~60 patients identified worldwide. There are approximately 9 patients with SPG50 in North America and **1 with SPG50 in Canada**

We endeavored to build a customized Gene Therapy with a 1st class team from around the world, focused on changing the lives of children with SPG50



Path To SPG50 gene therapy

Base Biology

Understanding the fundamentals of the disease and how it affects the patients

Began
April 2, 2019

Complete

Safety Testing

Officially test Gene Therapy to confirm safety for a clinical Trial

Ended Oct 2021

Complete

Gene Therapy

Create Gene Therapy & test that it works

Completed

Manufacturing

Manufacturing of Gene Therapy for a clinical trial

Begins April 1, 2021

Completed

In-Progress

Health Canada

Begin clinical trial in Nof1 child at SickKids Hospital

Began March, 2022

SickKids

FDA Application

FDA filing for the clinical of the gene therapy

FDA

In-Progress

Clinical Trial

Begin clinical trial in children affected by SPG50

Expected To Begins Aug, 2022

FDA Approval

Treatment day – March 24, 2022

The trial so far

- Safety (adverse events)
  - therapy generally well tolerated with no grade 4 or 5 serious adverse events (SAE)
  - transient neutropenia 4-6 weeks post treatment (no intervention required)
  - episodic abdominal pain at 5-6 months post treatment (infection vs tacrolimus side effect)
- Efficacy
  - measured by qualitative assessment and two spasticity scales
  - improvements in time standing and tolerance of therapy
  - stabilization of spasticity
  - improvements in development

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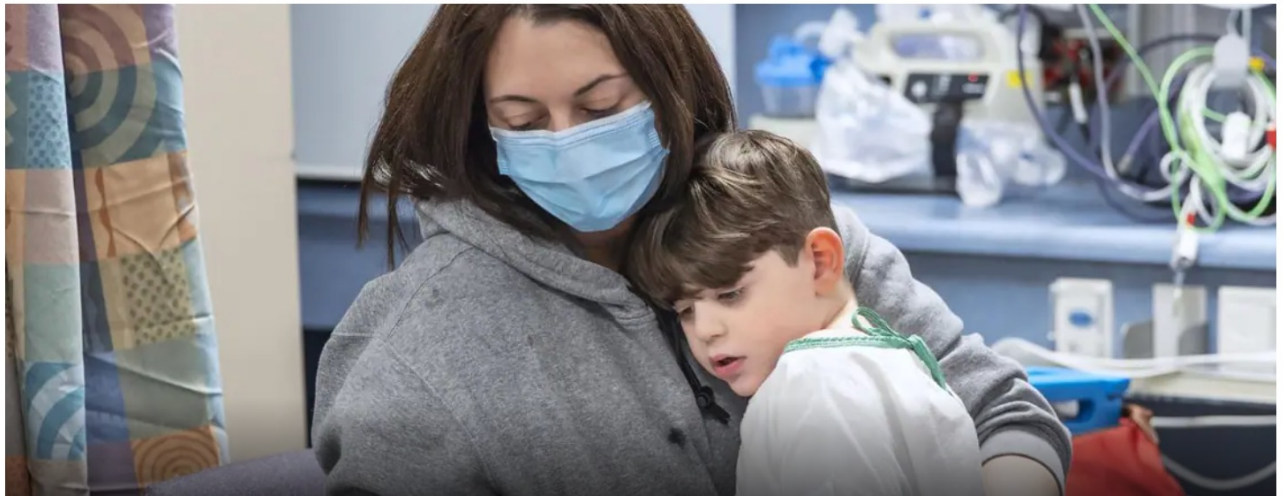
Toronto boy whose parents raised $3M to treat his rare genetic disorder starts clinical trial

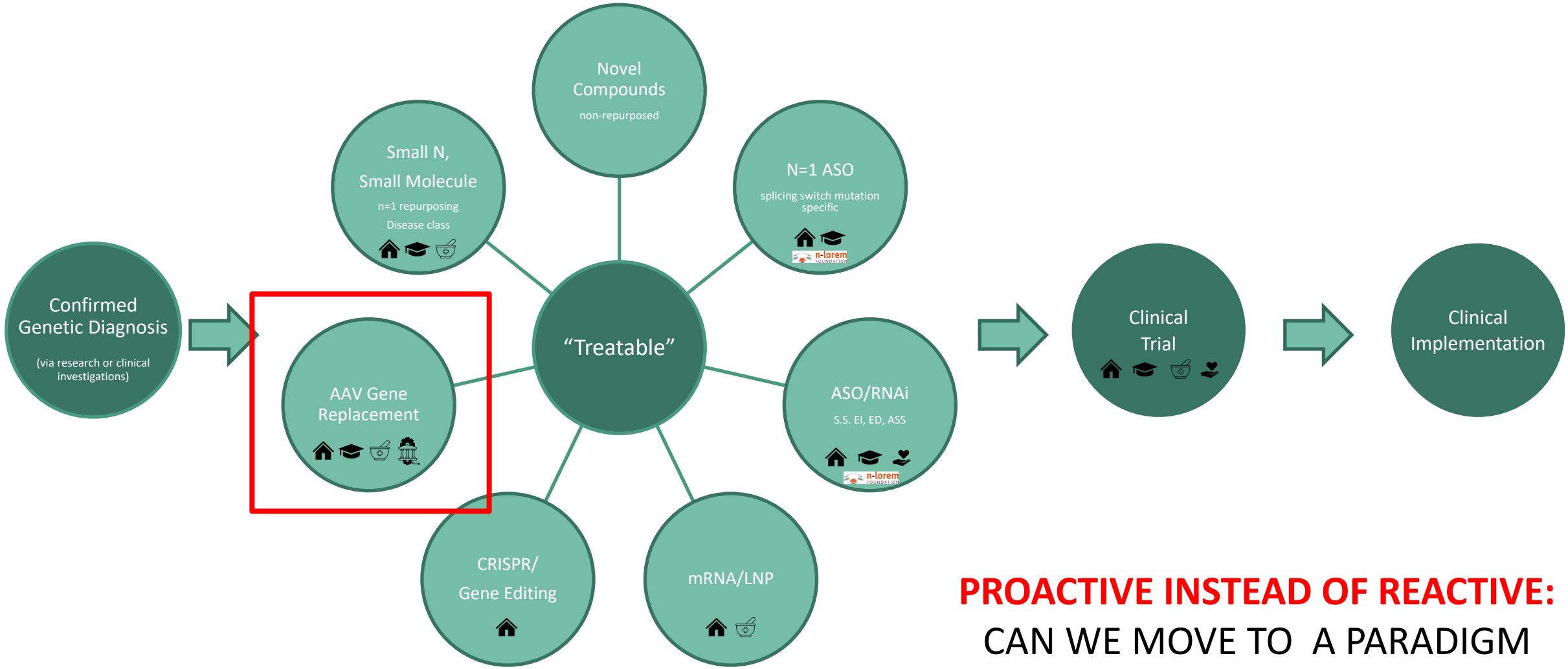
Michael Pirovolakis is the only participant in the groundbreaking clinical trial

Ioanna Roumeliotis, Perlita Stroh · CBC News ·
Posted: Aug 15, 2022 4:00 AM ET | Last Updated: August 16



Summary

- We performed a First-In-Human, single patient gene therapy trial for SPG50
  - This represents one of the first N=1 gene therapy trials for rare disease
- Trial is on-going, but thus far the treatment has been well tolerated, and qualitative improvements in motor function have been noted
- A phase I/II/III trial for SPG50 (n=10) has received FDA permission to proceed
- **Can this trial serve as a springboard for how we develop therapies for all patients with nano rare genetic disease?**



Feasibility

- In house
- Academic
- Foundation
- Industry
- N-Lorem
- Government

PROACTIVE INSTEAD OF REACTIVE:

CAN WE MOVE TO A PARADIGM WHERE WE CONSIDER (AND THEN DEVELOP) PERSONALIZED THERAPY FOR ALL RARE DISEASE PATIENTS?

Our approach to individualized therapy development for rare disease: SickKids PCH Centre for Advanced Therapeutics (CRAFT)

1

rare or ultra-rare disease or variant

2

3a

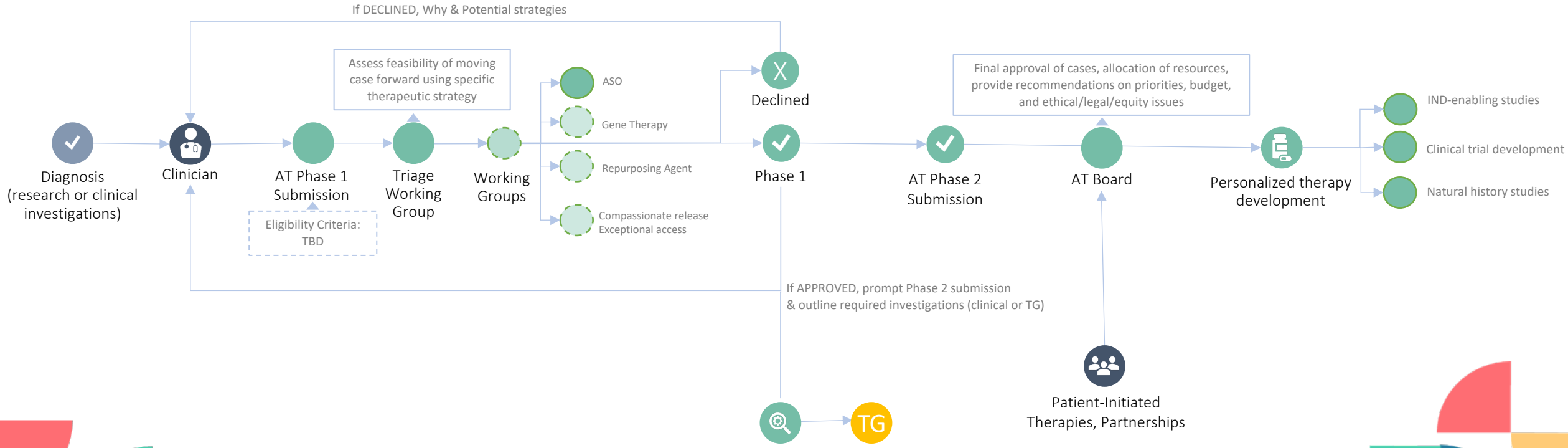
, RNASeq

3b

4

clinic

Our approach to individualized therapy development for rare disease: SickKids PCH Centre for Advanced Therapeutics (CRAFT)



How do we ensure equitable access to advanced therapeutics at SickKids? What do we need to consider?

How do we ensure equity and inclusion as we develop precision therapeutics? Advanced Therapeutics Board

Scope of the Board

- Review cases selected for individualized therapy development
- Determine resource allocation and prioritization of cases
- Provide final approval to move to clinical development
- Provide recommendations on node priorities and ethical, legal, and equity issues

CRAFT Board Members

Gregory Costain, MD, PhD
Clinical and Metabolic Genetics

James Dowling, MD, PhD
Neurology

Brian Kalish, MD
Neonatology

Wendy Bordman, BScPharm, CDE, RPh
Pharmacy

Lauren Dempsey
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Brent Derry, B.Sc., M.Sc., PhD
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Ashish Deshwar, MD, PhD
Developmental & Stem Cell Biology, Genetics & Genome Biology

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Elizabeth Stephenson, MD, M.Sc.
Cardiac Electrophysiology, REB

Stephanie Telesca, MS, CGC
Patient Advisor

Randi Zlotnik Shaul, JD, LLM, PhD
Bioethics

TOGETHER (The Ontario Gene Therapy Network)

- Goal: create a community of scientists, clinicians, advocates, patients/families to help advance gene therapy
- Ultimate goal – creation of a Canada wide gene therapy network/society

- Progress thus far:
  - hosted Toronto focused GT meeting in Spring 2023
  - seed funding for academic GT pre clinical development project
  - clinical working group at SickKids focused on implementation and treatment
    - developing SOPs related to common side effects and challenges of GT
  - Ontario focused GT meeting in Spring 2024

Summary and future thoughts part 2

- Gene therapy is an exciting modality with the potential for treating many rare diseases by addressing their root cause
  - The first successful programs have led to clinically available GT for a (very) small number of
- GT has important and unique clinical care requirements and has a high cost
- GT can be developed for even ultra rare diseases
  - n=1 GT for SPG50
- WE HAVE THE ABILITY TO MAKE GENETIC THERAPIES FOR 100s OF ELIGIBLE DISORDERS.
  - WE NEED TO DO THIS…. BUT HOW????

Thanks!

- SK Neurogenetics clinical trial team -> Hernan Gonorazky, Ana Stosic
- SPG50 -> Terry Pirivolakis , Keshini Devakandan, Steven Gray
- TOGETHER -> Kim Amburgey
- SK Gene Therapy team -> Hernan Gonorazky, Elisa Nigro
- SK PCH Advanced Therapeutics -> Greg Costain, Brian Kalish, Tomasz Czerny, Eriskay Liston, Kim Amburgey

- contact (Jim Dowling): james.dowling@sickkids.ca

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  - Salma Gessiah
  - Zachary Coulson
  - Mo Zhao
  - Emmy Pannia
  - Evangelina Aristegui
  - Vanessa Raileanu
  - Lily Huang

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  - **Bob Dirksen**
  - Carsten Bonnemann
  - **Alan Beggs**
  - Matt Alexander
  - E RARE team (Volker Hauke, **Bernard Payastre/Julien Viaud**, Jocelyn Laporte, Ale Bolino)
  - Susan Hamilton
  - Eva Feldman (K08 Mentor)
  - Lois Weisman and Miriam Meisler

  - <u>NM project (Coen Ottenheijm and Henk Granzier)</u>

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

NSERC CRSNG

myotubular trust
FINDING STRENGTH

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases
NATIONAL INSTITUTES OF HEALTH

GenomeCanada

MDA