Stem Cell and Gene Therapy for Ocular Genetic Disease

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Trial details?
Today’s talk

- basic principles
- where are we at
  - trials and tribulations
  - challenges
- where are we headed
- accessibility
- Q & A
Why bother finding genes?
Gene=Diagnosis/Counseling
Gene=Etiology=?Cure
Gene Therapy: The Eye

Immune privilege
Accessible (injections in/around eye)
Target cells can be visualized
Hard vs easy

Topical?
Gene Therapy: Routes

injections
  peribulbar
  AC
vitreous
subretinal
Metalloproteinase gene [increased] transcription in human ciliary muscle cells with latanaprost
Weinred RN, Lindsey JD, IOVS 2002;43:716-722

= Gene Therapy!!
What is “gene therapy”? 
Gene Therapy

- replaces protein
- up/down regulate genes
- replaces genes/gene function
- fix genes
Gene Therapy

regulation control
e.g. apoptosis
   up: bcl-2, bcl-x
down: p53, Bax
regulate other steps
   PR1 downregulates NR2E3
   promotes cones over rods
   Rx for rod disease
Gene Therapy: Inheritance Patterns

- autosomal recessive
  - replace gene function
- autosomal dominant
  - increase expression of nl allele
- dominant negative
  - inhibit abnormal allele
Gene Therapy

prerequisites...

- genetics of disease understood
- Rx is efficient & nontoxic
- control of gene expression
- animal model for testing
Gene Therapy: Viral Vectors

*adeno-associated viruses (AAV)*

limited capacity
Human LCA Gene Therapy

2008 NEJM
RPE65 (LCA2)

UK n = 3 young adults
no improvement

Phila n = 3 young adults
1 macular hole (larger volume injection)
slight vision and VF improvement
1 change in function

...the process had started...
Human LCA Gene Therapy

Lancet 2009

12 patients, 8-44 y/o (4 kids)

Phila and Italy

one eye (worst) in each

subretinal viral vector
Human LCA Gene Therapy

Lancet 2009

1 foveal hole
All say vision better
  acuity: 7 better, 1 worse, 4 same – no correlation with age
  improvements small but real
Authors say all VF’s better (not really)
Flat ERG’s before and after
follow up stable

obstacle course in kids dramatic improvements
Luxturna

Approved by FDA Jan 2018

biallelic $RPE65$

$\geq 1$ year old
Other trials...

Other LCA genes
  CEP290 – mask an intron
Retinitis pigmentosa genes
  USH2A – break in two and rejoin
  XLRP
Choroideremia – disappointing?
JXLR – disappointing?
And more…
Other trials

Stargardt
gene based
lipofuscin removal
LHON (11884)
Neuronal ceroid lipofuscinoses
Achromatopsia gene therapy

Sheep, dogs...
Will it work in humans?

we are not sheep, dogs etc
answer: we don’t know!
= do research
Gene agnostic approaches

siRNA
Rod derived cone viability factor
Anti-apoptosis (retinal rescue)
Optogenetics
And more…

Stem cell?
Stem cell

3mm skin punch
convert fibroblasts to stem cells
to photoreceptors
CRISPR correct
reimplant
500,000 cells
Stem cell

Do you even need a gene?

ex vivo fix before implant

vs

late onset dx implant without fix

Or use agnostically

e.g. cone viability factor

intravitreal?
From small to big dreams...
PAX6 gene
This is exciting!!

But…
Is this success?

RPE65 = 1 gene

20 years

maybe 250 eligible people

only works on some

< 10 centers

$425,000 per eye!!!
Questions remain

when to treat?
  early vs later?
  presymptomatic?
does treatment place limits?
durability?
what about the ultra rare genes?
who should treat?
who should pay?
what is “success”?
Ethical Issues?
Eugenics??

Source Nature Genetics
Eugenics?

Mancuso K et al:
Gene therapy for red-green colour blindness in adult primates
Nature 2009
Redheaded donors not wanted at world’s largest sperm bank

20/09/2011 01:58:00 AM

by Monica Burzgari

Cryos International, the world’s leading sperm bank, is turning away redheaded donors because of a low demand for redheaded children. Why is there a preference for non-redheads?

If given the choice, would you have a redheaded child? According to the world’s largest sperm bank, Cryos International, the answer for most people is no.

The sperm bank, which supplies over 65 countries, is no longer accepting sperm from redheads because of a low demand for redhead babies. The bank’s stores are at full capacity, and there are already 600 redheads on a donor waiting list.

Ola Shou, the bank’s director, believes that clients do not choose to have redheaded children unless the sterile male has red hair himself or the single mother is a redhead.
The desperate patient
Patients ask

Does it apply to me?
Will it ever apply to me?
What can I do to get gene therapy?
The Process…

adults first
poor vision first
Phase 1, 2, 3…
observation period for each phase
limited enrollment
inclusion/exclusion criteria
But...

every family/patient is different
unpredictable results
stopping progression vs Va reversal
How do I know if there is a study going on?

http://www.clinicaltrials.gov/

Need someone “in the know”
It isn’t treatment!!
Get a gene diagnosis!!
I tell my patients...

Diagnosis first!
extensive workup
clinical phenotype
DNA etc testing
genotype
The Holy Grail
The “rest of the world”
The “rest of the world”

Most of the world remains poor or low-income

- Poor: 29% (2001), 15% (2011)
- Low income: 50% (2001), 56% (2011)
- Middle income: 7% (2001), 7% (2011)
- Upper middle income: 9% (2001), 7% (2011)
- High income: 6% (2001), 7% (2011)
Low income

71% of world lives on < $10/day

Luxturna = $425,000 per eye
$1164/day for one year!
Can they get gene therapy?

What does it take to get there?

diagnosis
clinical
diagnostic testing (OCT etc)
genetic counselling
genetic testing
treatment
Diagnosis = ocular geneticist

Ocular Genetic Counsellors = 30-40?
How do you make an ocular geneticist?

Fellowships!
Ocular Genetics Fellowships

few funded?

varying length

with or without research
It can be done!

Thailand (3)
India
Chile
Philippines (2)
Taiwan
Indonesia
Saudia Arabia
Oman
Nigeria
(Brazil)
Ocular Genetics GCs

University of Rochester
funded
6 months
techs or GCs
The need for widely available genomic testing in rare eye diseases: an ERN-EYE position statement

Graeme C. Black\(^1\), Panagiotis Sergouniotis\(^1\), Andrea Sodi\(^2\), Bart P. Leroy\(^{3,4,5,6}\), Caroline Van Cauwenbergh\(^3\), Petra Liskova\(^7\), Karen Grønskov\(^8\), Artur Klett\(^9\), Susanne Kohl\(^10\), Gita Taurina\(^11\), Marius Sukys\(^12\), Lonneke Haer-Wigman\(^13\), Katarzyna Nowomiejska\(^14\), João Pedro Marques\(^15\), Dorothee Leroux\(^{16,17}\), Frans P. M. Cremers\(^13\), Elfride De Baere\(^17\), Hélène Dollfus\(^{16,18,19}\) and ERN-EYE study group

Short conclusion: Despite technological advances, critical gaps in genomic testing remain in Europe, especially in smaller countries where no formal genomic testing pathways exist. Even within larger countries, the existing arrangements are insufficient to meet the demand and to ensure access. ERN-EYE promotes access to genetic testing in RED and emphasizes the clinical need and relevance of genetic testing in RED.
Access to genetic testing for rare diseases: Existing gaps in public-facing information

Julie M. Robillard¹,²  |  Tanya L. Feng¹  |  Katarzyna Kabacińska¹
“Free” panels

Clinically Focused Molecular Investigation of 1000 Consecutive Families with Inherited Retinal Disease

Edwin M. Stone, MD, PhD,1,2 Jeaneen L. Andorf, BA,1,2 S. Scott Whitmore, PhD,1,2 Adam P. DeLuca, PhD,1,2 Joseph C. Giacalone, BS,1,2 Luan M. Streb, BA,1,2 Terry A. Braun, PhD,1,2 Robert F. Mullins, PhD,1,2 Todd E. Scheetz, PhD,1,2 Val C. Sheffield, MD, PhD,1,2,3 Budd A. Tucker, PhD,1,2

Recommendations for Genetic Testing of Inherited Eye Diseases


Edwin M. Stone, MD, PhD (Chair), Anthony J. Aldave, MD, Arlene V. Drack, MD, Mathew W. MacCumber, MD, PhD, Val C. Sheffield, MD, PhD, Elias Traboulsi, MD, Richard G. Weleber, MD
“Free” panels

False genome rate
Genetic counselling
“Ownership” of patients
Cultural/political barriers
Technology challenges

diagnostic equipment

treatment technology
What if...

Open access/no patents
Accurate low cost testing
Low cost treatment
Nonprofit
Lowering Cost

gene testing
tiered, longer turnaround
avg < $1000
free?! (philanthropy)
gene therapy
$20,000
HOW??????

philanthropy
It’s happening now

Ed Stone at Iowa
Going international

Education
  fellowships
  Orbis Cybersight
Information pipeline (telemedicine)
  diagnosis
Information pipeline
  after care
Step 4: Cost
Step 4: Cost
Philanthropy

There are rich people everywhere!!
(and International NGO support)
underwrite the effort
diagnostic technology
Treatment?

Stem cell can’t travel..
Local Institutional Buy In

Volume
dedicated time
Fundraising
Our world is changing...

...we can do this!
No more...

I’m not sure...see you later
He/she will go blind...see you later
Nothing we can do...see you later
“There will be treatment in your lifetime”

When?
What?
Stop progression vs cure?

BUT...
“There will be treatment in your lifetime”
Questions?

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