Gene-based Therapies for RTT (and Mecp2 Related Disorders)

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Nemours

Wilmington DE

May 2008

Outcome measures in Rett syndrome

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Treatment

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Measure of "function"

Repeat Measure of "function"

Is she better?

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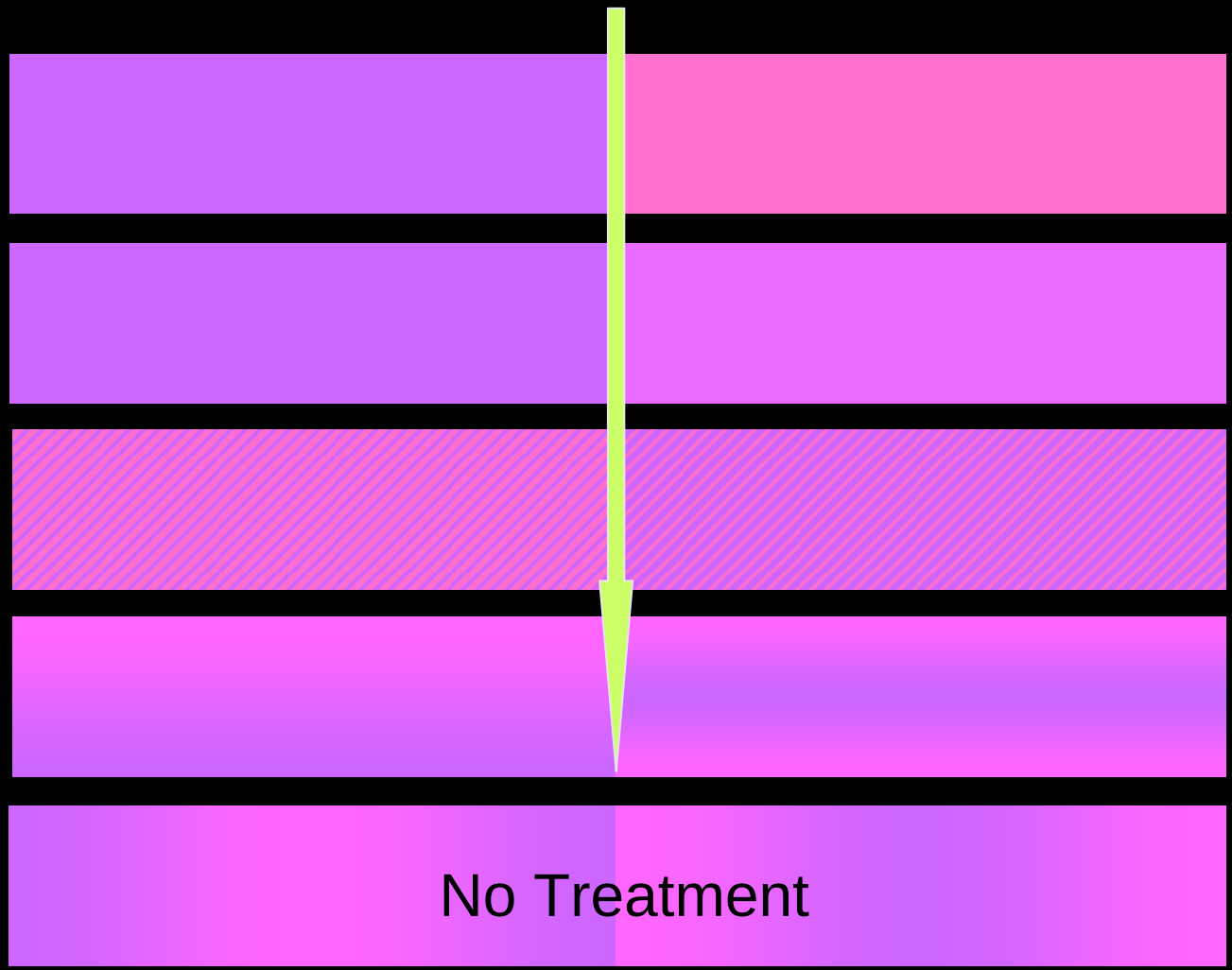
http://www.circ.uab.edu/Sparks/Rett/index.html


Treatment X
No Treatment

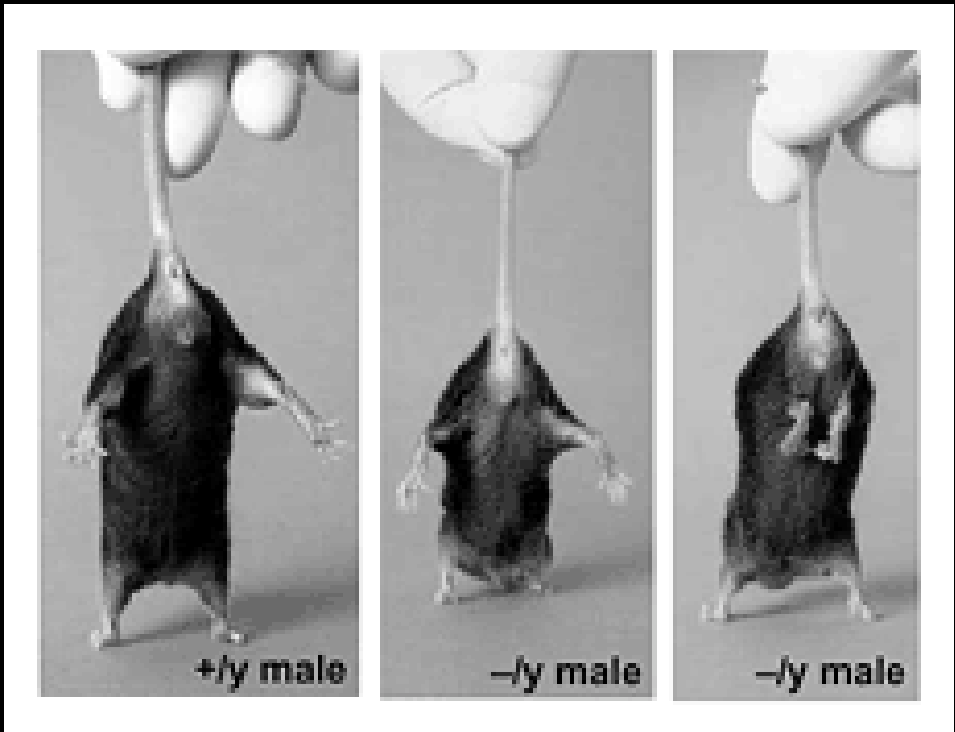
Challenges across the board in Rett

- No clear-cut reliable outcome measure for all the girls
  - Natural history study may be key
  - ?EEG or other physiology measure
- Girls will be heterogeneous in background
- Even in cultured cells, outcome measures are tricky (but we are working on that one!)
- But the mice can help us here…..

Some good things

- Presence of ‘common mutations’ in many of the girls
  - Common classes of mutations
    - Missense and nonsense
    - Specific mutations
- Active support group and network to activate when treatments are on-line
  - Address recruitment issues
  - Motivated families
- Mouse model

Mouse models of RTT



Guy et al, Nature Genetics (27) 322-326, 2001.

- Removed or damaged the Mecp2 gene
- Useful for testing new treatments and understanding what is going on in the brain

Some new treatments are already on-line

- Anxiety management
- Nutritional management
- Scoliosis management

New treatments on the horizon?

Can we fix the gene?

- Gene therapy strategies: can we actually put in a new copy of the Mecp2 gene?

Can we help the mutated gene make a better protein?

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Targeted treatments based on what Mecp2 does in a cell in the brain

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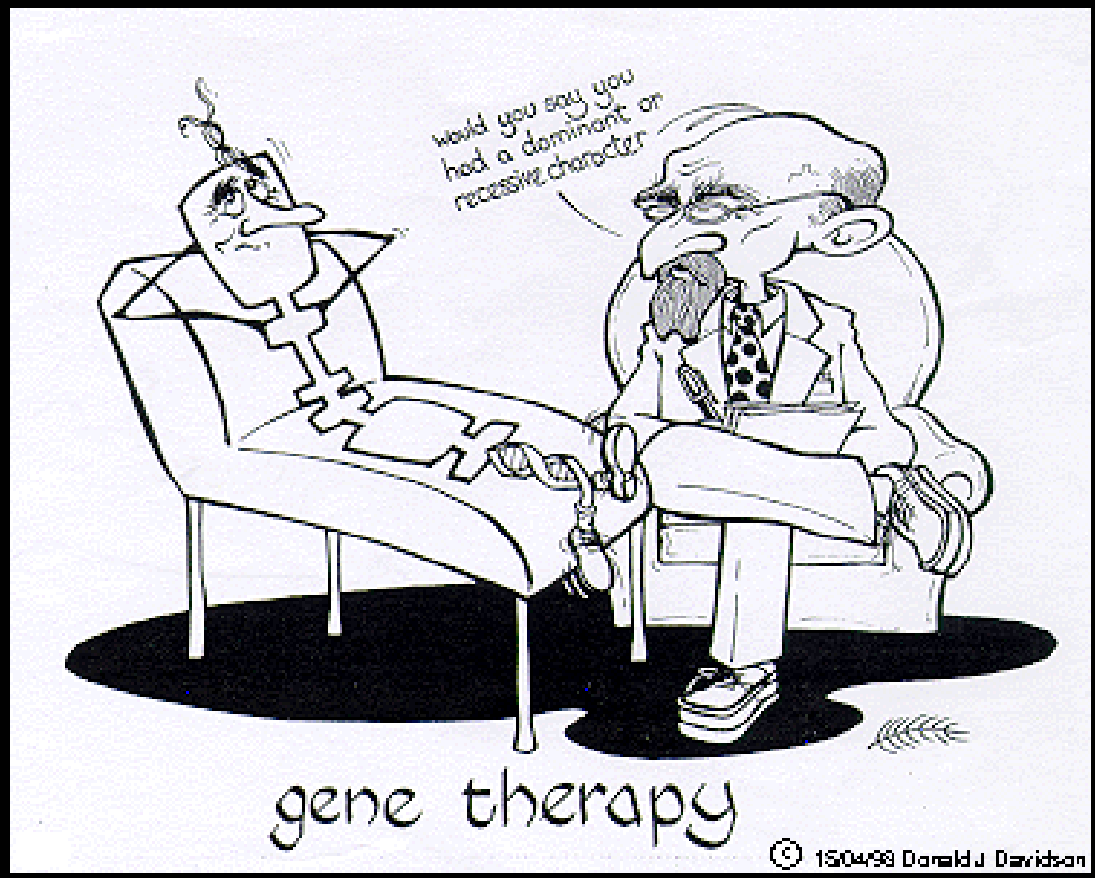
Gene therapy

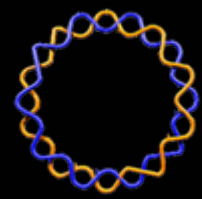


Which disorders are candidates for gene therapy treatment?

Disorders due to mutations in one or more genes

- Single-gene disorders are more easily treated

The responsible gene is known



+/- The role of the protein encoded by the gene is known

+/-Adding a normal gene will fix the problem

The affected tissues are known and accessible

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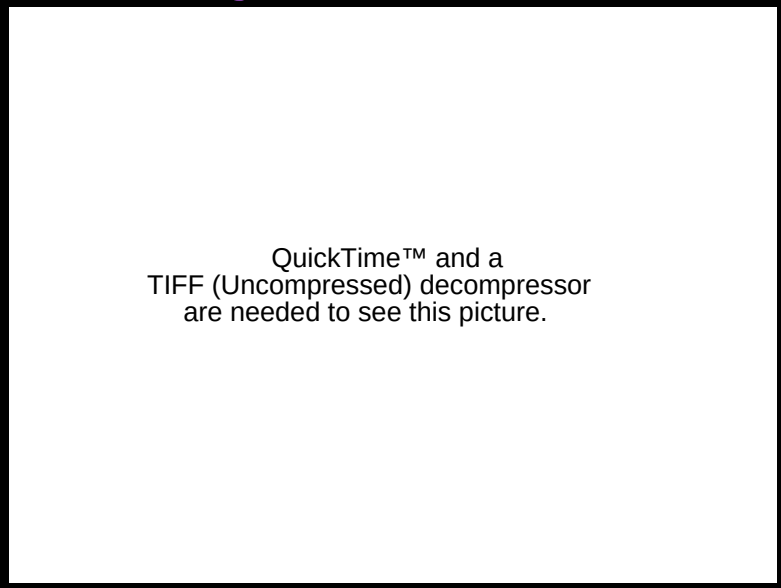
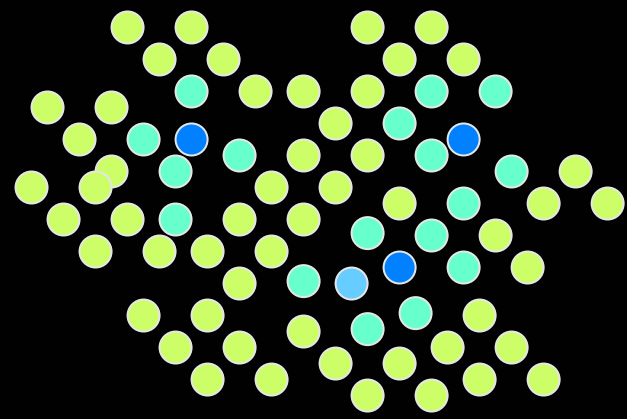
What about gene therapy for Rett syndrome?



- How gene therapy works in 2008
  - Gene is introduced into cell by a virus that has been modified to express the gene of interest and to not express viral genes (so it does not make more virus)

What about gene therapy?

- Works best:
  - Cells are actively dividing (making new cells and growing, like liver cells)
  - The product of the gene is something that can be secreted out of the cell to help neighboring cells
- Hurdles:
  - Immune response to virus, low efficiency of process



Gene Therapy Successes

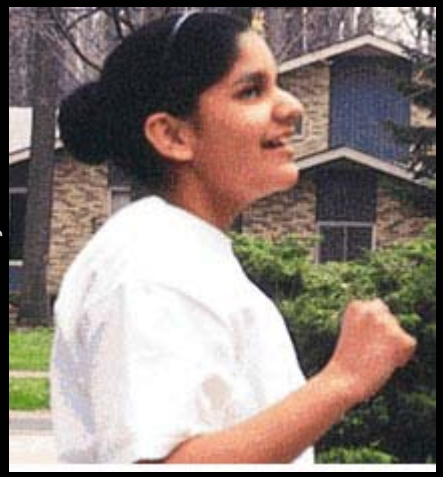


Photo courtesy of Van de Silva

Ashanti de Silva successfully treated for ADA deficiency - 1990

Ryes Evans successfully treated for SCID - 2001

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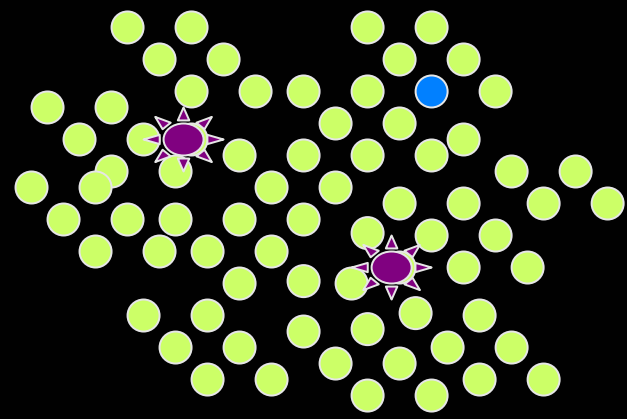
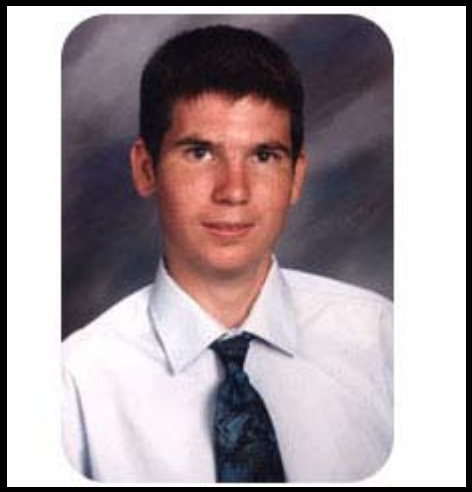
What about gene therapy?

Hurdles:

- Virus only infects a small number of cells
- The immune attacks the virus
  - Lose expression over time
  - Can have life threatening immune reaction



Gene Therapy Problems



Jesse Gelsinger died of complications due to an immune system response while participating in a clinical trial

Two boys treated for SCID developed leukemia due to disruption of a gene that regulates cell division

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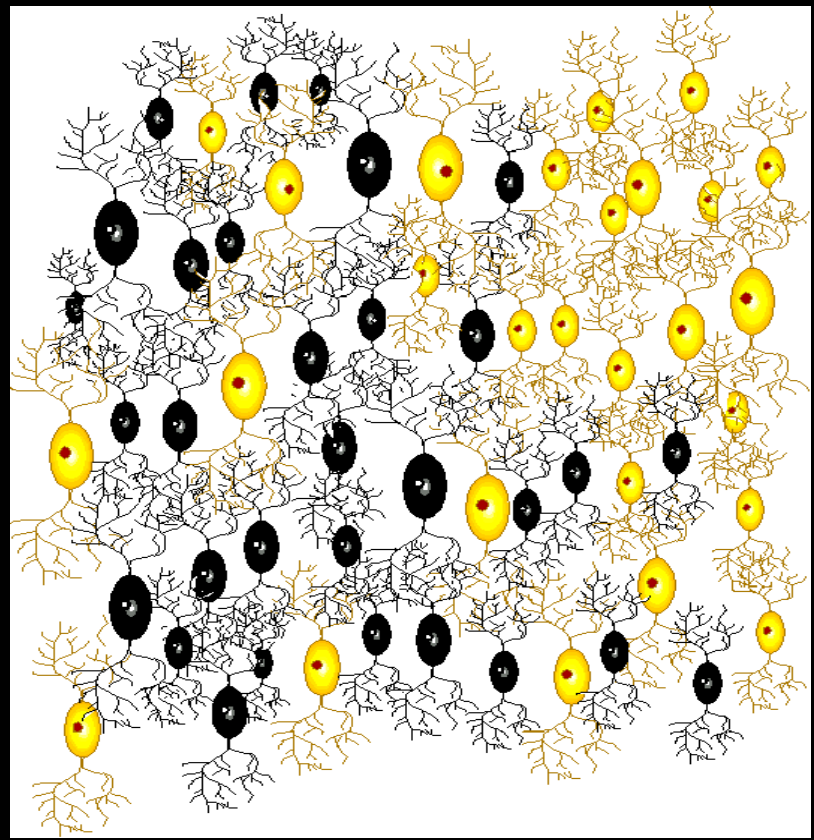
What about gene therapy?

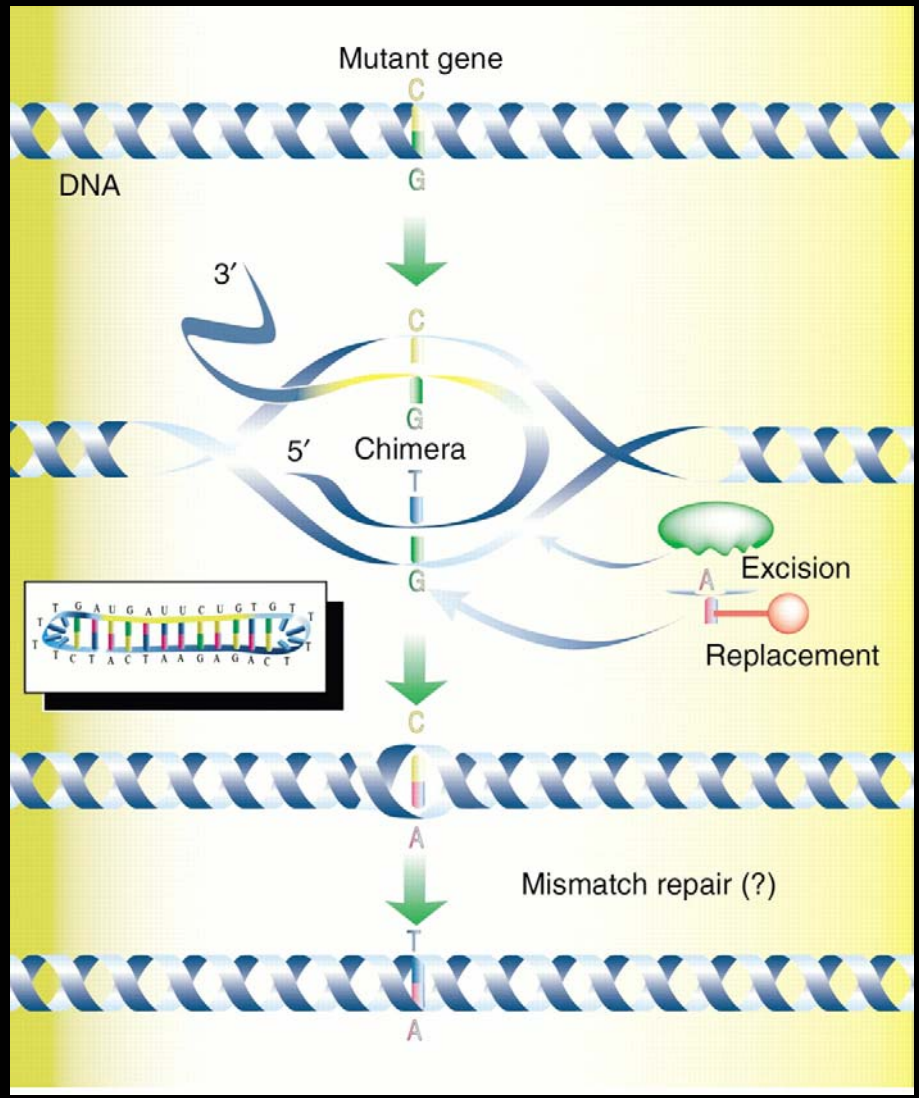
- Hurdles in Rett syndrome:
  - Brain cells are not dividing
  - Hard to get virus into the nervous system effectively
  - MeCP2 would not be shared with neighboring cells (only infected cells would respond)
  - Other concerns: cells expressing the normal copy would also take up the virus and too much MeCP2 can be a problem too



Gene therapy

- We are just not there yet…
- New results from mice show that the mild over expression that might be expected with this approach could be tolerated.
- IRSF funded studies directed at working toward feasibilit of these approaches.

Proposed mechanism of targeted gene repair directed by chimeric RNA/DNA oligonucleotides



Kmiec, E. B. J. Clin. Invest. 2003;112:632-636

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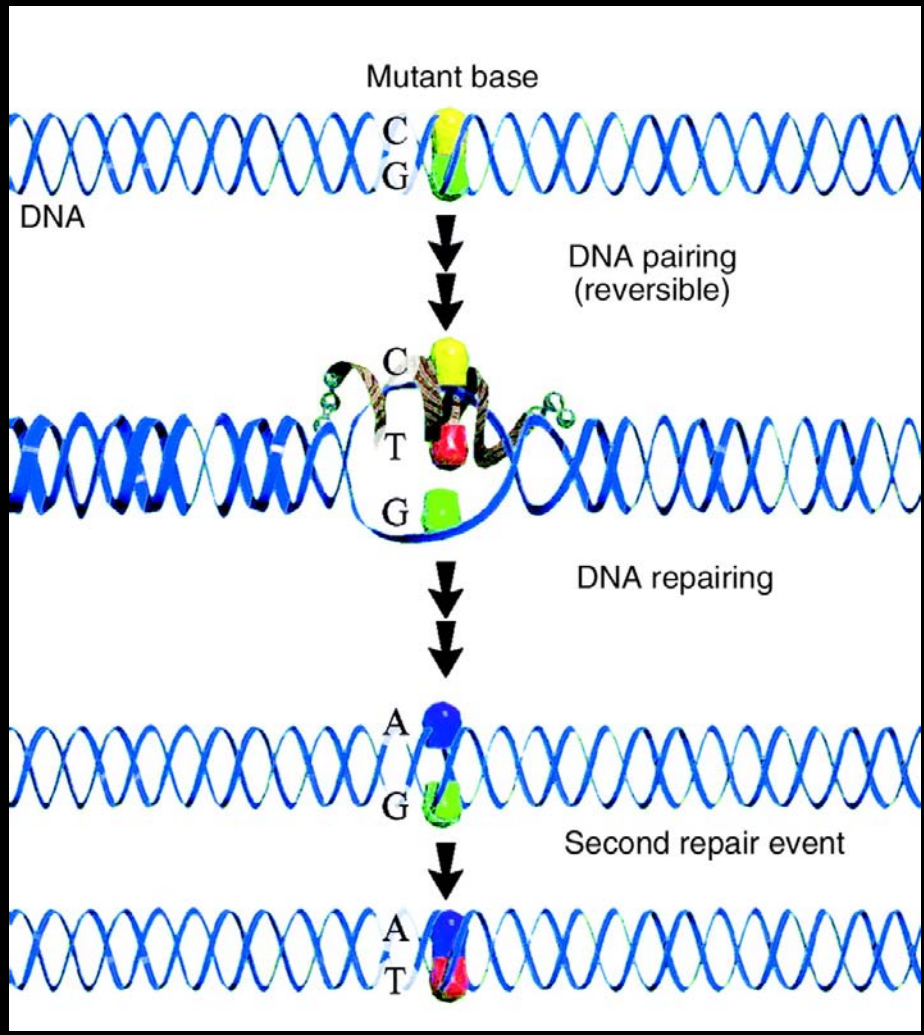
Targeted gene repair with modified single-stranded oligonucleotides



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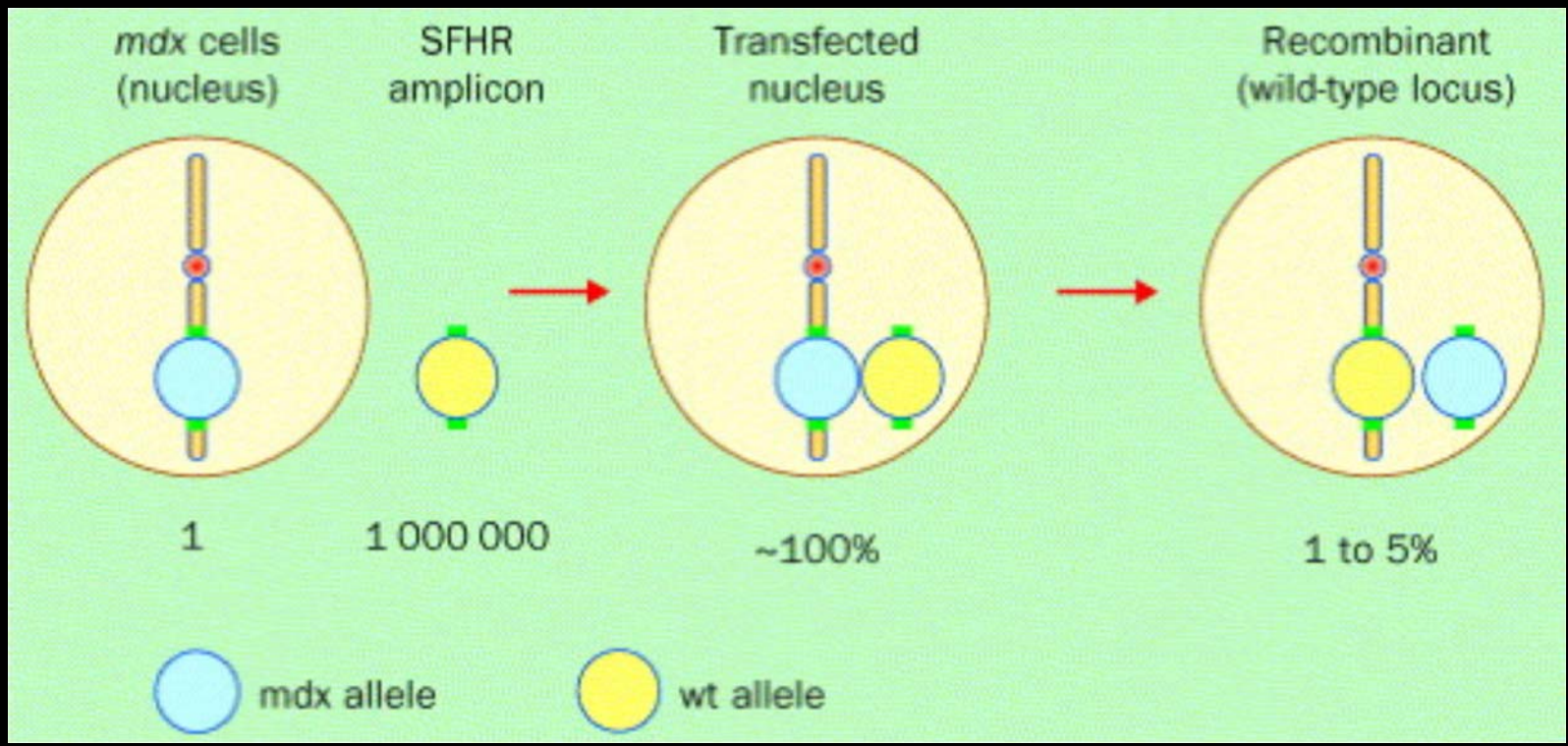
Efficiency remains an issue



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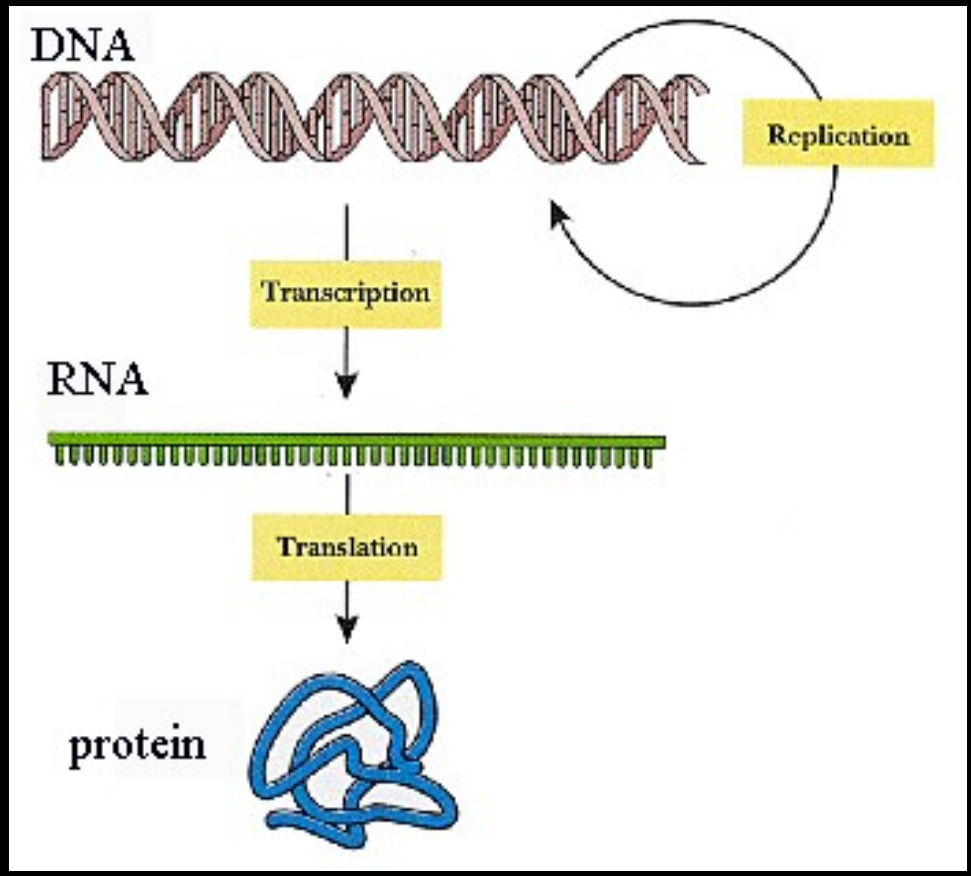
Post-transcriptional repair: what does that mean?



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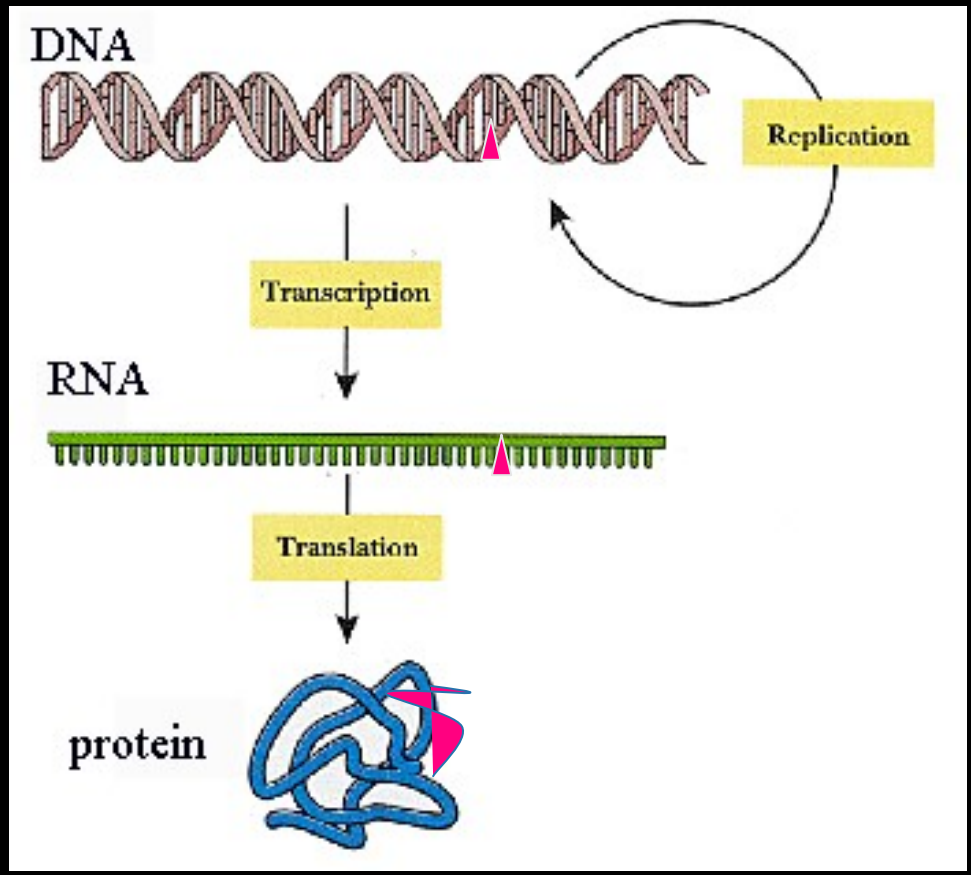

Modified from cellbio.utmb.edu

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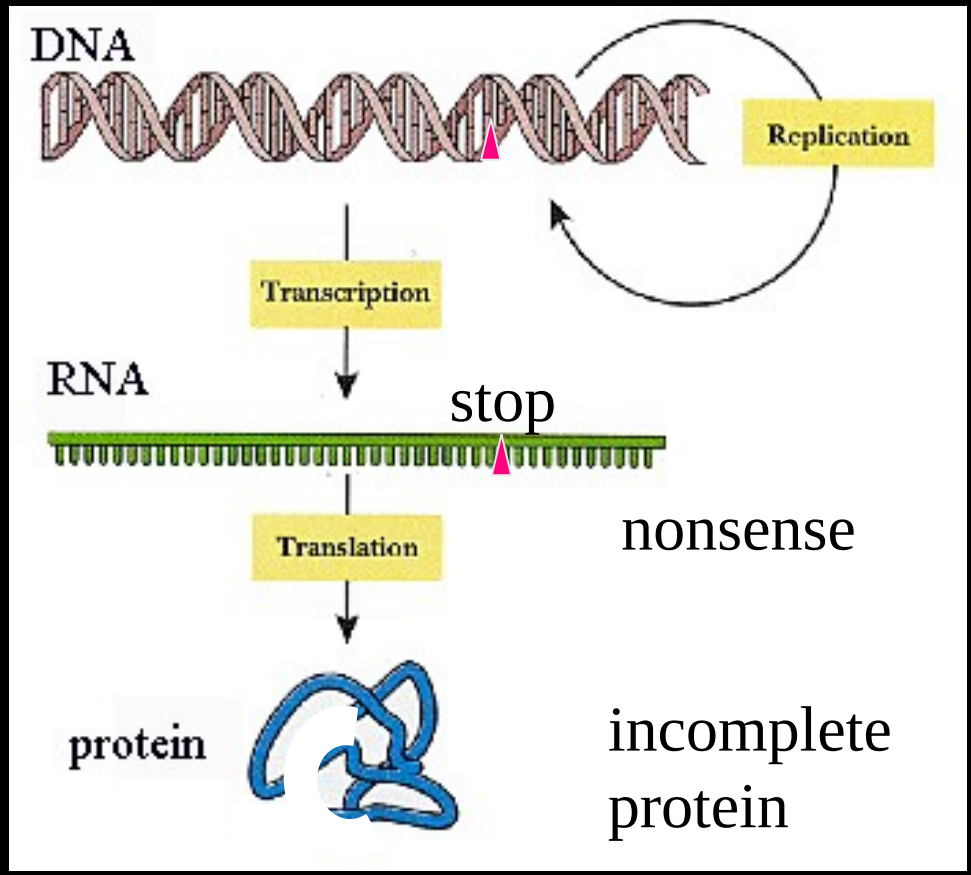
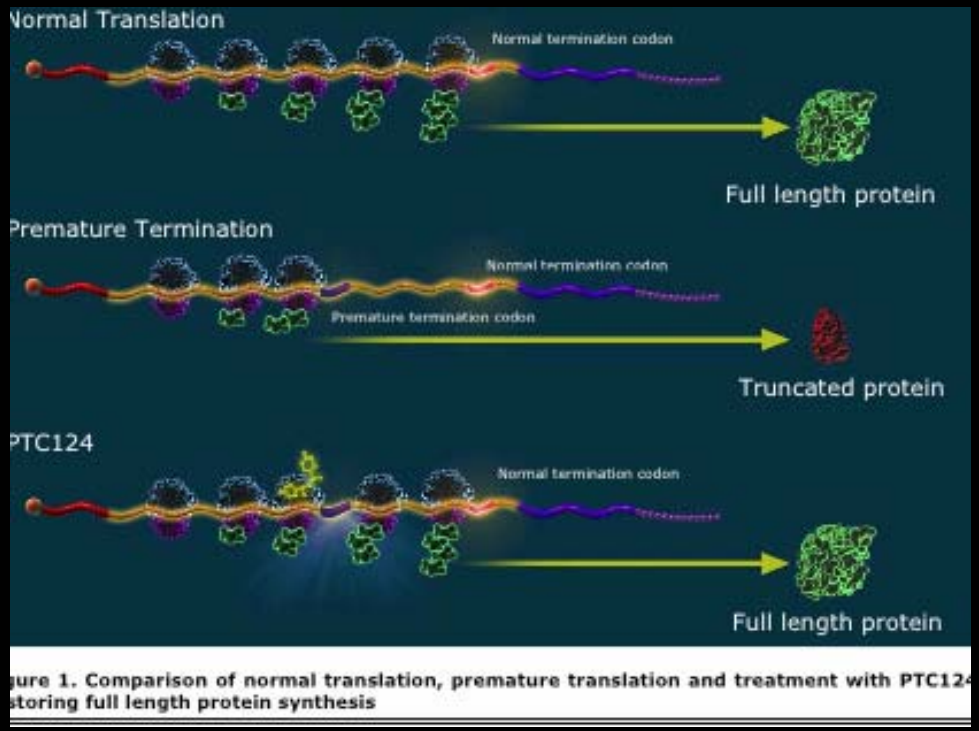


Modified from cellbio.utmb.edu

Post-transcriptional repair?

- Aminoglycoside antibiotics allow “read-through” of premature stop signals
  - Nonsense mutations
  - Problems with toxicity
  - Need to be given IV

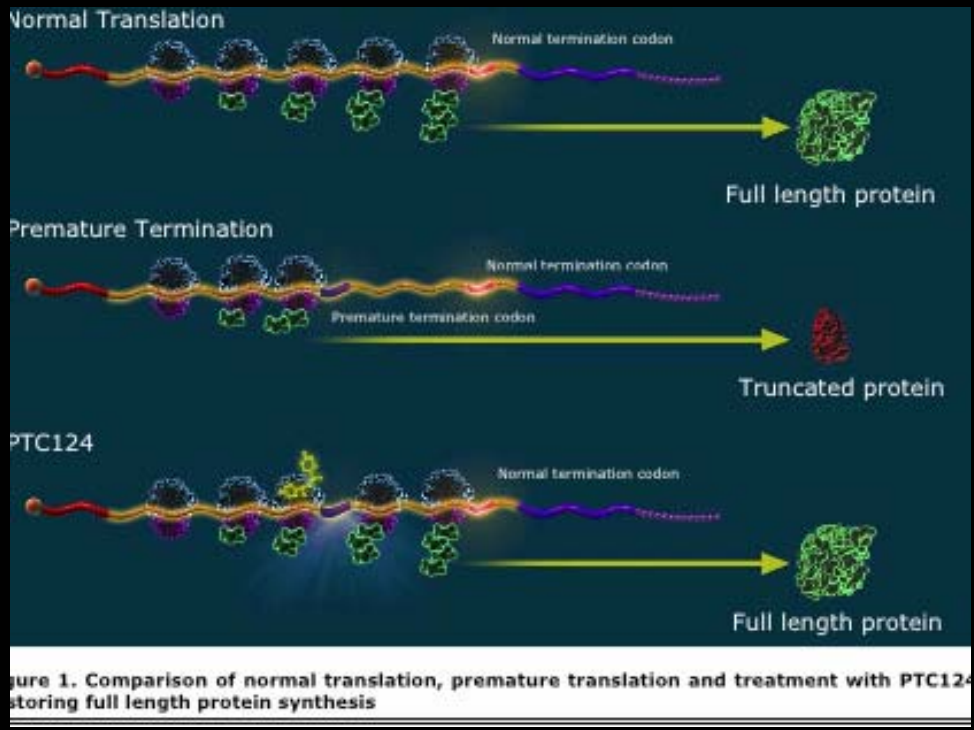


ure 1. Comparison of normal translation, premature translation and treatment with PTC124
storing full length protein synthesis

http://www.ptcbio.com/3.1.1_genetic_disorders.aspx

Post-transcriptional repair?

- New Agents Developed by PTC Therapeutics with similar action
  - Orally available
  - Less toxic
  - Being tested in cystic fibrosis and Duchenne Muscular Dystrophy



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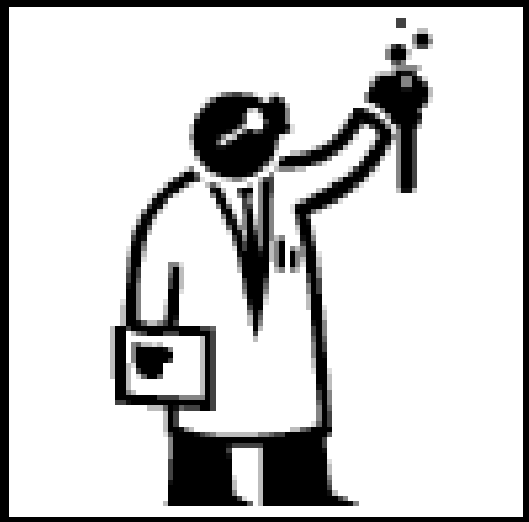
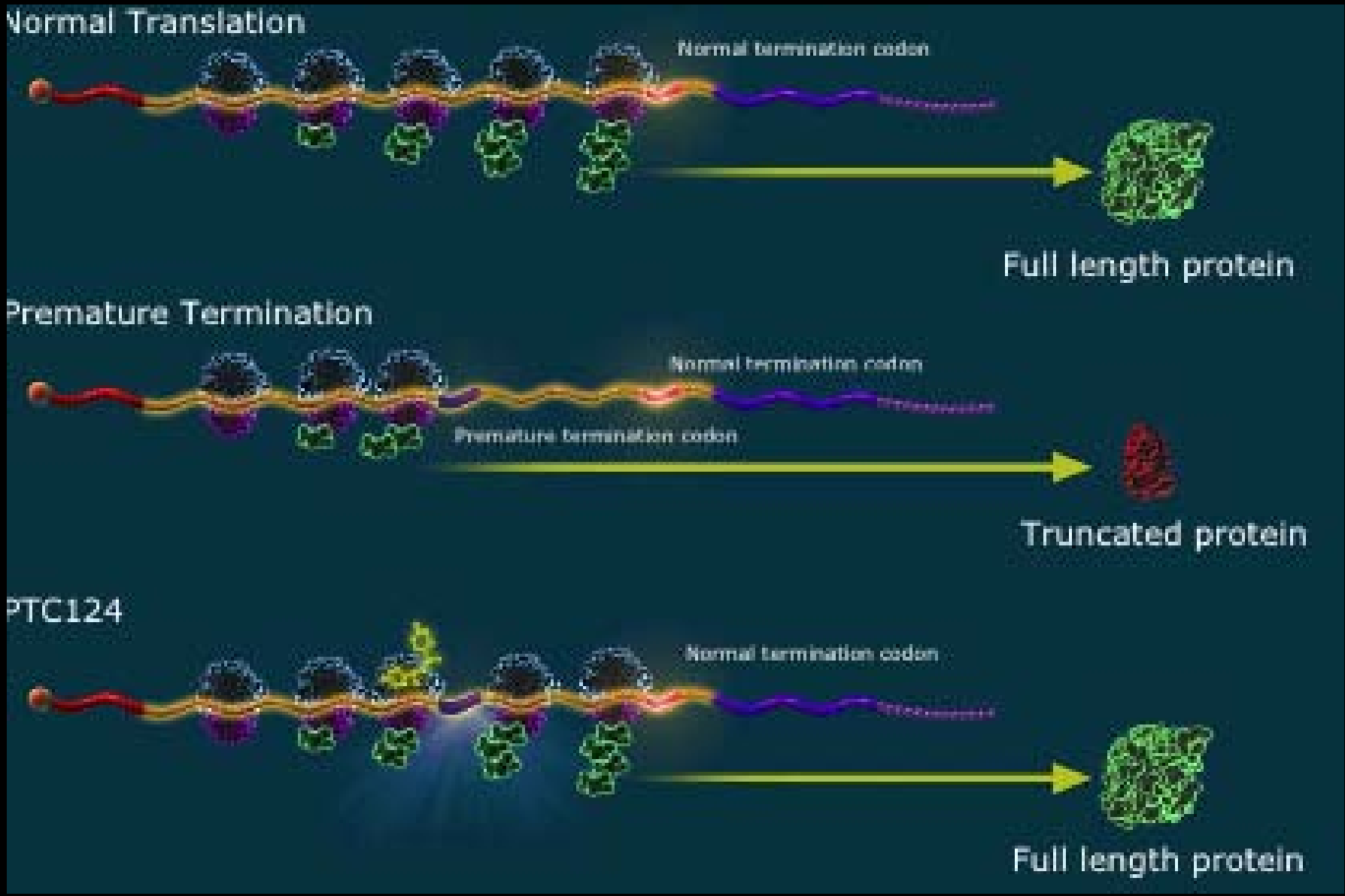
Outcome measures



- Duchenne MD
  - Muscle biopsy
  - Strength assessments
  - Serum CPK
- Cystic Fibrosis
  - Chloride conductance
  - Clinical improvement (cough, infection, mucus thickness)



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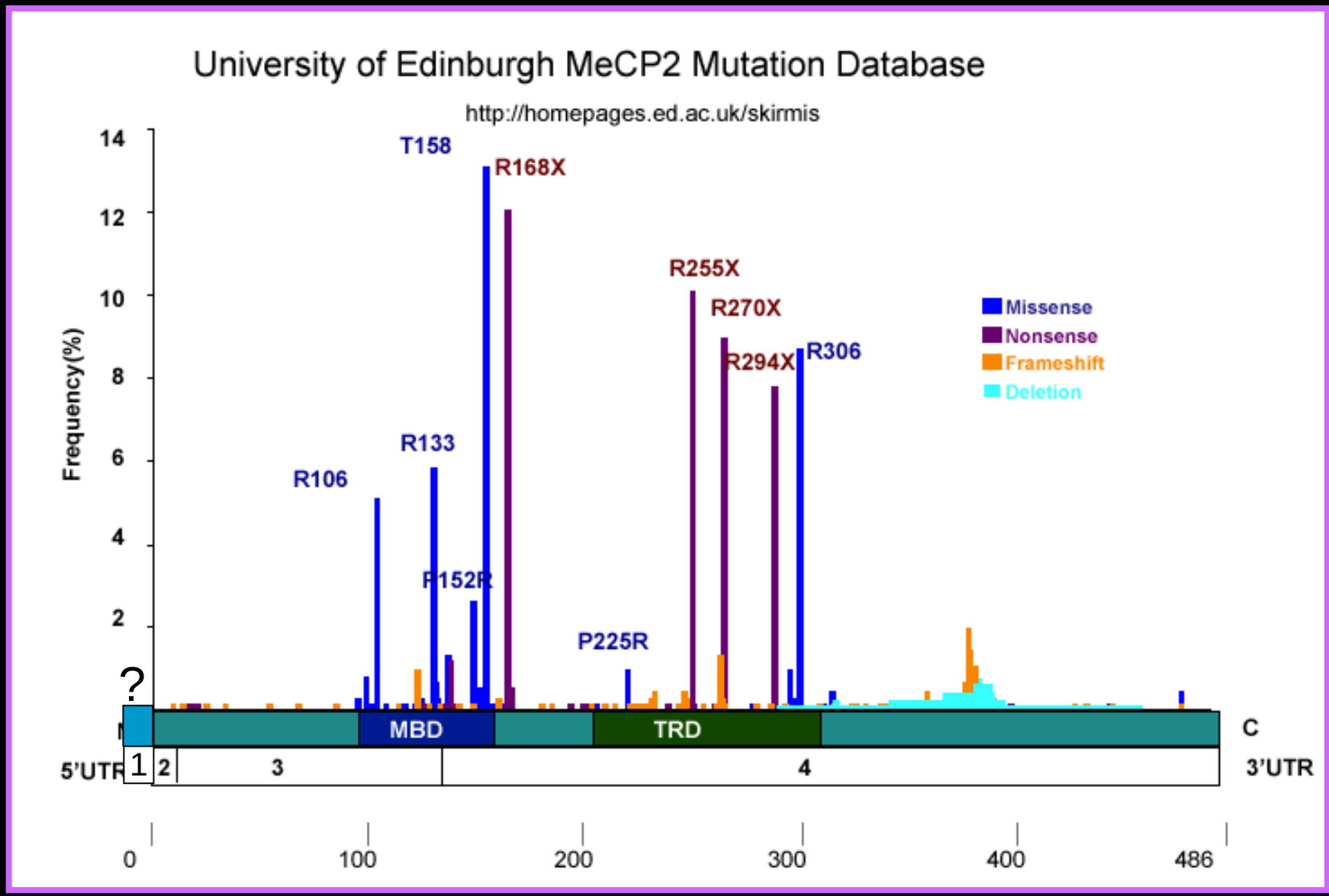
For information on the clinical trials ongoing with PTC124 in cystic fibrosis and Duchenne muscular dystrophy by PTC Therapeutics, please visit their website at http://www.ptcbio.com/3.1.1_genetic_disorders.aspx


University of Edinburgh MeCP2 Mutation Database
http://homepages.ed.ac.uk/skirmis
Frequency(%)
14
12
10
8
6
4
2
T158
R168X
R255X
R270X
R294X
R306
R133
R106
R152R
P225R
Missense
Nonsense
Frameshift
Deletion
?
MBD
TRD
C
5'UTR
1
2
3
4
3'UTR
0
100
200
300
400
486

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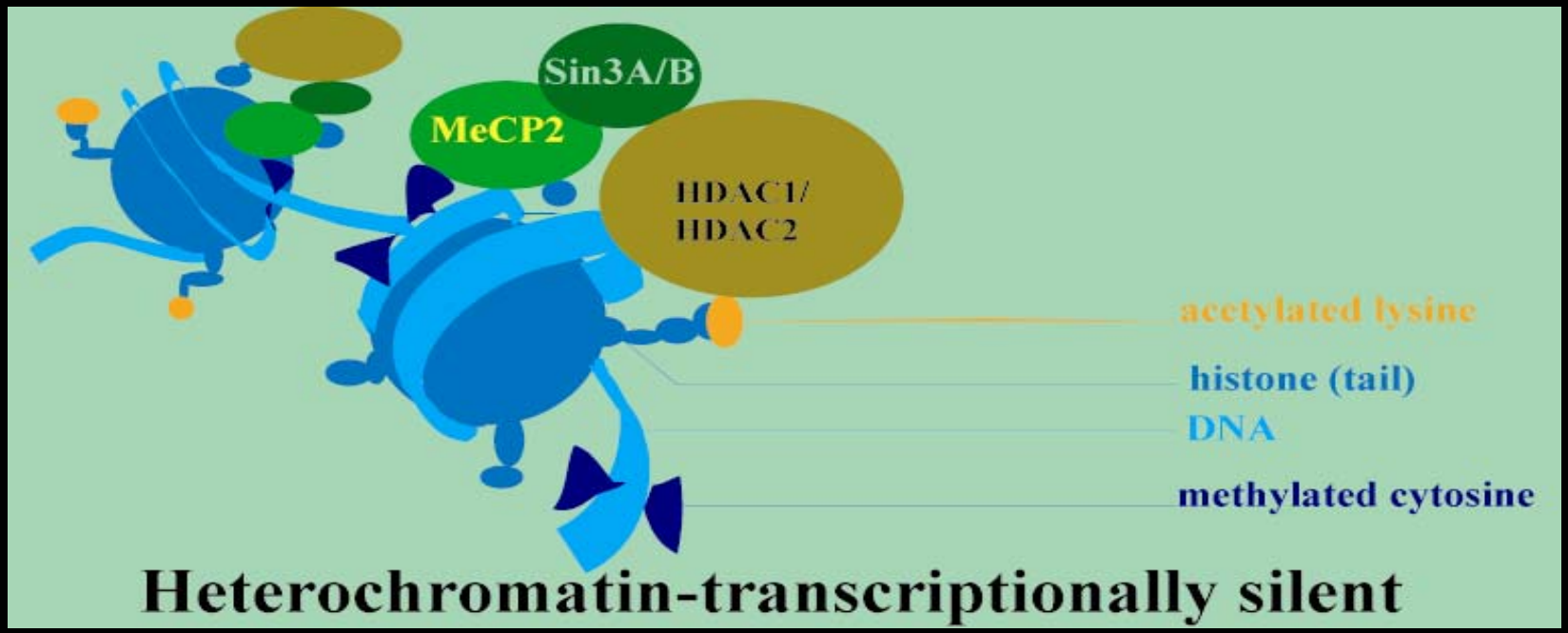

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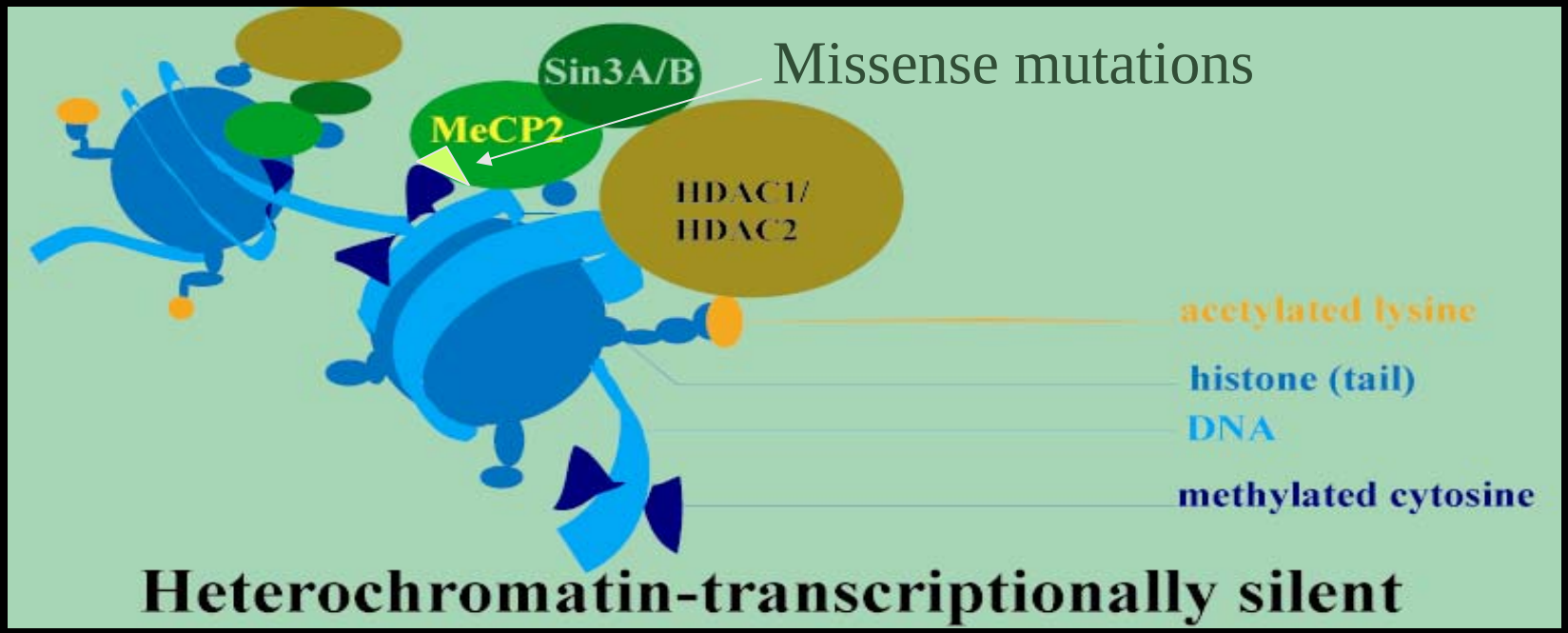

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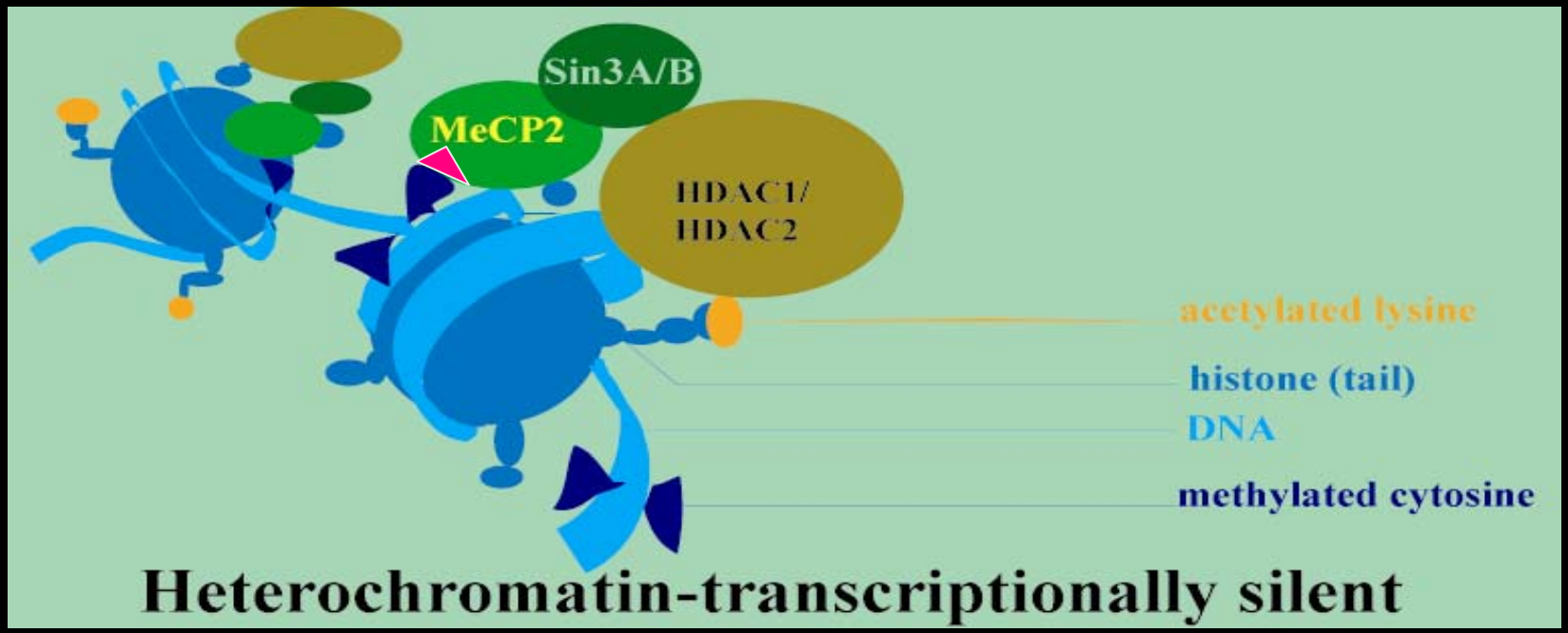

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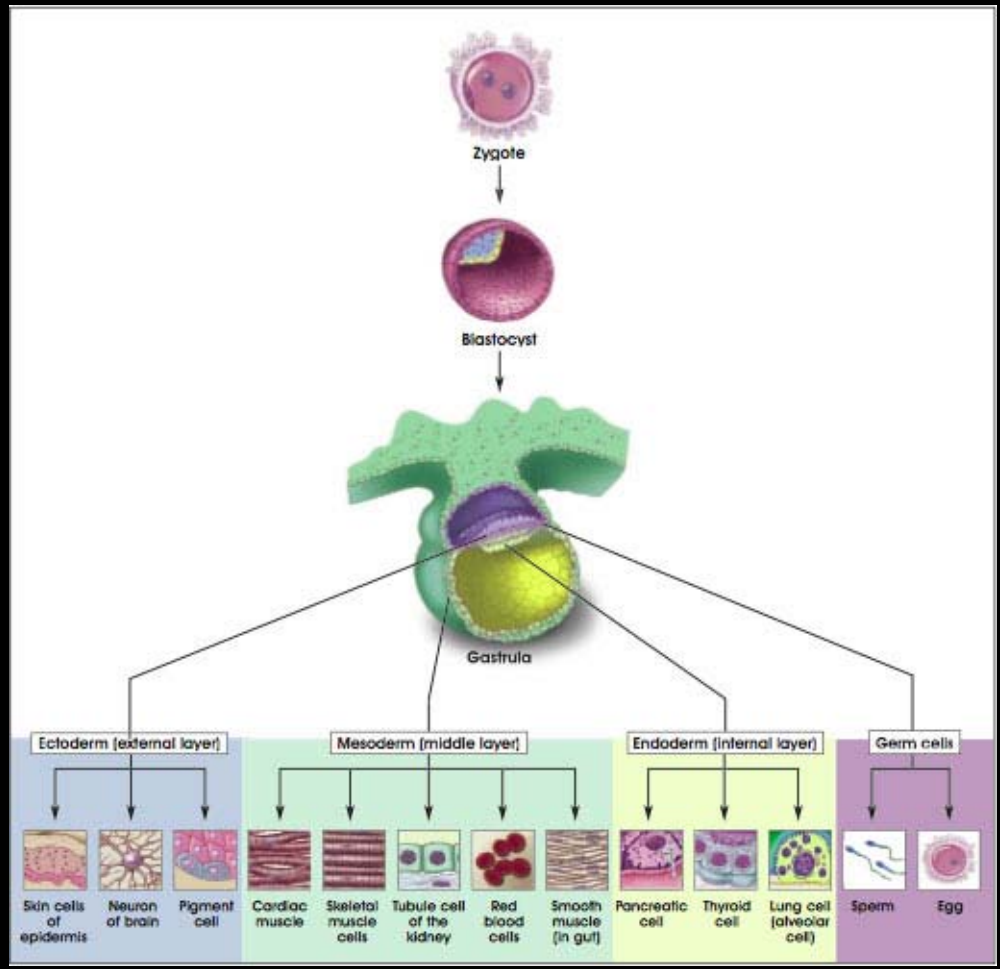
What is an embryonic stem cell?



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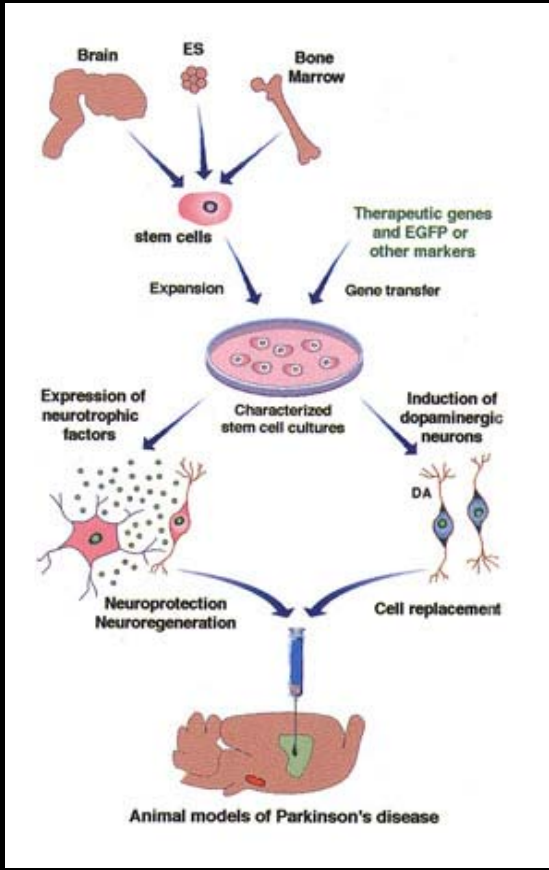
http://stemcells.nih.gov/info/scireport/chapter1.asp

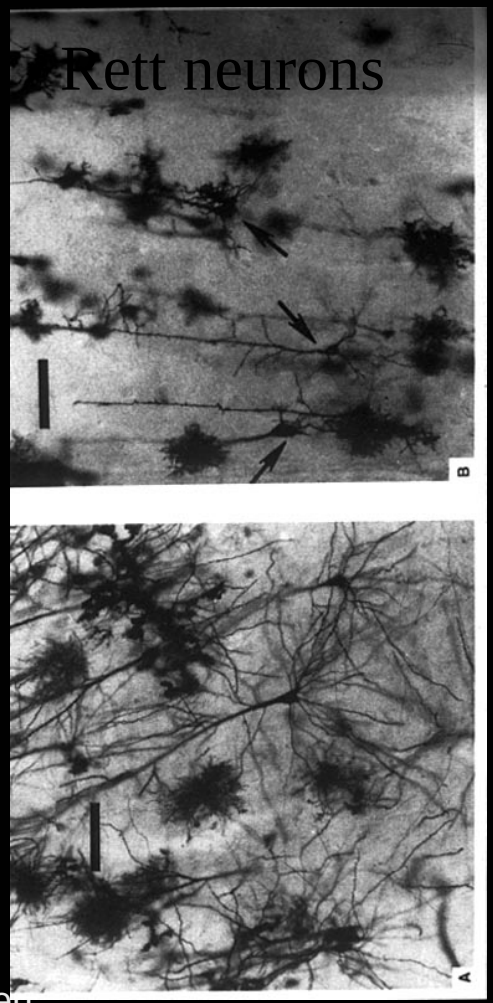
Stem cells in Parkinson Disease



- Stem cells repair isolated region of brain damaged by disease or injury: Parkinson disease

http://cajal.mbb.ki.se/Projects.html

Stem cells in Rett



Limitations:

In Rett brain, the injury is not localized.Nerve cells throughout the brain are affected

Roughly half the nerve cells are already expressing the normal copy of the gene

The number of stem cells would be small in comparison

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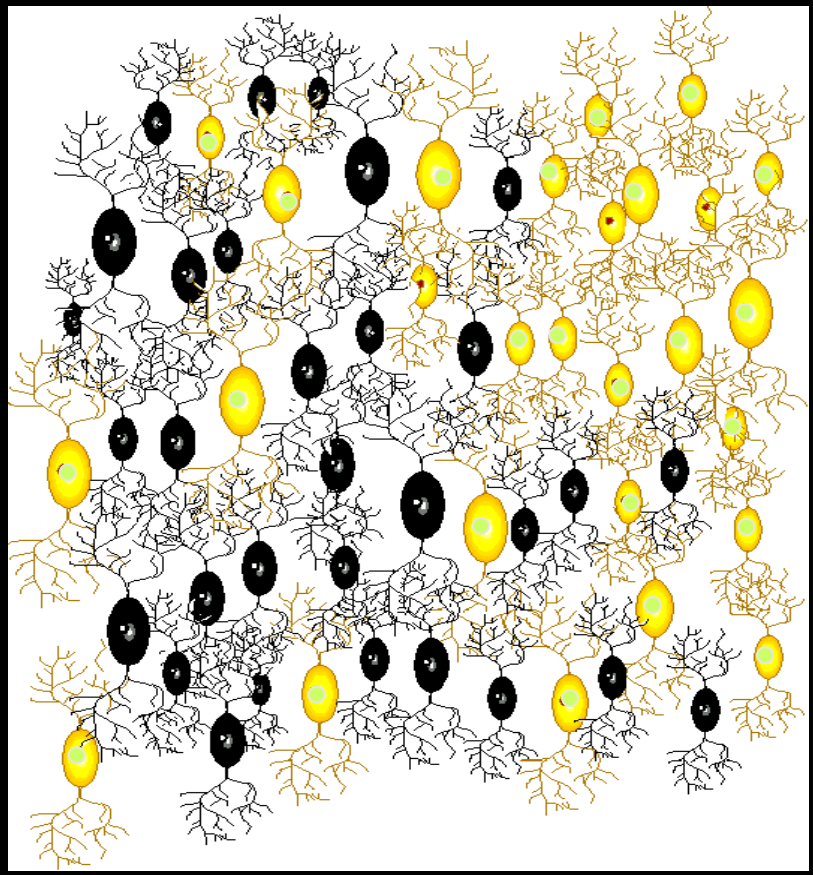
MeCP2 levels are lower than expected in the normal cells in brain



- Would a drug that increased the amount of MeCP2 made in the normal cells be clinically effective?

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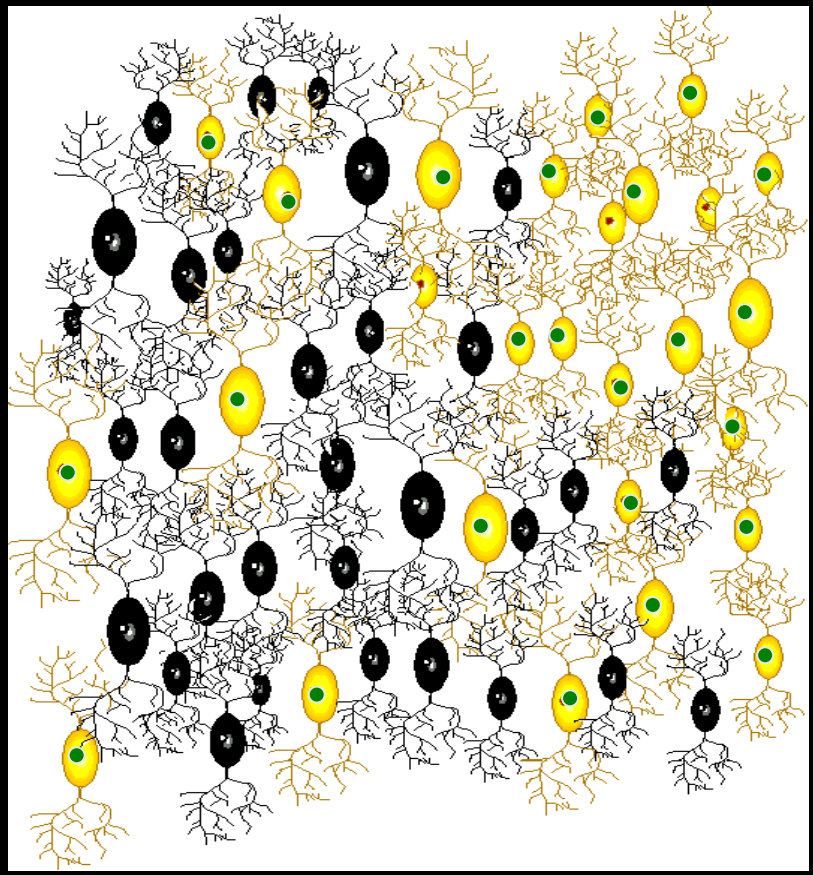

- Would a drug that increased the amount of MeCP2 made in the normal cells be clinically effective?
- Potentially, and is actively being explored.

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Discovery
will lead to
recovery in
the future for
Rett
syndrome.

Acknowledgements

- IRSF
- PTC Therapeutics
- Rettbase