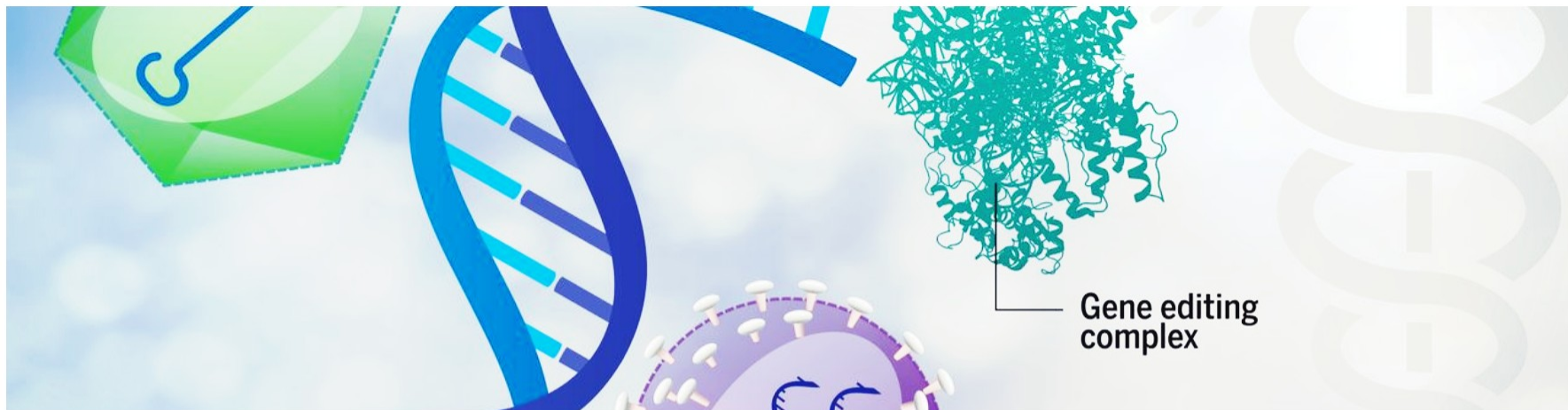




GENE THERAPY CLINICAL TRIALS

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April, 2019



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SUMMARY

- **GENE THERAPY UNIQUENESS**

INVASIVENESS (in vivo) or COMPLEXITY(ex-vivo)

DURABILITY

- **PLACEBO CONTROL IN GTCT.**

- **PATIENT RECRUITMENT**

AVOIDING “THERAPEUTIC MISCONCEPTION”

GENE THERAPY DEFINITIONS

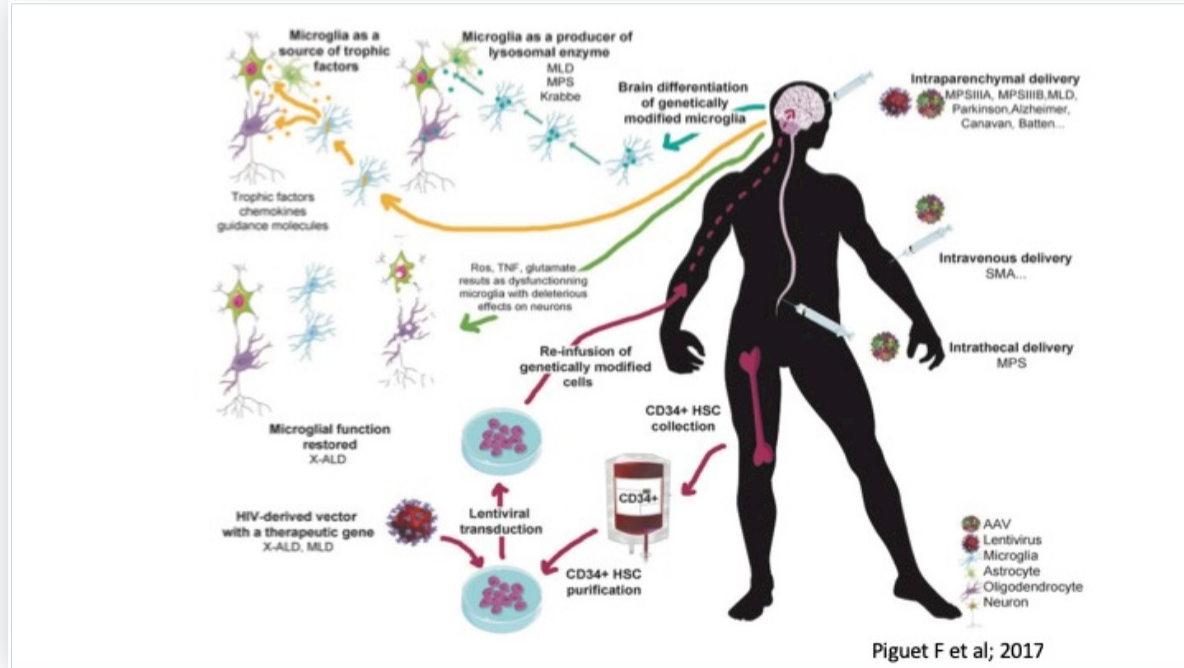
EMA

Gene therapy medicinal products generally consist of a vector or delivery formulation/system containing a genetic construct **engineered to express a specific transgene** (therapeutic sequence) for the regulation, repair, replacement, addition or deletion of a genetic sequence. By using such gene therapy constructs in vivo, genetic regulation or genetic modification of somatic cells can be achieved in situ. The same gene therapy vector can be used ex vivo for the manufacture of genetically modified cells.

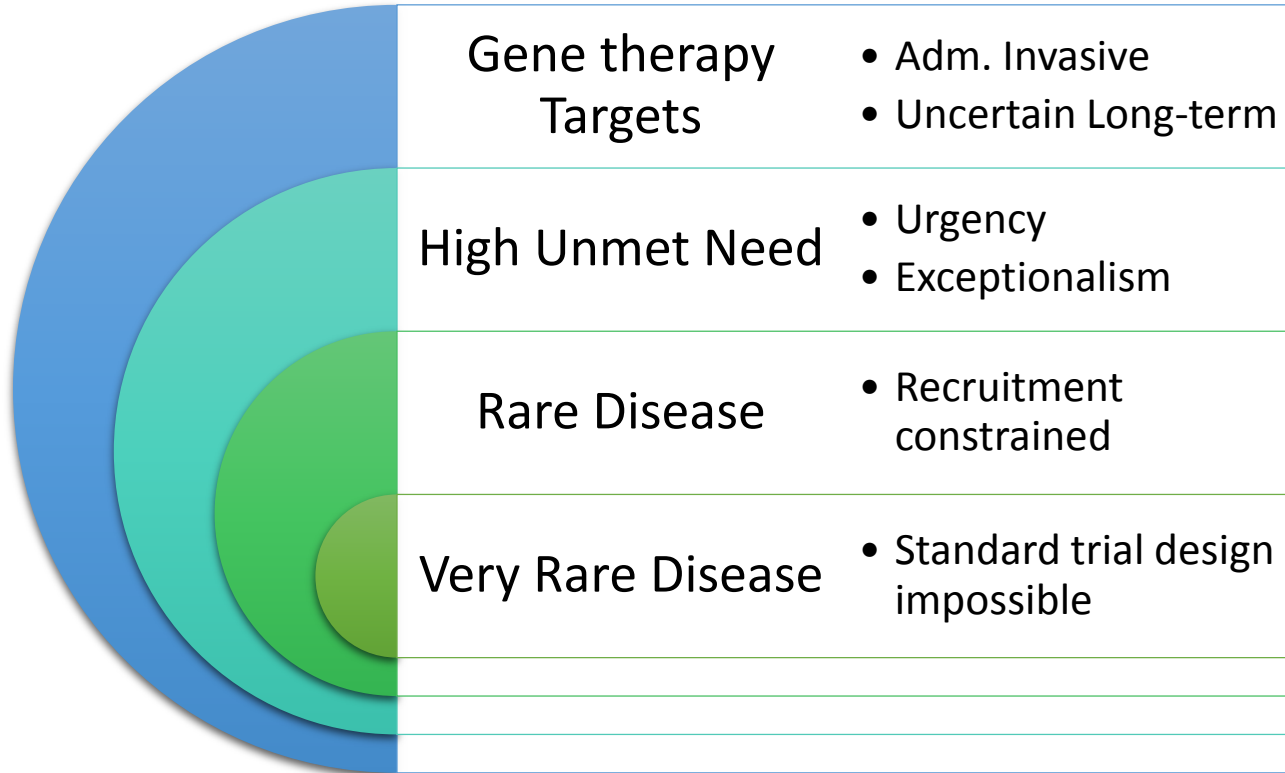
FDA

GTMP is a **product that mediates their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome** and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient.

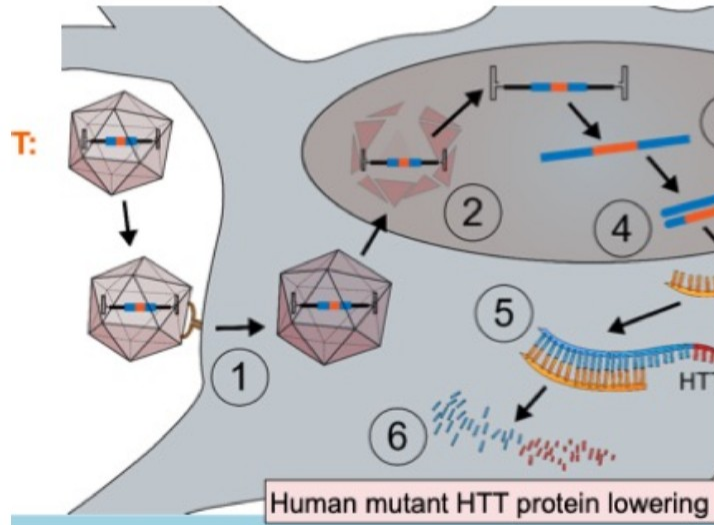
GT FOR CNS DISEASES - INVASIVE/COMPLEX ADMINISTRATION



Gene Therapy Clinical Trials – Uniqueness



HUNTINGTON'S DISEASE 1ST GTCT START ANNOUNCED IN JAN 2019.



- AMT-130 COMPRISES A RECOMBINANT AAV5 VECTOR CARRYING A DNA CASSETTE ENCODING A MICRORNA THAT NON-SELECTIVELY LOWERS OR KNOCKS-DOWN HUMAN HUNTINGTIN PROTEIN IN HUNTINGTON'S DISEASE PATIENTS.

IMPORTANT CONSTRAINTS IN GTCT IN NEURODEGENERATIVE DISEASES

EVEN FOR NON-RARE DISEASES THE NUMBER OF POTENTIAL PARTICIPANTS IS SMALL.

The invasiveness/complexity of administration makes scalability of procedures difficult.

PARTICIPANTS

Too high expectations

Too much progressed

PLACEBO/ SHAM/DUMB INTERVENTION ARE COMPLEX

Logistics and Practice difficult to implement.

OUTCOMES

Timeline for clinical readout is long.

Paucity of “reasonably like” surrogates.

Monitoring of Gene expression in the target organ/ ROI limited.

SOLUTIONS FOR GTCT IN NEURODEGENERATIVE DISEASES

“Traditional” therapies set for incremental improvements

Augmented Information need before trial compared to “traditional” therapies.

PERSECUTION OF LARGE EFFECT SIZES IN SOME CASES CURATIVE EFFECT.

LONG DURABILITY OF EFFECT, EVENTUALLY LIFE LONG.

RISK MITIGATION

“Traditional” therapies last for the duration of the administration.

GTCT IN NDD ARE TYPICALLY SMALL IN SIZE AND COMPLEX HOWEVER A PLACEBO/SHAM/DUMB ARM IS OF CRITICAL IMPORTANCE TO SECURE BLINDING.



AVOIDS SAFETY UNDER OR OVER REPORTING



**ALLOWS BALANCED
INTERPRETATION OF
BIOMARKER AND EARLY
EFFICACY DATA**



**HELP MANAGE
PARTICIPANT
EXPECTATIONS.**

PARTICIPANTS HIGH EXPECTATIONS MAY BE CONSEQUENCE OF “THERAPEUTIC MISCONCEPTION”

- **THERAPEUTIC MISCONCEPTION EXISTS WHEN INDIVIDUALS DO NOT UNDERSTAND THAT THE DEFINING PURPOSE OF CLINICAL RESEARCH IS TO PRODUCE GENERALIZABLE KNOWLEDGE, REGARDLESS OF WHETHER THE SUBJECTS ENROLLED IN THE TRIAL MAY POTENTIALLY BENEFIT FROM THE INTERVENTION UNDER STUDY OR FROM OTHER ASPECTS OF THE CLINICAL TRIAL.**

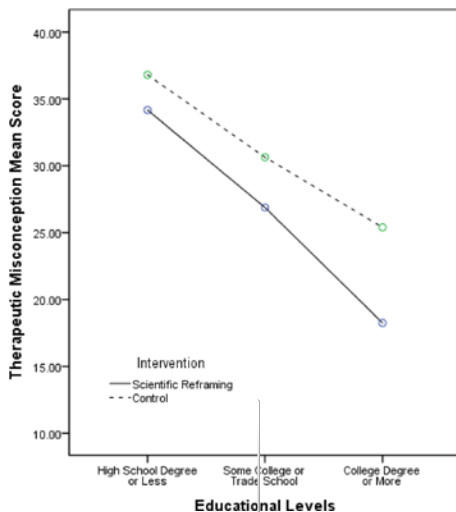


Fig 2. Group differences in therapeutic misconception scores by educational level.

RESEARCH ARTICLE

Reducing therapeutic misconception: A randomized intervention trial in hypothetical clinical trials

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TAKE HOME MESSAGE

- Standards of evidence for Gene Therapy must guarantee proof of efficacy and solid safety data.
- GTCT will necessary be smaller than trials for traditional therapies because of scalability issues.
 - GTCT major advantage is the potential large effect sizes of the therapeutic benefit.
- Management of the expectations both for participants and health professionals (and media) is critical.