Gene Therapy for Xeroderma Pigmentosum Cockayne Syndrome (XP-CS) and XP- Neurological Disease (XP-ND)

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Driven to Discover®

Outline:

- UMN DNA Repair Disorder Gene Therapy Program
- Gene Therapy 101
- Pre-clinical gene therapy development in a mouse model of XPG deficiency
- Future directions

UMN Gene Therapy Program

Clinical Studies

(Dr. Kang's team)

- Natural history studies (XP, CS, TTD, and others)
- Clinical trial planning

Pre-Clinical Studies

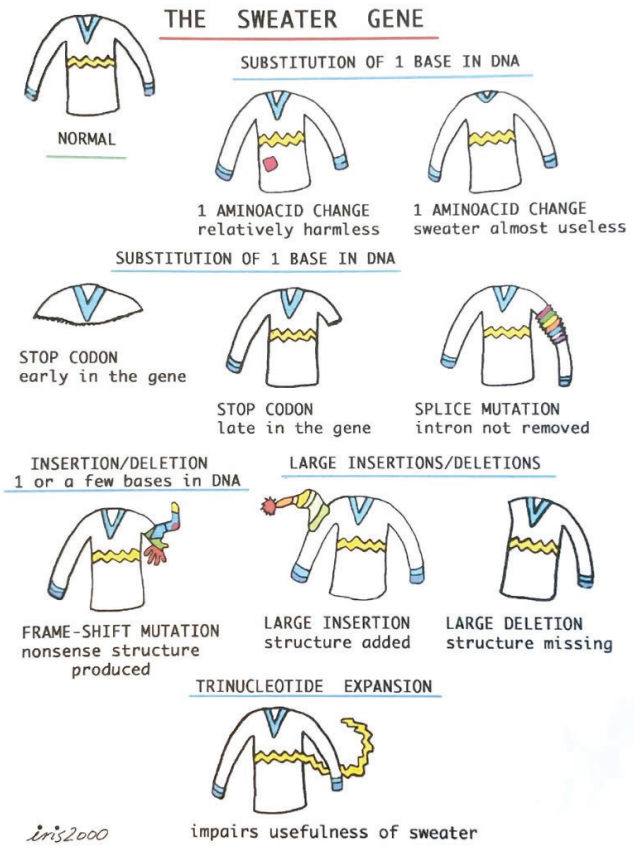
(Pacak Lab)

- Model development
- Gene therapy optimization

Manufacturing

(Aslanidi Lab)

- Capsid development
- Scaling up, product quality control



Iris Gonzales

Gene Therapy

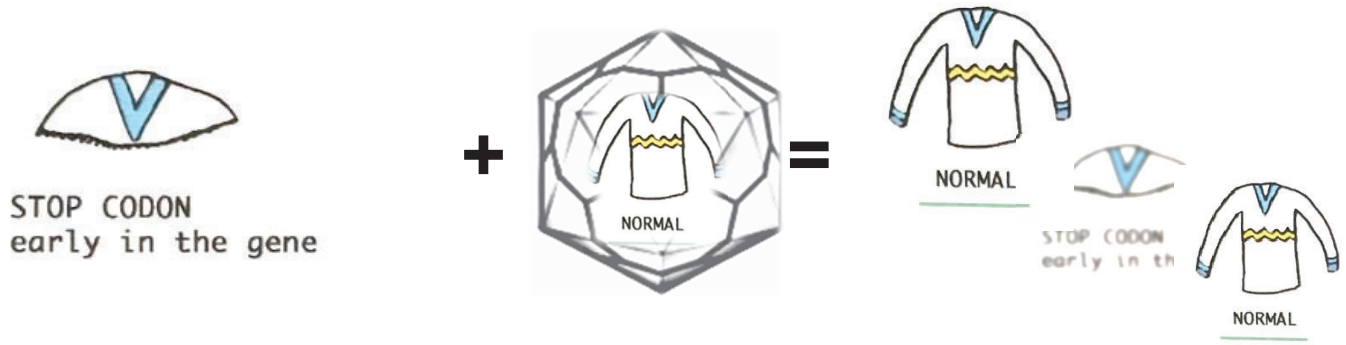
- **Gene delivery** – delivery of a healthy version of cDNA into cells with a missing or defective version
- **Genome editing** – delivery of genetic components needed to edit the genome directly (many different versions exist). The approach taken depends upon the genetic variant

Similar Challenges Exist

- Either approach requires the ability to deliver genetic material

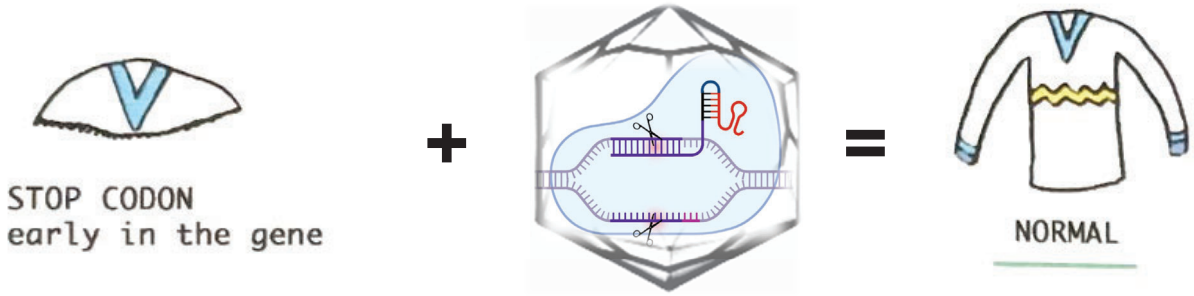
Gene Therapy – Gene Delivery

- **Gene delivery** – delivery of a healthy version of cDNA into cells with a missing or defective version



Gene Therapy – Genome Editing

- **Genome editing – delivery of genetic components needed to edit the genome directly (many different versions exist). The approach taken depends upon the genetic variant**



Usually patient specific

Gene Therapy (Gene Delivery) - Our goals:

- **Long-term expression**
- **Focus on neurological tissues but would be wonderful to treat skin or other targets as well – avoid the liver**
- **Ameliorate the disease phenotype and improve quality of life**
- **Minimal effective dose**
- **Patient safety**

Gene Delivery Vehicles

Many exist (plasmid delivery systems, retroviruses, lentiviruses, adenoviruses, adeno-associated viruses, extracellular vesicles) and all have strengths and limitations

Adeno-associated virus (AAV)

Adeno-Associated Virus (AAV)

- **Discovered as a contaminant in adenovirus preparations – requires help for replication**
- **Recombinant AAV (rAAV) used for gene therapy lacks elements necessary for replication**

Wild-Type AAV (wtAAV)

4,680 bp

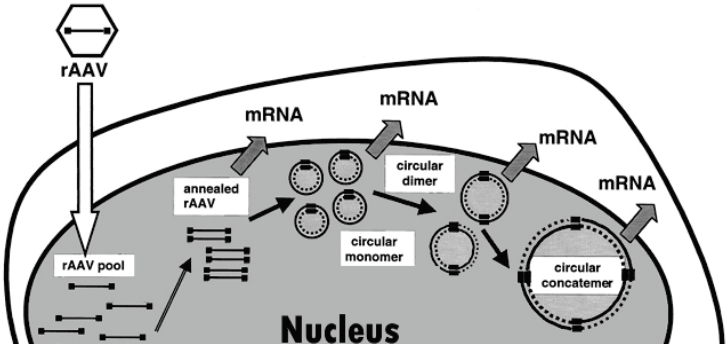
Recombinant AAV (rAAV)

Up to ~5,000 bp

Humoral Immunity to AAV Vectors in Gene Therapy: Challenges and Potential Solutions
June 27, 2013. Elisa Masat, Giulia Pavani, Federico Mingozzi

General AAV Attributes

- rAAV persists as an episome within the nucleus – stable for many years *in vivo* in non-dividing cells and eventually diluted out in dividing cells
- Integration into the genome is extremely rare
- This has implications for treating a target like skin



http://signagen.com/AAV-FAQs

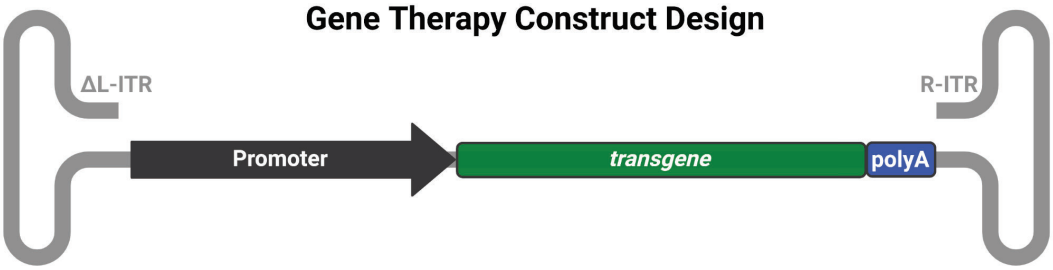
Control of Expression – Many Layers of Optimization

- Capsid serotype
- Vector sequence design
- Dose
- Delivery route

Control of Expression - Capsid Serotype Selection

- Many natural and engineered serotype options – different AAV capsids have different tissue tropisms
- Capsid choice influences many things: AAV packaging, receptor binding preferences, efficiencies can be destroyed or enhanced, tendency for degradation pathways depending upon receptor, trigger host immune response

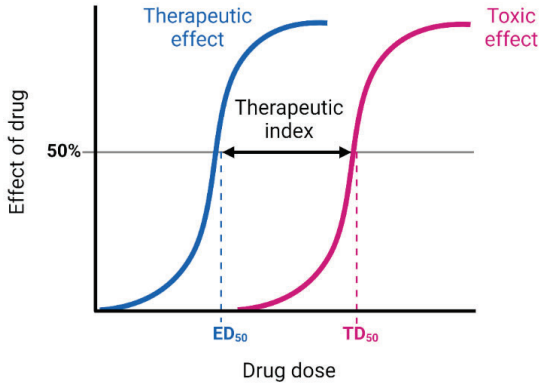
Control of Expression – Vector Sequence Design



- Promoter choice: Can be general or tissue restrictive
- Codon optimization (human co*ERCC5*)

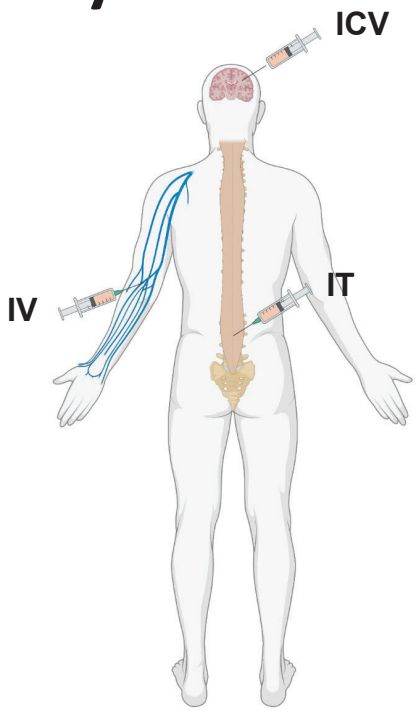
Control of Expression – Dose

- **Dosage studies guide how much is needed to achieve a therapeutic effect (start low and go higher) (MED)**



Control of Expression – Delivery Route

- **Delivery route:**
  - **Intravenous (IV) (systemic)**
  - **Intrathecal (IT) (spinal cord)**
  - **Intracerebral Ventricle (ICV) (direct brain administration)**



Gene Therapy Risks

- Risk tolerance of patient and family depends upon many things – gene therapy cannot be undone.
- Clinical trials determine how safe and effective a therapy is at relieving symptoms or treating aspects of a condition.
- Informed consent is essential
  - May or may not provide benefit
  - May or may not be exposed to unknown risks
- Even approved gene therapies can carry risk due to immune responses

AAV Gene Therapy Successes

- Luxturna – FDA approved therapy for inherited retinal disease (Biallelic RPE65 mutation-associated retinal dystrophy)

- Zolgensma - FDA approved therapy for spinal muscular atrophy (SMA).

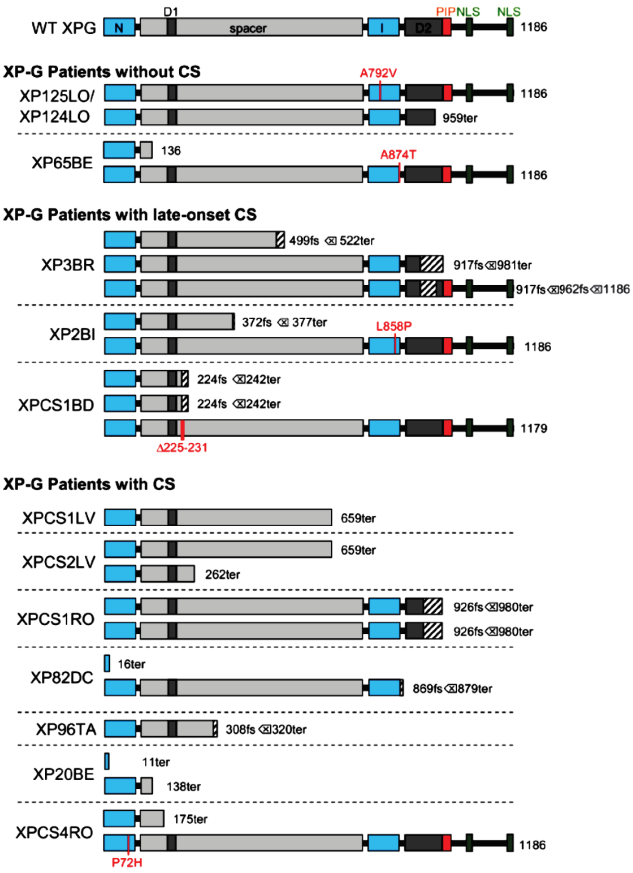
(*Watching these patients to understand therapeutic durability)*

Pre-Clinical Gene Therapy Studies
(XP-CS, XP-ND, CS, TTD, etc.)

- **Model development: mice, induced pluripotent stem cells (iPSCs) differentiated into neurological cells and organoids**
- **Gene therapy optimization (general for the program):**
  - **AAV capsids**
  - **Promoters**
  - **Delivery routes**
  - **Doses**
- **Gene therapy for XPG deficiency (*ERCC5*) – good mouse model of XP-CS**

XPG/*ERCC5*

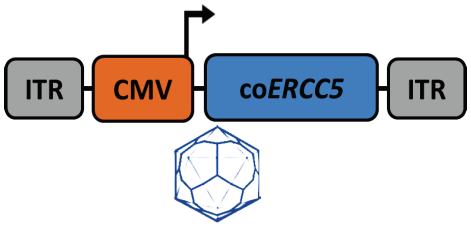
- Wide range of clinical phenotypes
- XPG mutations that lead exclusively to XP symptoms are deficient in NER
- XPG likely has important role/s outside of NER
- May play an important function in RNA polymerase II transcription (the XPG homologue Rad2 in *S. cerevisiae* does) through TFIIH



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721477/

Gene Therapy for XP-CS:
Experiment 1 - IV administrations

- Xpg$^{-/-}$ mouse model IV delivery of AAV-*ERCC5*



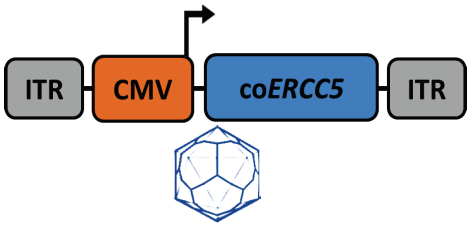
Silveli Suzuki-Hatano, Audrey Daugherty

XPG Experiment 1 (IV) Conclusions:

- **Gene therapy can have a beneficial effect in XP-CS (delayed onset of neurological phenotypes and improved survival)**
- **However - Doses are too high**

Gene Therapy for XP-CS:
Experiment 1 - IT administrations

- **Xpg$^{-/-}$ mouse model IT delivery of AAV-*ERCC5***



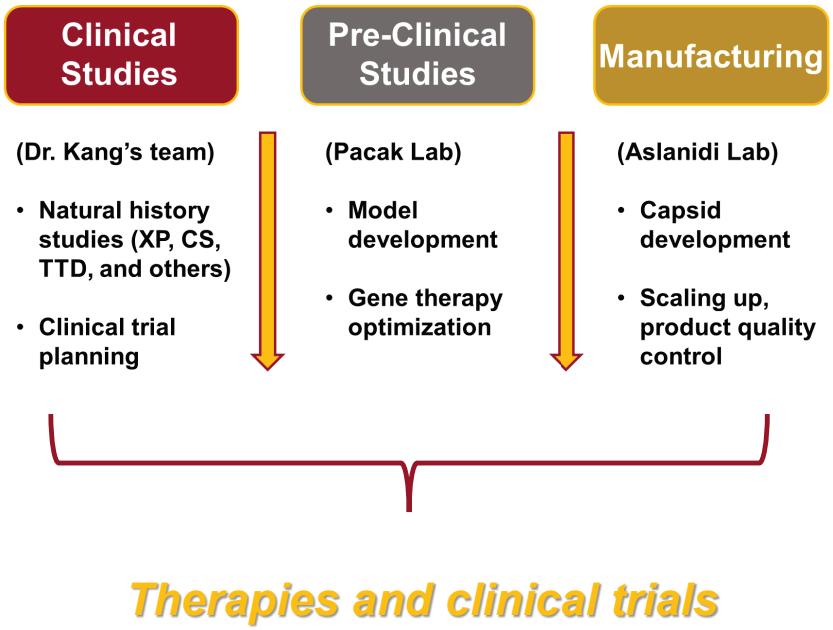
Monika Chauhan, Ellie Khadir, Audrey Daugherty

XPG Experiment 2 (IT) Conclusions

- **Delayed onset (prevention) of some aspects of neurological phenotypes**
- **Some improvement in survival**

Will use this information to guide further optimizations (delivery route, promoter, capsids)

Ongoing Work!



A good gene therapy resource…

- American Society of Gene and Cell Therapy website (ASGCT.org – patient education)

Thank you!

Thanks to those participating in research studies!

Collaborators

Peter B. Kang (UMN Pediatric Neurologist)

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