

Emerging Treatments & How They Work

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Emerging Treatments

Background

Lysosomal enzyme synthesis

Mutations leading to enzyme deficiencies

Treatments

Gene therapy

Stop codon “readthrough”

Chaperone therapy

Stem cell therapy

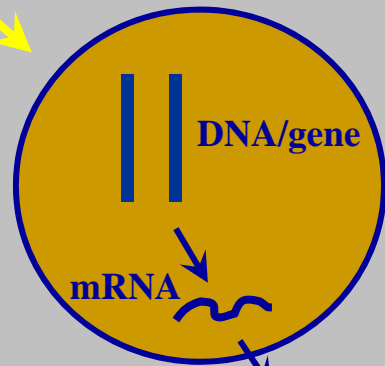
Enzyme replacement

Substrate reduction therapy

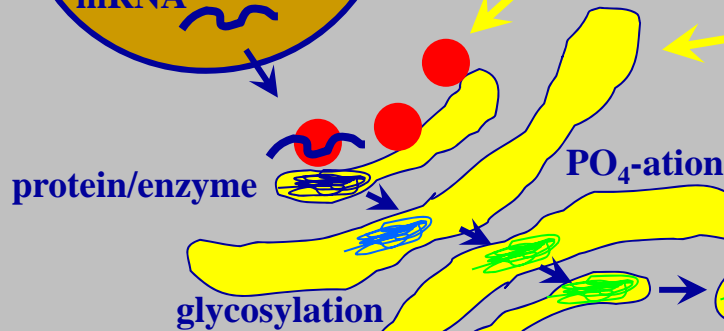
Future Directions/Challenges

Lysosomal Enzyme Synthesis and Trafficking

Nucleus

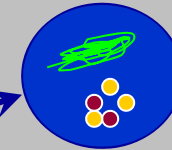


Ribosome



ER/Golgi

transport

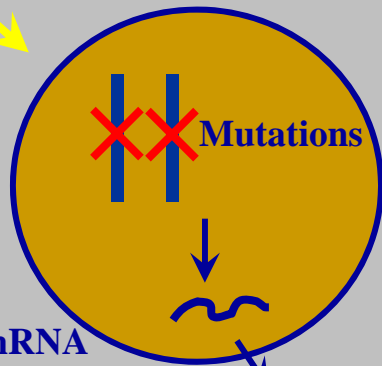


Lysosome



Mutations Leading to Deficient Enzyme

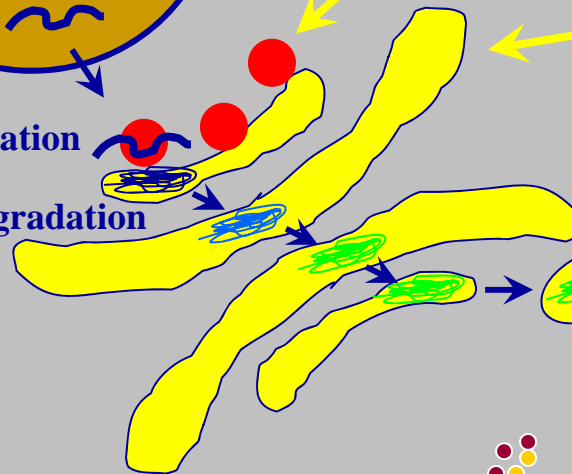
Nucleus



Ribosome

Interrupted Translation

Protein Degradation



ER/Golgi

No Enzyme

Lysosome



Emerging Treatments

Gene Therapy

Carrier

Affected

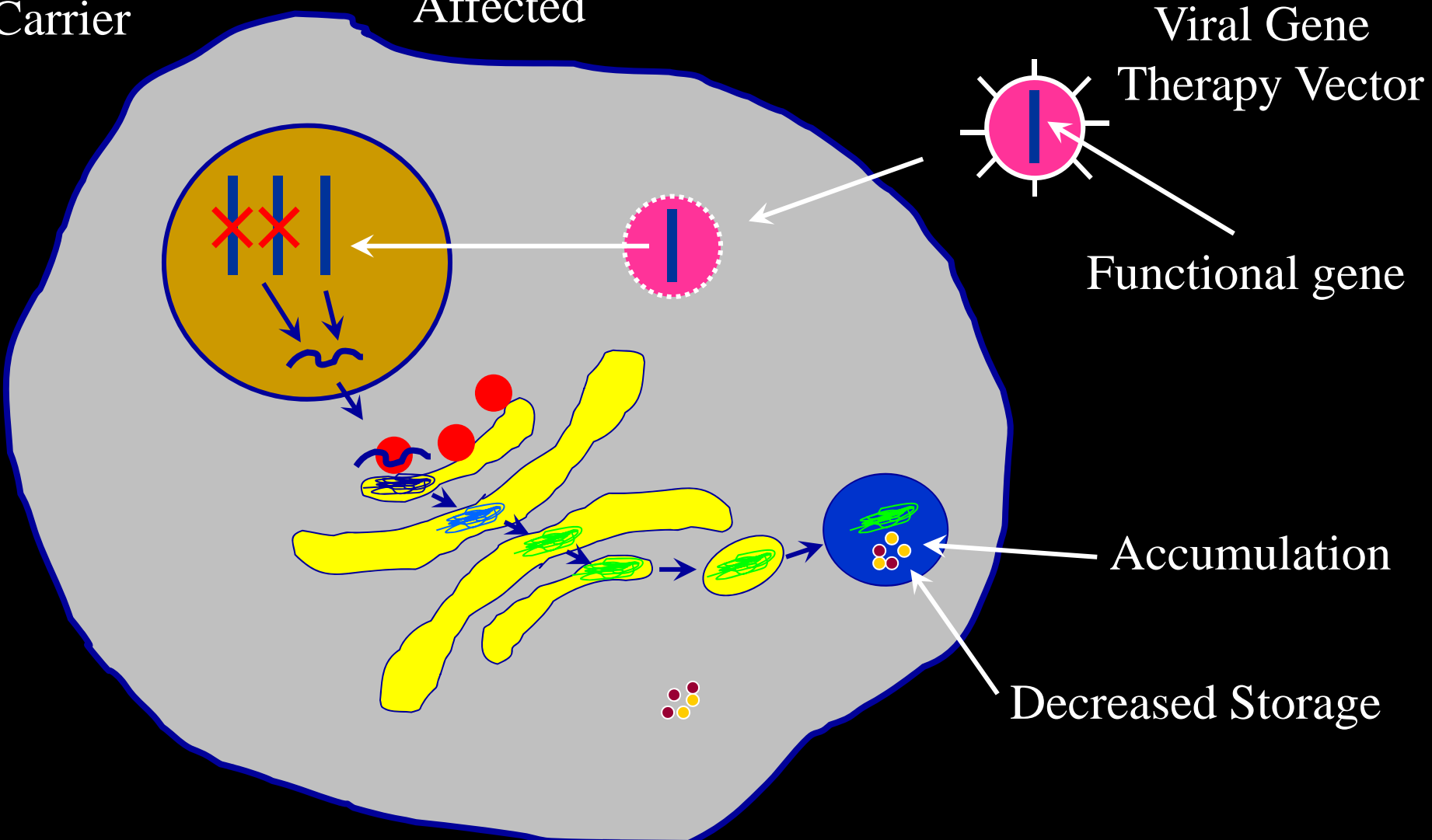
Viral Gene

Therapy Vector

Functional gene

Accumulation

Decreased Storage



Gene Therapy

Advantages:

- High level expression
- Long-term (possibly permanent) source of enzyme
- Ease of administration (systemic)
- Useful for any mutation

Limitations:

- Safety?
 - over-expression
 - genotoxic
- Can only correct a minority of cells
- Invasive administration (brain)
- Immune reactions

Stop Codon "Readthrough"

Nucleus

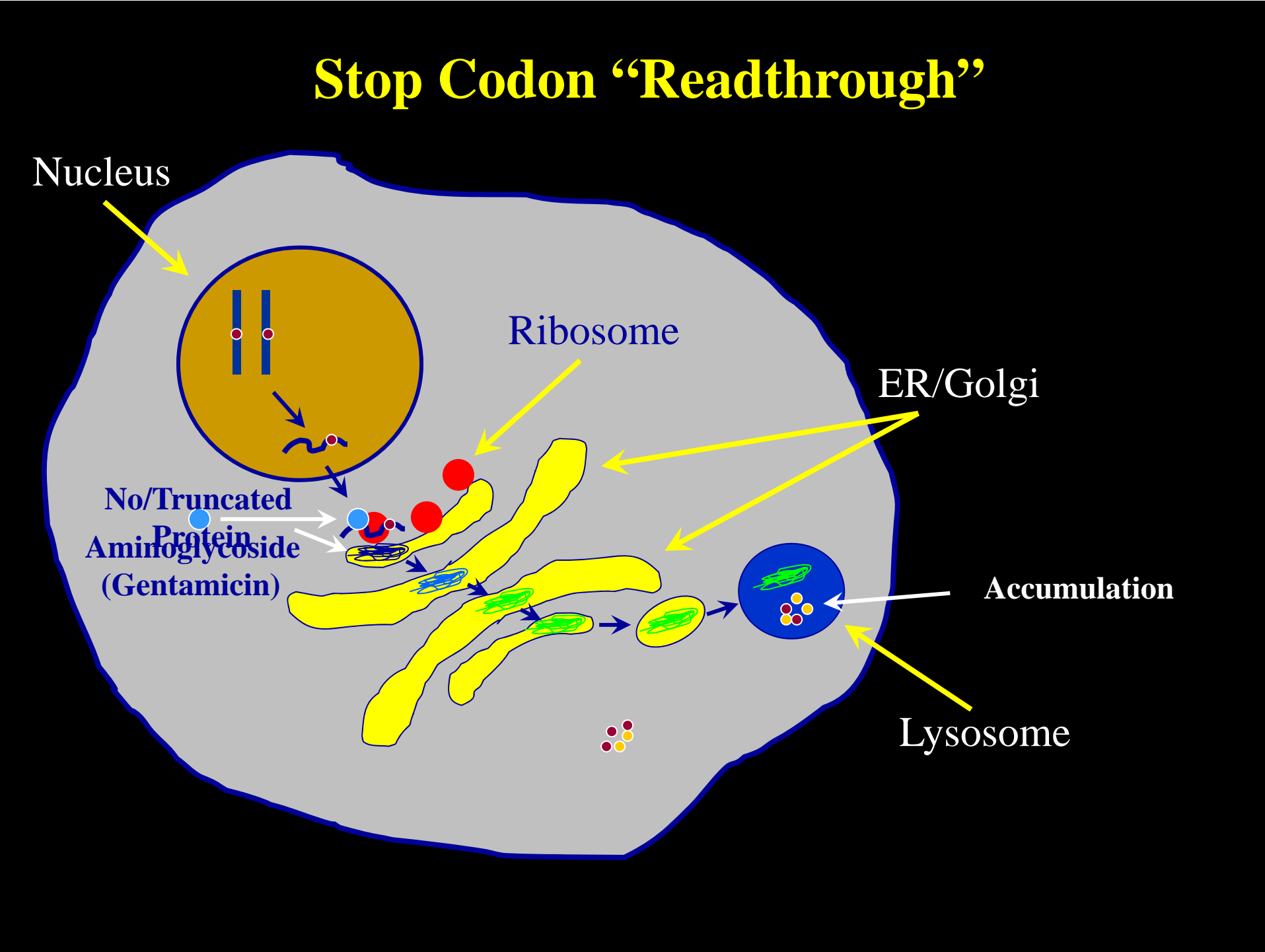
Ribosome

ER/Golgi

No/Truncated
Protein
Aminoglycoside
(Gentamicin)

Accumulation

Lysosome



Stop Codon “Readthrough”

Advantages:

- Small molecule drug (oral delivery)
- Good bioavailability (blood brain barrier?)

Limitations:

- Only effective for certain mutations
- Low level expression
- Toxicity?
- Off-site effects?

Chaperone Therapy

“Unfolded Protein Response”

Nucleus

Ribosome

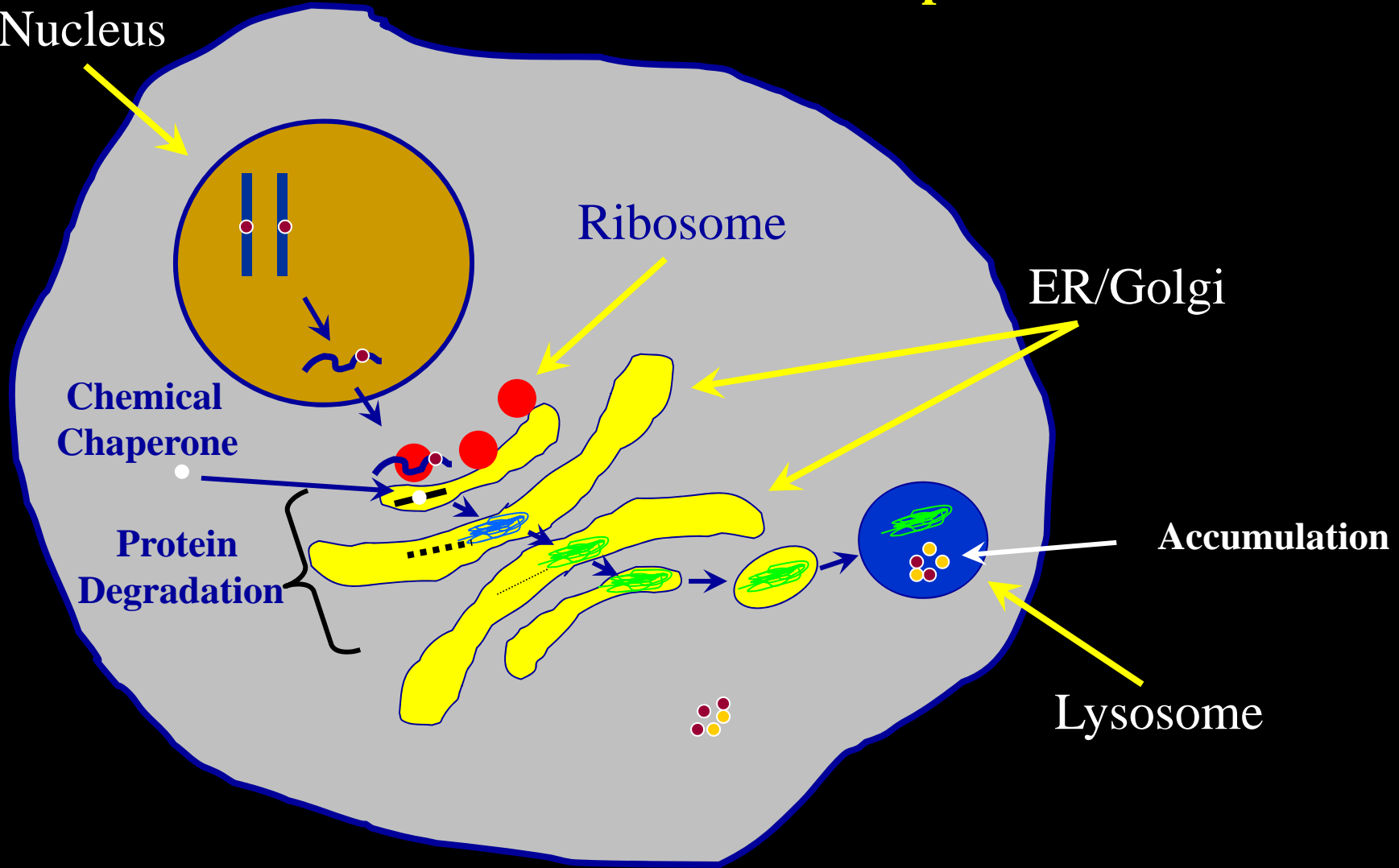
ER/Golgi

Chemical
Chaperone

Protein
Degradation

Accumulation

Lysosome



Chaperone Therapy

Advantages:

- Small molecule drug (oral delivery)
- Good bioavailability (blood brain barrier?)

Limitations:

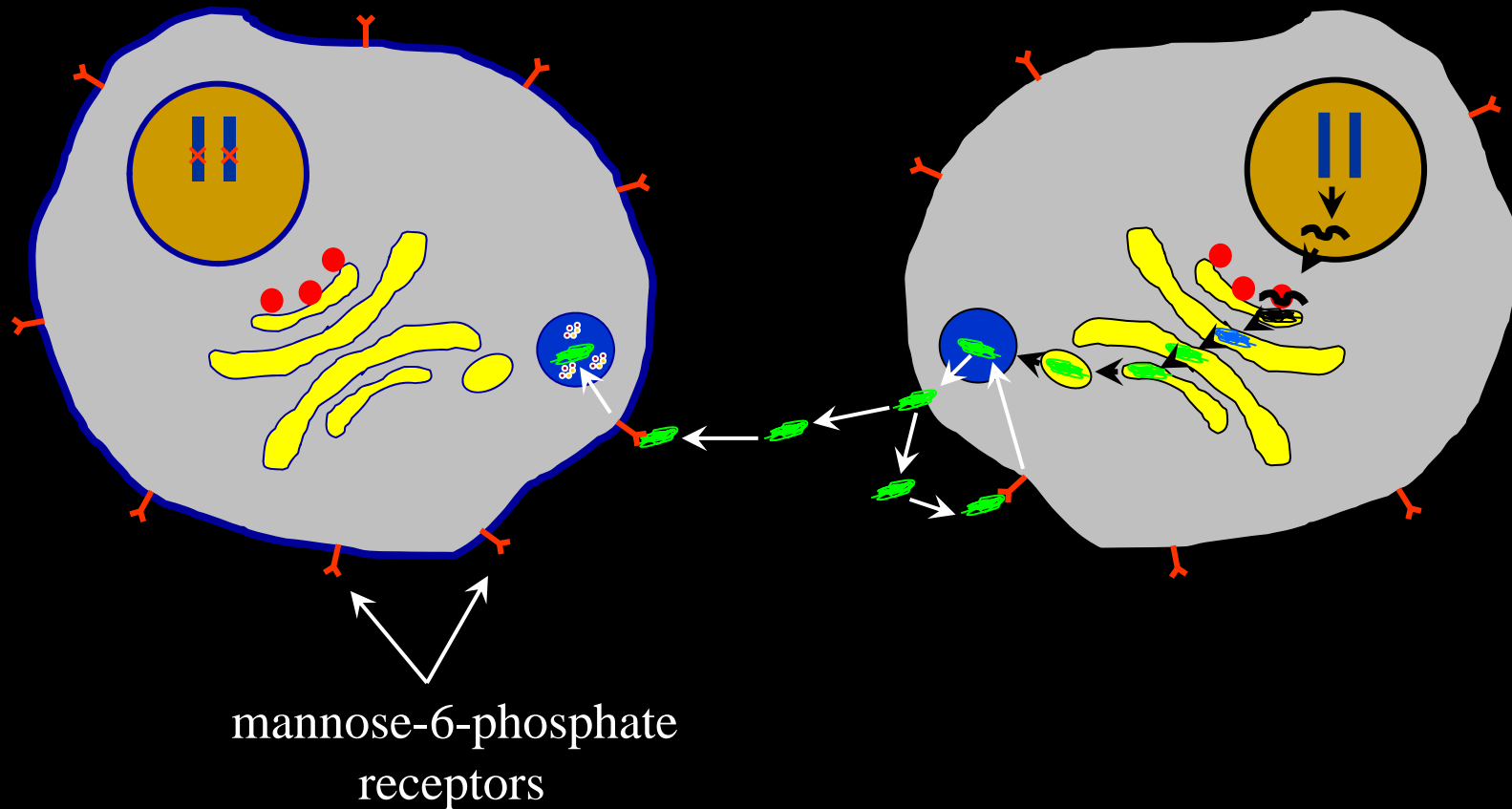
- Only effective for certain mutations
- Low level expression
- Toxicity?

Stem Cell-Mediated Therapy

(Hematopoietic, Neuronal, Mesenchymal, etc.)

Patient's Cells
(enzyme-deficient)

Donor or Patient's
Gen. Mod. Cells
(enzyme-positive)



Stem Cell-Mediated Therapy

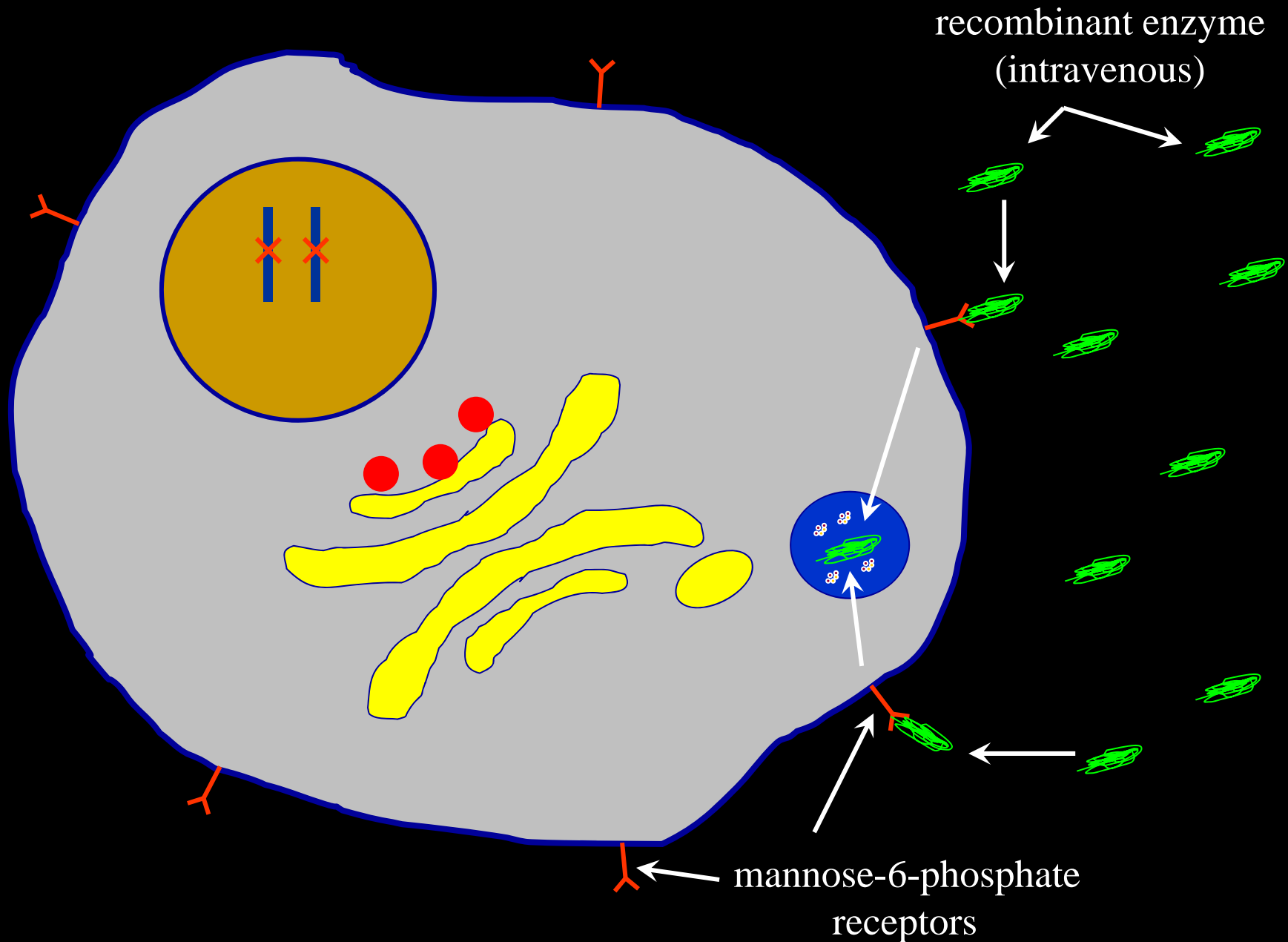
Advantages:

- Good bioavailability (widespread distribution)
- long-term (possibly permanent) expression
- Can genetically modify cells (increase expression)
- Can use autologous (affected patient's) cells?
- Useful for any mutation

Limitations:

- Cell rejection (non-patient donor)
- Immune reactions
- Safety?

Enzyme Replacement Therapy



Enzyme Replacement Therapy

Advantages:

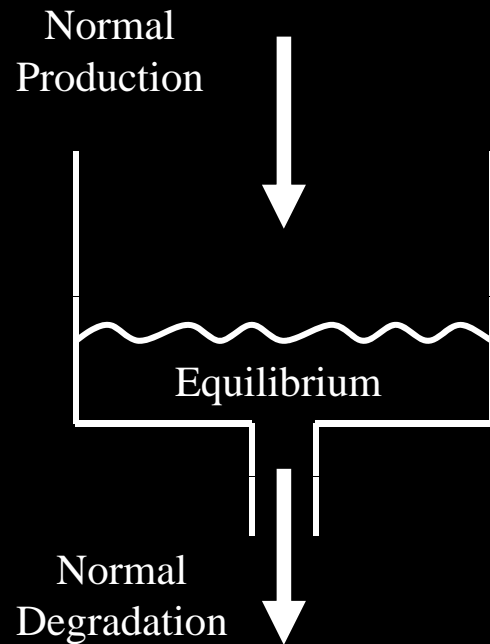
- Non-invasive (intravenous)
- Good bioavailability (systemic)
- Good safety record
- Useful for any mutation

Limitations:

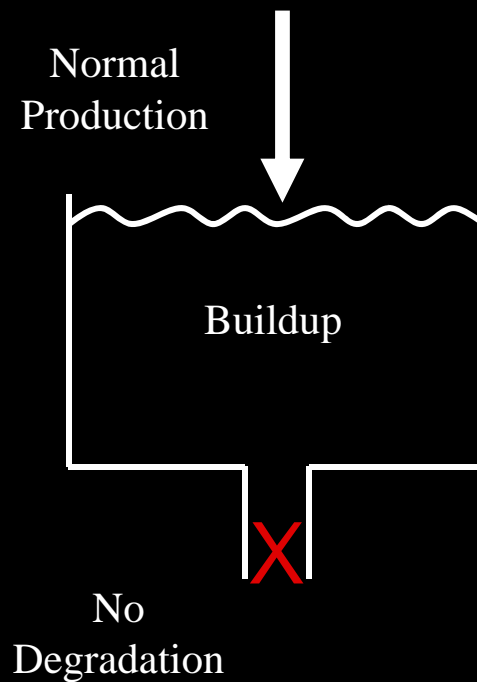
- Repeated administration (weekly)
- Cost
- Immune reactions
- Blood brain barrier (CNS correction?)

Substrate Reduction Therapy

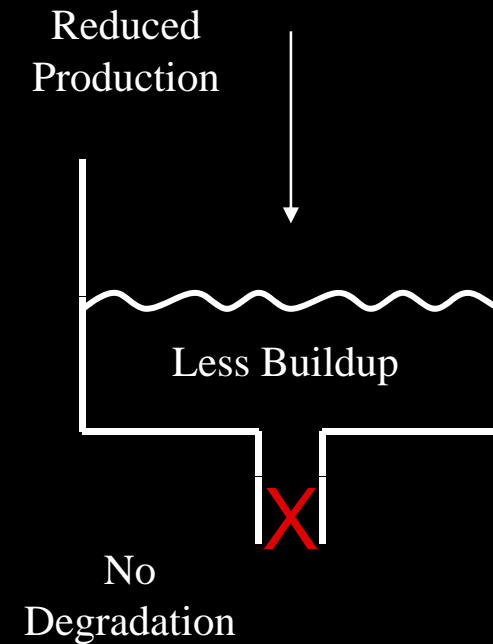
Normal System



Lysosomal Enzyme Deficiency



Treatment with Substrate Reduction Therapy



Substrate Reduction Therapy

Advantages:

- Small molecule drugs (orally available)
- Good bioavailability (systemic)
- Useful for any mutation

Limitations:

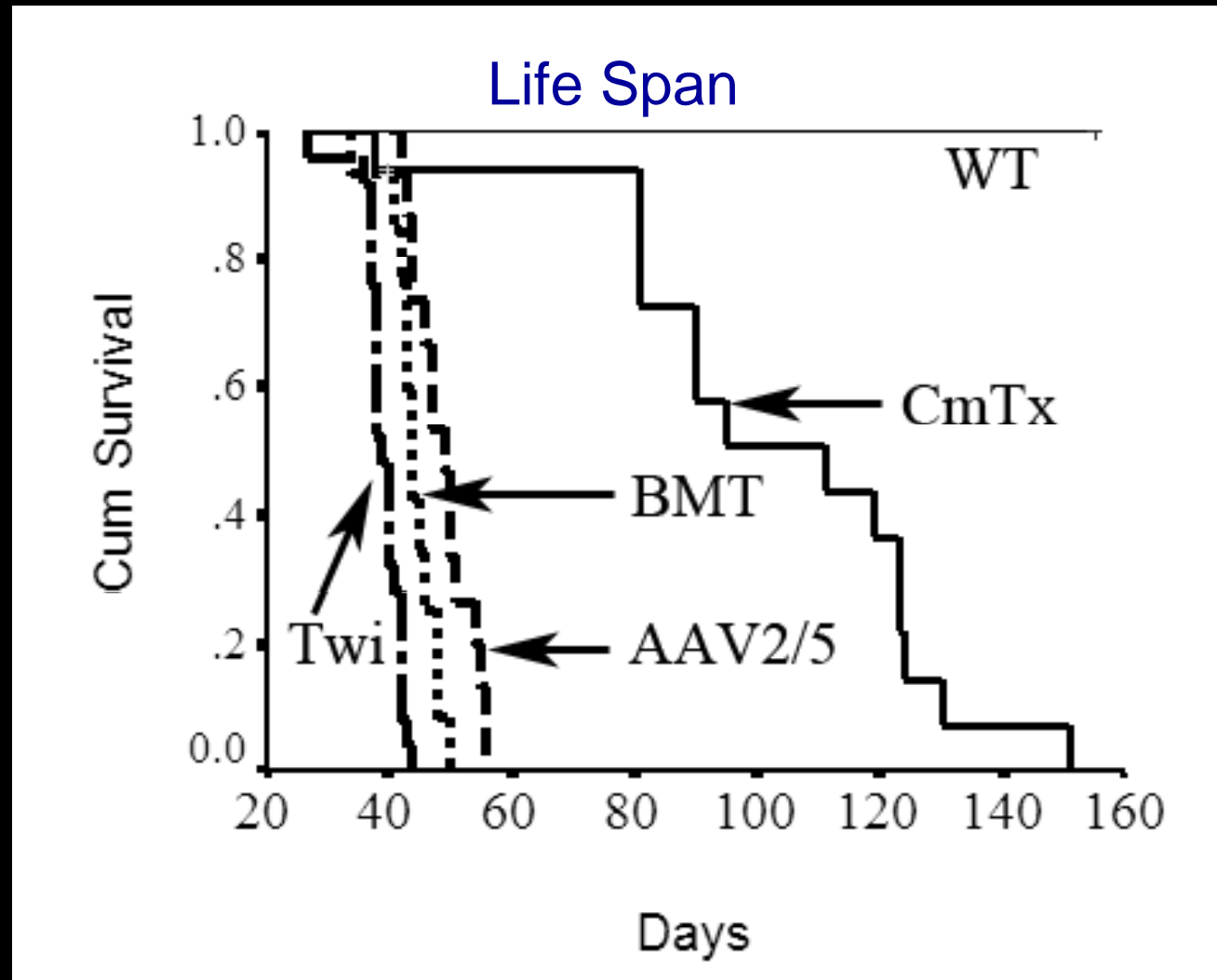
- Does not address the underlying defect
- Will likely only slow disease progression
- Toxicity

Future Directions/Challenges

Unlikely that any single therapy
will “cure” the disease

-The most effective treatment will likely incorporate two or more
therapeutic approaches

Combination BMT/Gene Therapy (Krabbe Disease)

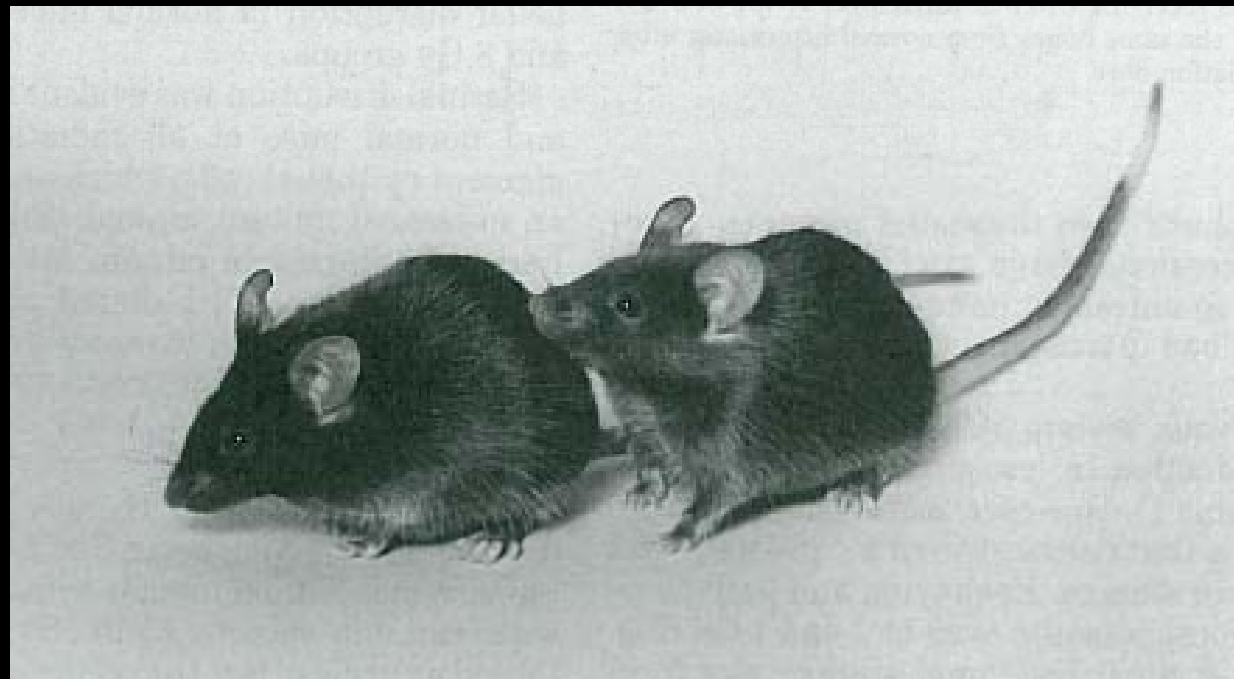
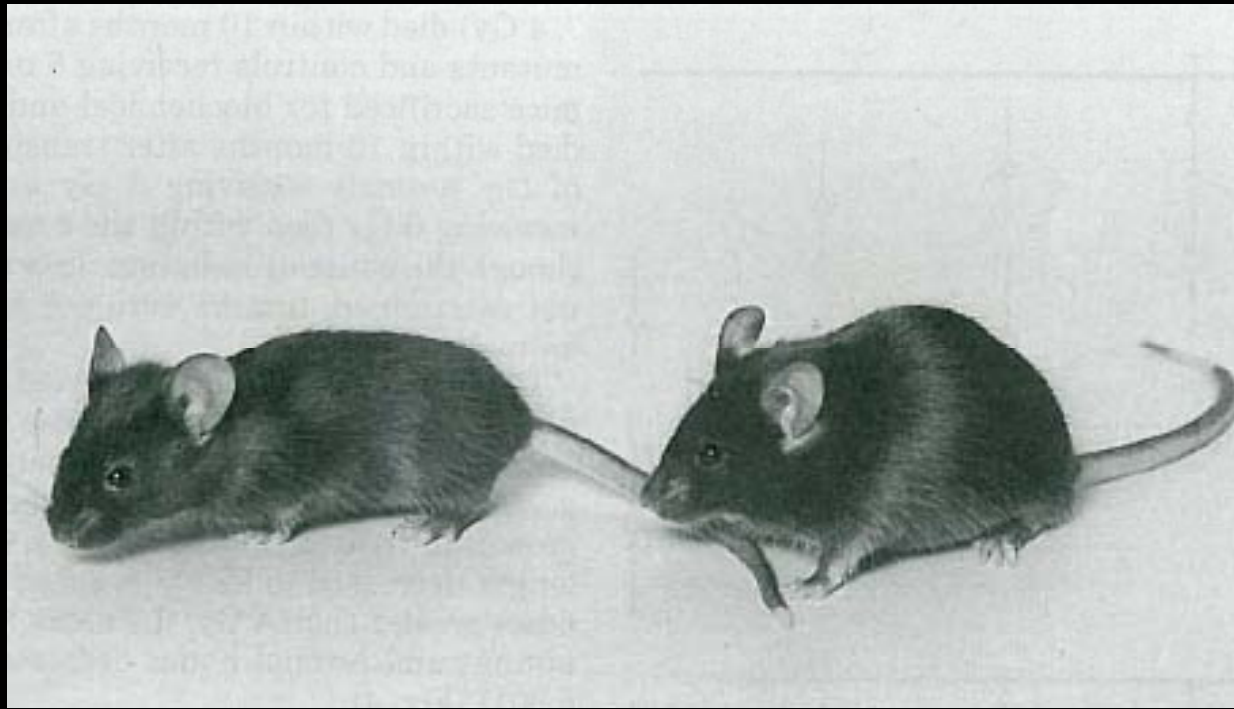


Lin, D. et al., (2007) *Mol. Ther.*, 15:44-52

Newborn Screening







Canine MPS VII (Newborn Systemic – Retroviral Vector)



Ponder et al., (2002) PNAS 99:13102

Conclusions

- New therapeutic targets are being discovered
- Increased arsenal of therapeutic options
- Promising future