

# What is Next in Therapeutic Development?

R. Sandhaus

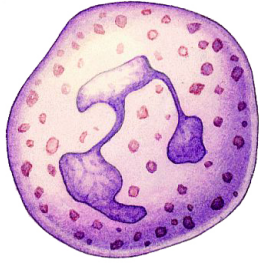
# Outline

- Near Next
- Further Next
- Distant Next

# Near Next

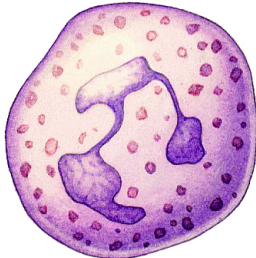
- Lung Disease
  - Augmentation of AAT levels
    - New Plasma-derived therapies/New doses of therapy
    - Recombinant AAT
    - Gene therapy
  - Inhaled Hyaluronan (hyaluronic acid)
  - Synthetic neutrophil elastase inhibitors
- Liver Disease
  - Gene silencing
  - ?Gene therapy
  - Chaperones
- Combination
  - Augmentation + silencing
  - (Liver transplant)

# Central Dogma



**EMPHYSEMA**

# Normal AAT

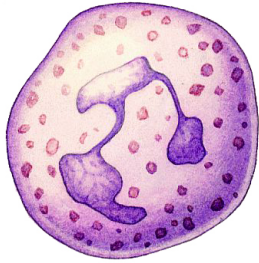


Elastase →



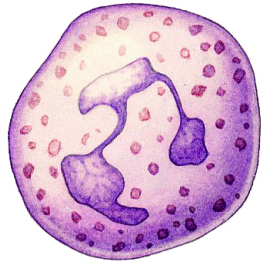
~~EMPHYSEMA~~

# AAT Deficiency

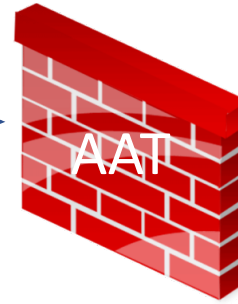


**EMPHYSEMA**

# Augmentation Therapy Recombinant AAT Gene Therapy\*



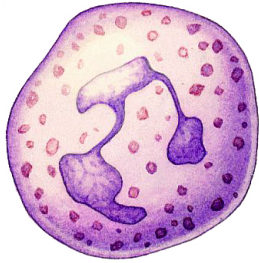
Elastase →



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\*Editorial comment: Likelihood of success low (with current technology)

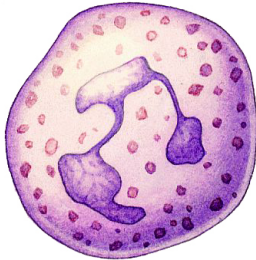
# Synthetic Elastase Inhibitor



~~**EMPHYSEMA**~~

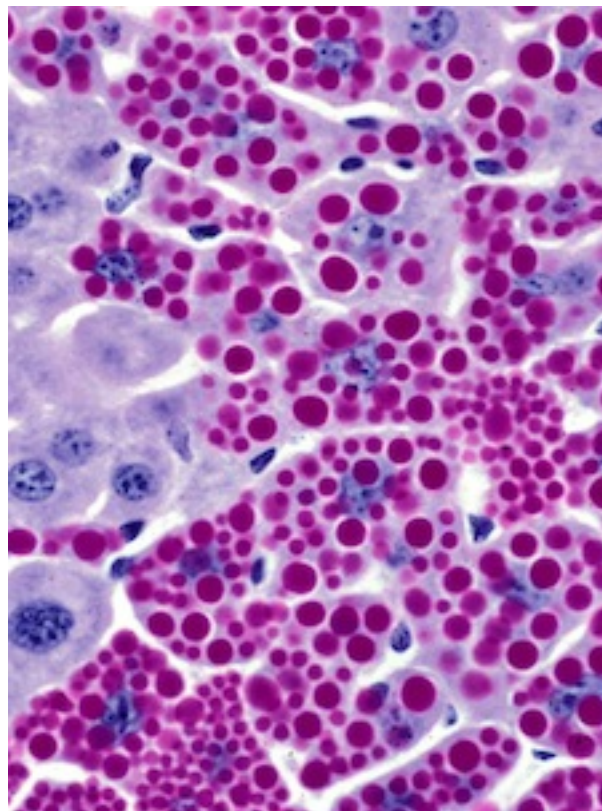


# Hyaluronan

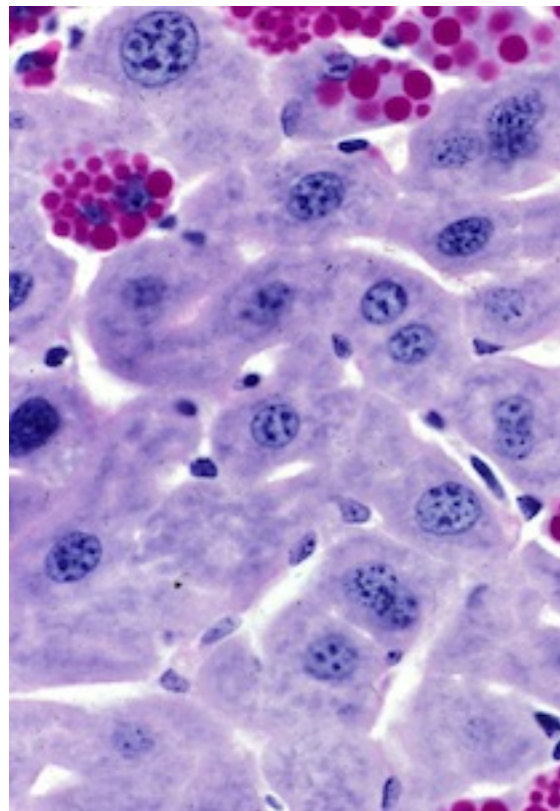


~~**EMPHYSEMA**~~

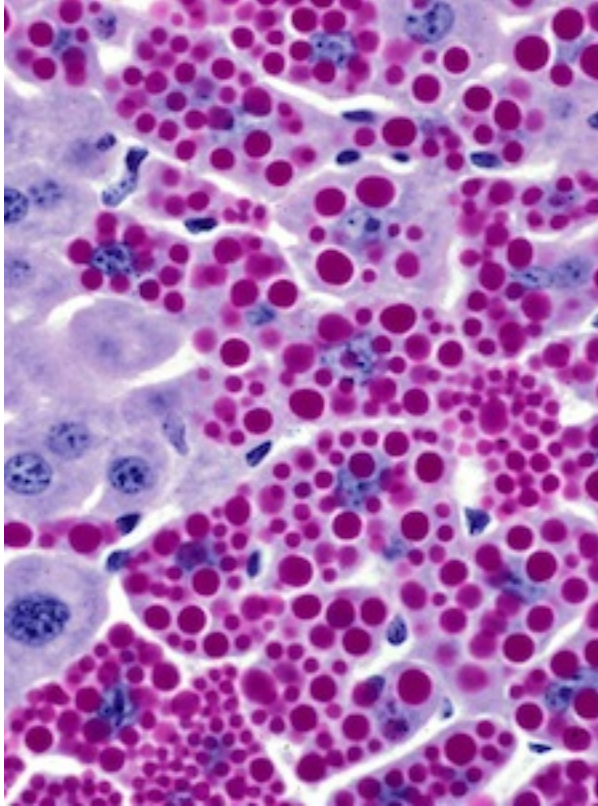
# Liver



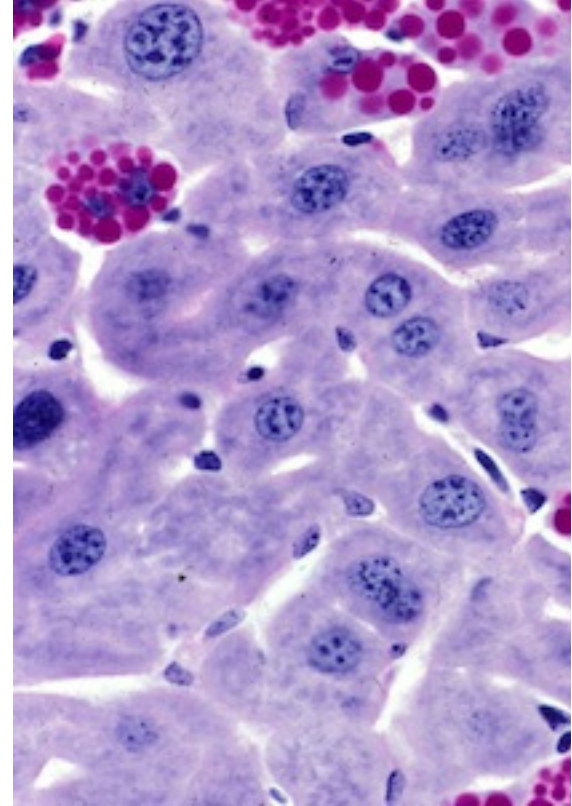
Gene Silencing



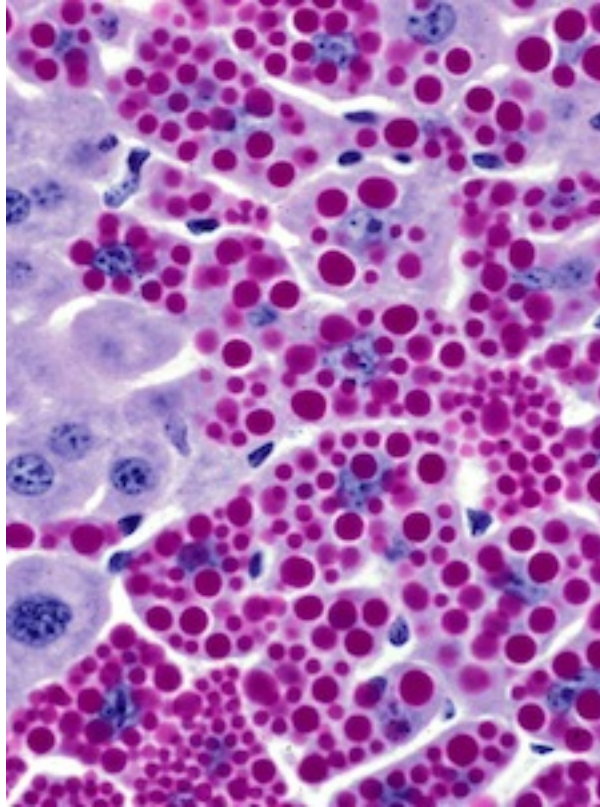
# Liver



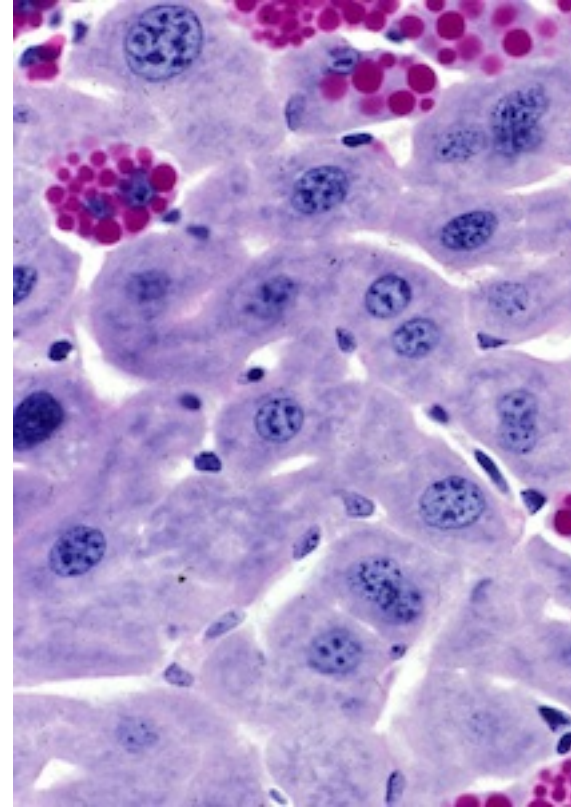
Gene Therapy



# Liver



Chaperones



# Near Next

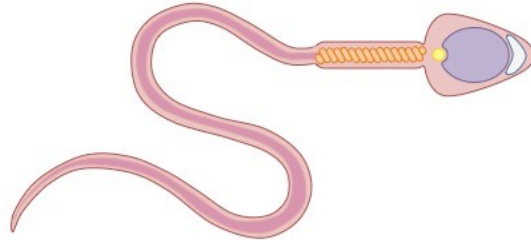
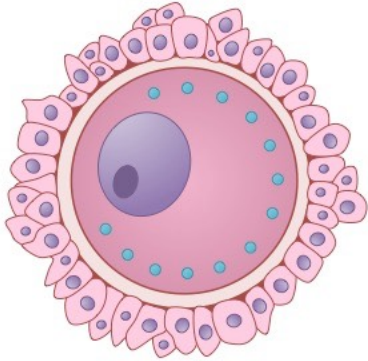
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  - Gene therapy + silencing
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# Further Next

- Gene therapy + Z silencing
- mRNA modification
- Gene correction
- Cell transplantation

# Distant Next

- Gene correction in Sperm or Egg
- Do all or any of this in the fetus



# Distant Next

- Artificial implantable lungs and livers
  - Printed or animal derived connective tissue architecture populated by lung or liver stem cells



# Summary

- We have entered a time of acceleration of therapeutic development in Alpha-1
- In many ways, this is due to
  - The work of the investigators attending this conference
  - The funding provided by Alpha-1 Foundation
- We hope that the wealth of potential therapeutic approaches will lead to prevention and an eventual cure for Alpha-1
- There are likely many paths to the cure