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# Optimisation of Aerosol Delivery of Lipid/DNA Complexes for Clinical studies

**Lee Davies**

**Gene Medicine Research Group**

**Oxford University**

**& United Kingdom Cystic Fibrosis Gene Therapy Consortium**

## **Lung gene therapy**

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- **Efficient delivery of vectors to the lung**
- **Topical aerosol delivery**
- **Inability to aerosolise many gene therapy vectors**
- **Delayed development of gene therapies for lung disease**

# UK CF Gene Therapy Consortium:



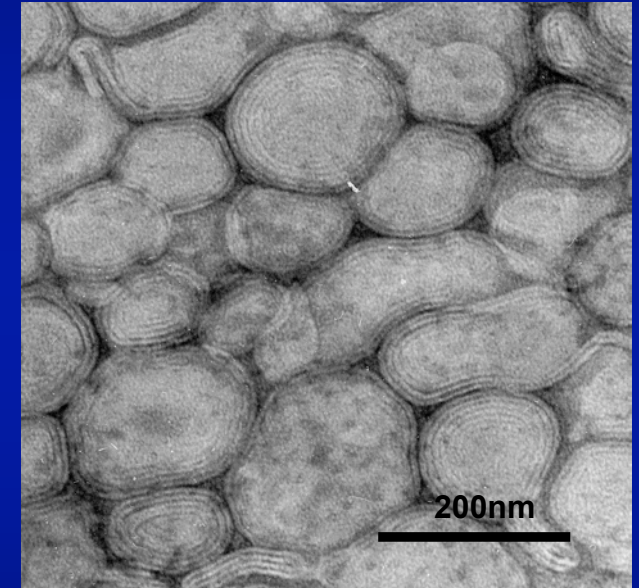
**Aim:** Select 'best' vector  
Multiple-dose lung trial  
Clinical benefit

**Method:** Systematic screening of non-viral vectors  
Suitability for aerosol delivery

**Results:** Genzyme lipid 67 (GL67)

# Genzyme Lipid 67

- Cationic lipid
- Stable lipoplexes with pDNA
- Single dose lung trial (Alton *et al* Lancet 1999)
- Nebulisation apparatus discontinued
- Select alternative nebuliser device for clinical delivery of GL67 complexes
- Range of aerosolisation devices



pDNA/GL67: DOPE:DMPE-PEG<sub>5000</sub> lipoplexes

# Nebulisers

- Jet nebulisers

Pari

LC+

Sprint

Sprint Junior

Sprint Star

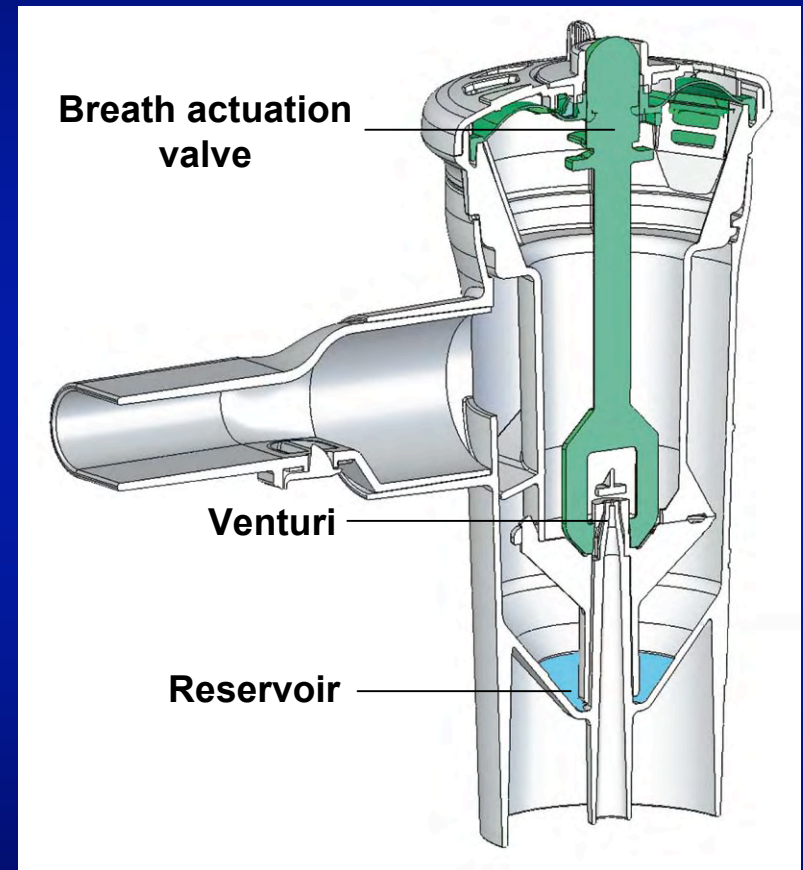
Trudell

AeroEclipse II BAN

- Assess suitability for clinical delivery

**Compatible with GL67**

**Aerosol characteristics**

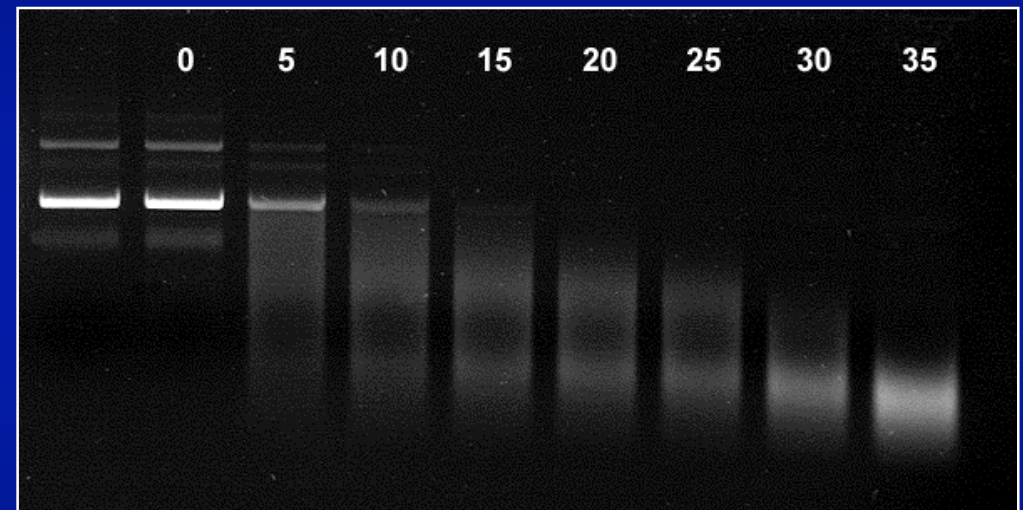


**AeroEclipse II breath actuated nebuliser**

## Formulation stability - Naked DNA

- **Naked DNA** unstable
- High shear forces
- Loss of biological efficacy

### Nebulisation time (mins)

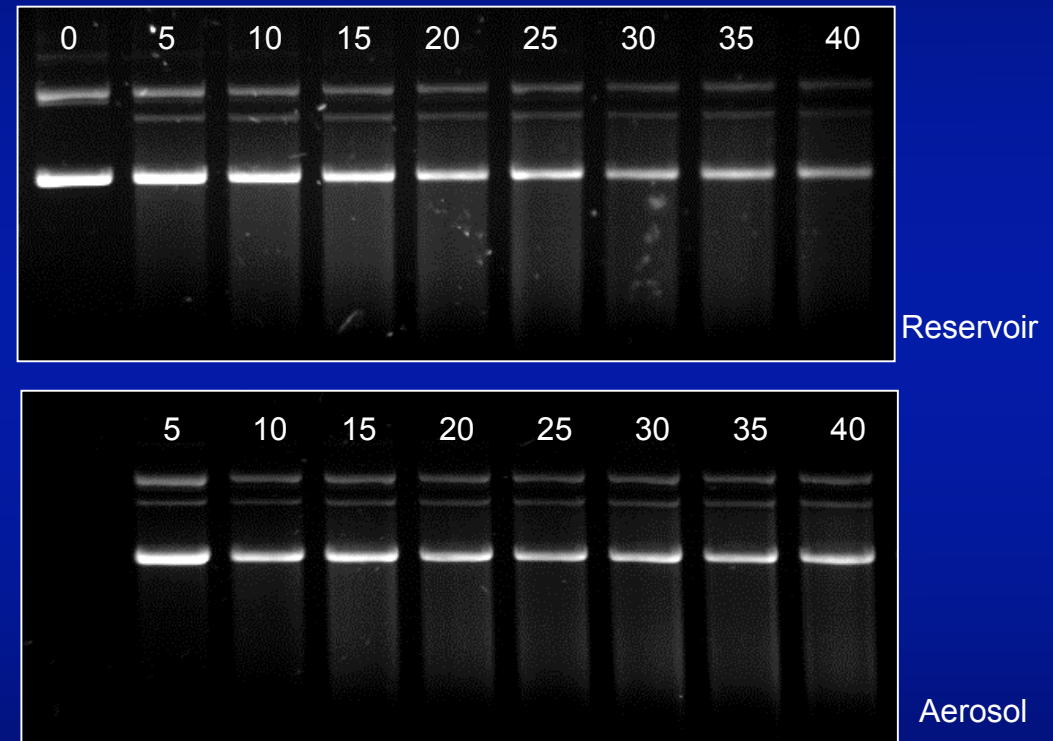


5.6kb plasmid Pari LC+ nebuliser

## Formulation stability - GL67

- DNA protected
- Minimal damage with all nebulisers
- Compatible with GL67 aerosols
- Biological efficacy

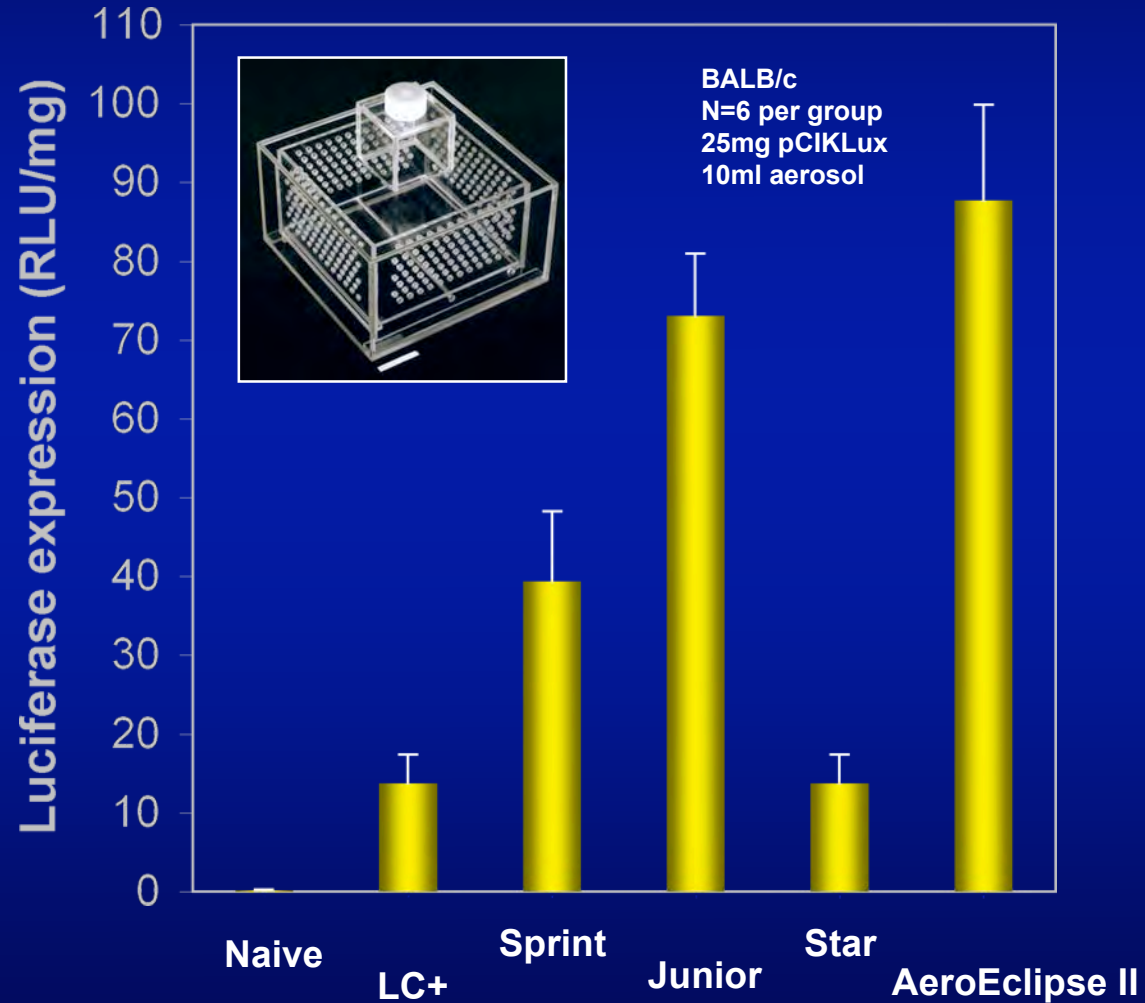
### Nebulisation time (mins)



5.6kb plasmid/GL67 Pari LC+ nebuliser

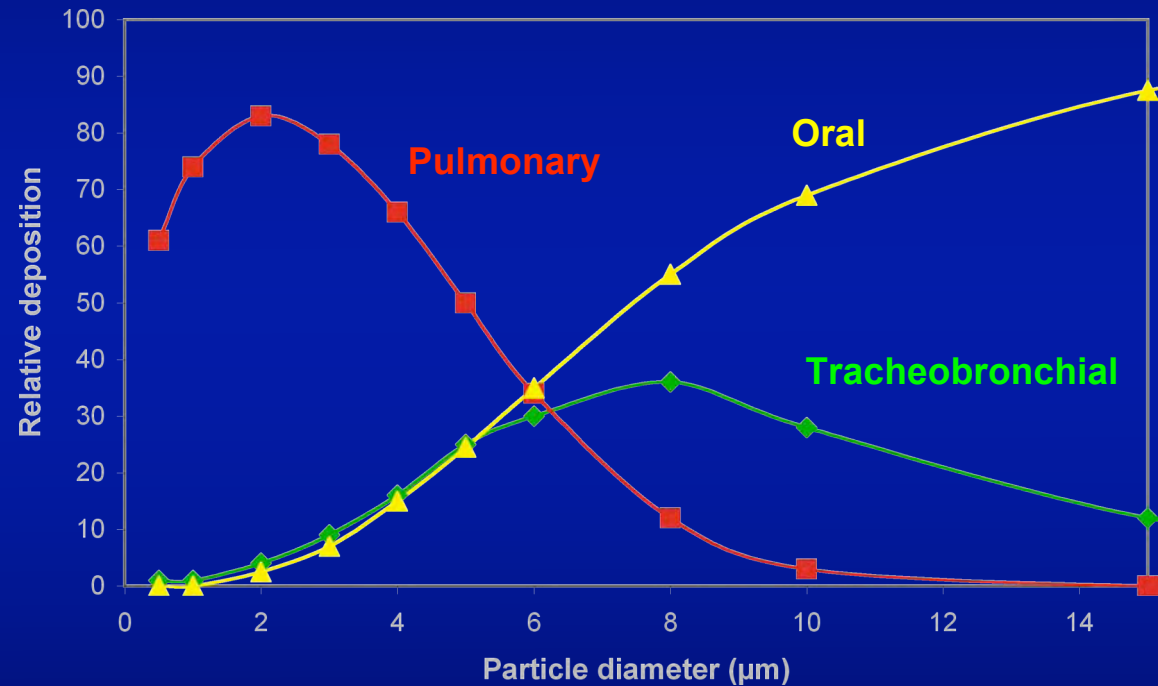
# Formulation stability

- Mouse lung aerosol model
- Variable expression
- Junior and AeroEclipse II
  
- Aerosol characteristics



# Aerosol droplet size

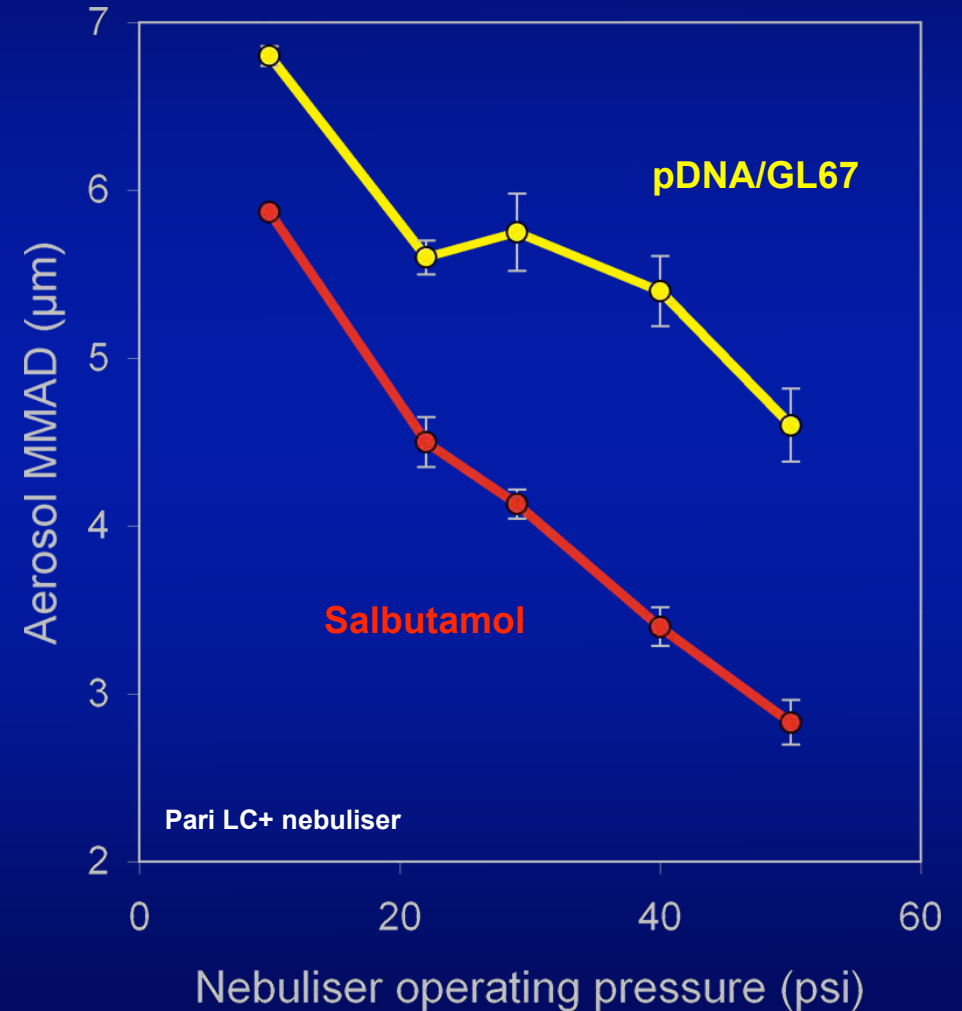
- Most important parameter
- Site of lung deposition
- Delivery efficiency
- CF patients 2-3  $\mu\text{m}$  droplets
- Essential to know droplet size



Clark *et al.* Respiratory drug delivery IV 1994

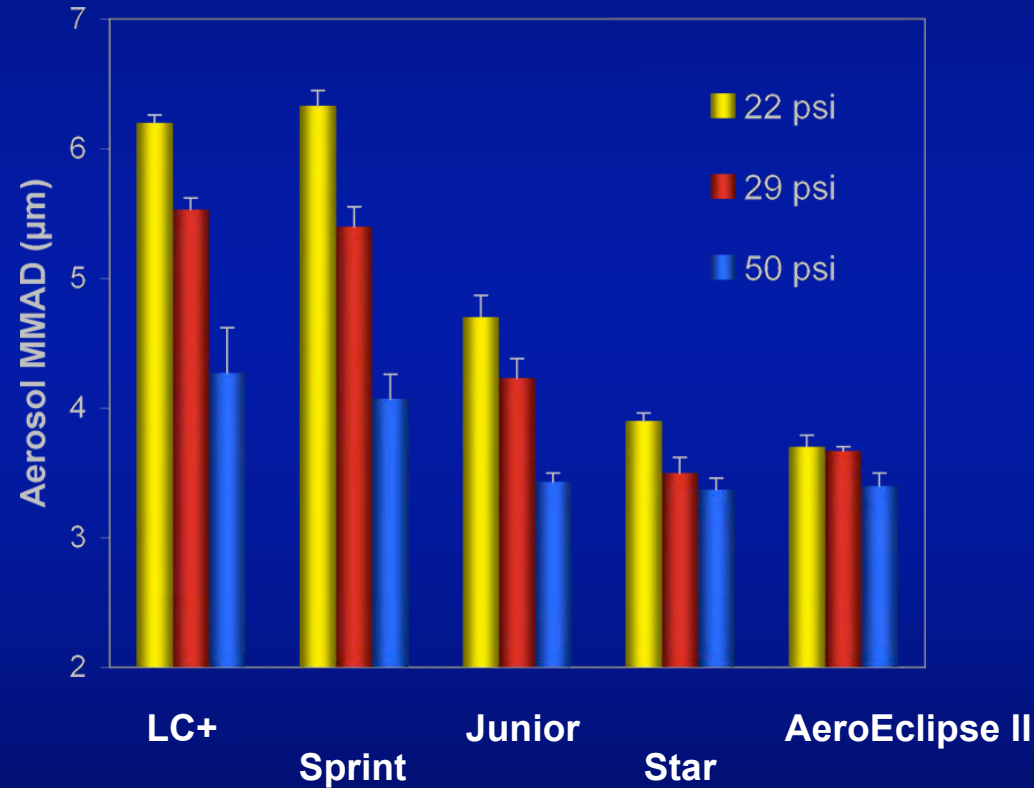
# Aerosol droplet size

- Aerosol droplet size
  - Nebuliser design
  - Operating pressure
  - Formulation
- Assess pDNA/GL67 formulations with each nebuliser



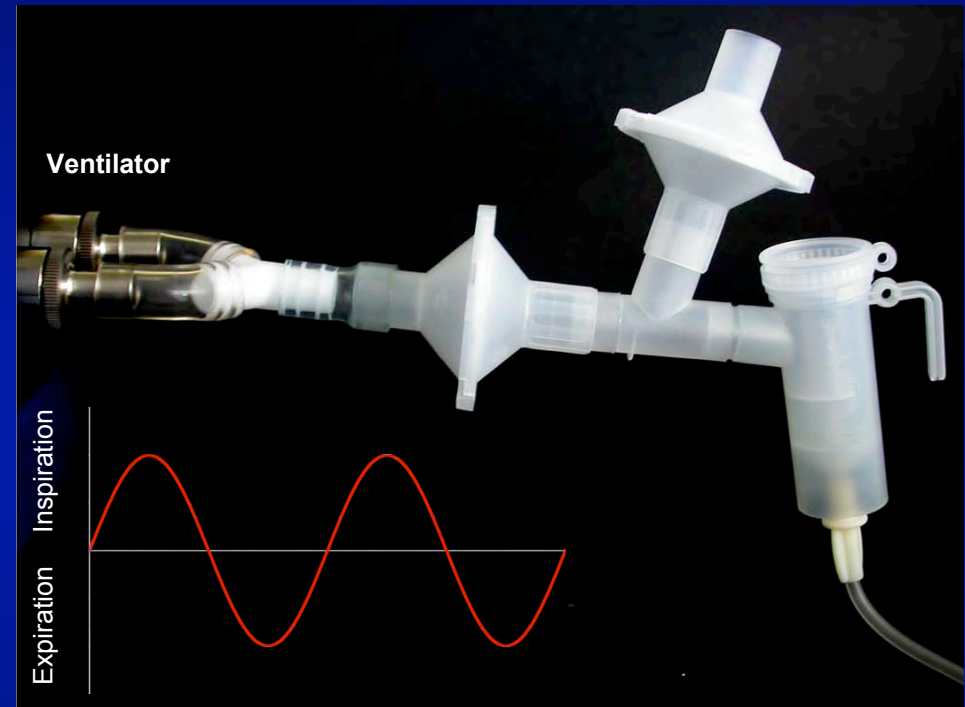
# Aerosol droplet size

- Significant variation between nebulisers
- Smallest droplets at 50 psi
- All larger than ideal 2-3  $\mu\text{m}$
- Optimal aerosols (50 psi)
- **Junior**  $3.43 \pm 0.07 \mu\text{m}$
- **Star**  $3.37 \pm 0.09 \mu\text{m}$
- **AeroEclipse II**  $3.40 \pm 0.1 \mu\text{m}$



## Aerosol delivery rate

- Therapeutic dose
- Clinically acceptable time-frame
- Formulation concentration
- Nebuliser output rate
- Requires simulated breathing
- Ventilator



**Sinusoidal wave form**

**15 breaths/min**

**500 ml tidal volume**

**Inspiration:Expiration 1:1**

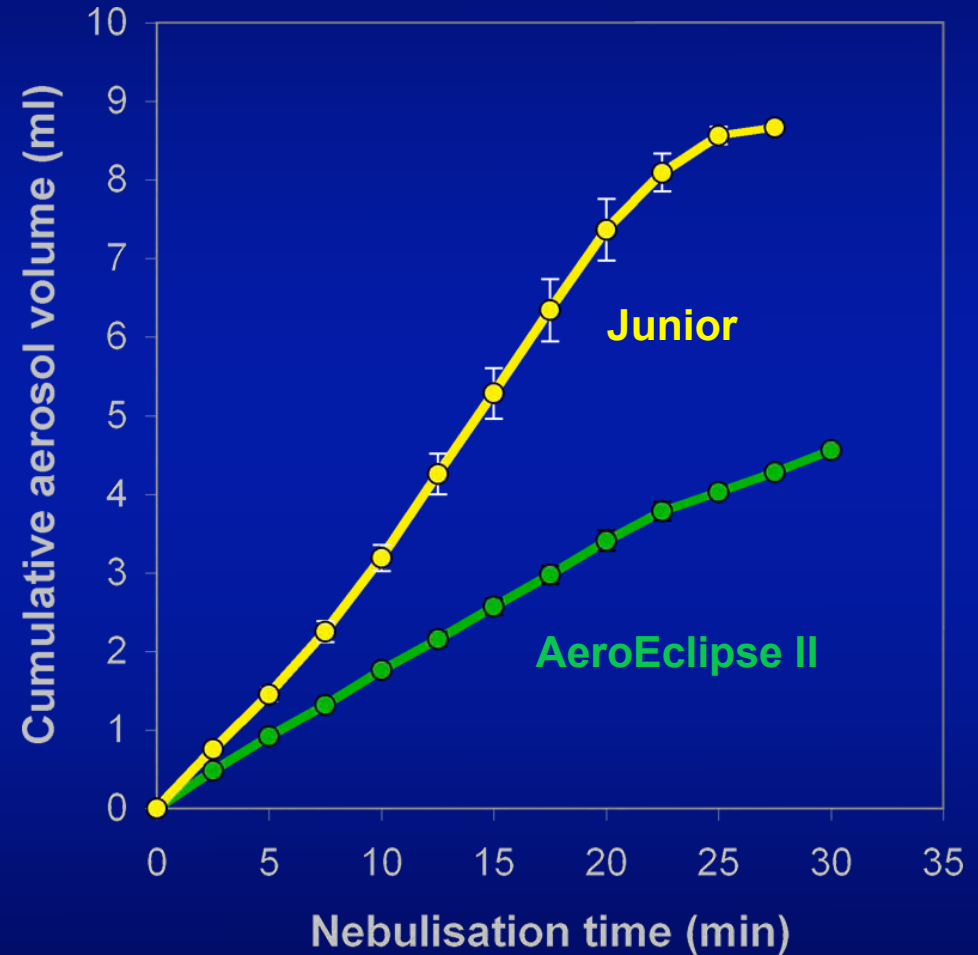
# Aerosol delivery rate

- DNA delivery rates very different

**Junior**  $882 \pm 15 \mu\text{g}/\text{min}$

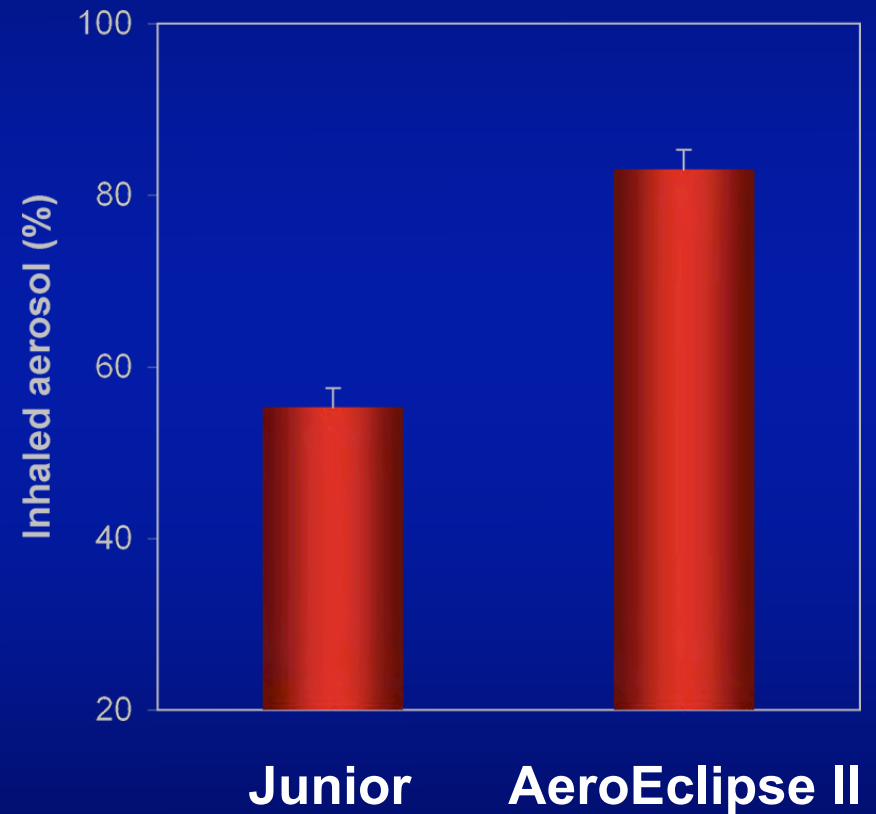
**AeroEclipse II**  $438 \pm 16 \mu\text{g}/\text{min}$

- 50 mg pDNA dose in 1-2 hrs
- Acceptable for patients
- AeroEclipse II breath actuated



## Aerosol delivery efficiency

- **Breath-actuated**  
**Aerosol during inspiration**
- **Increased efficiency**  
**Less wastage**  
**Higher lung dose**
- **AeroEclipse II slower but more efficient**



## Summary

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- **AeroEclipse II nebuliser selected for UKCFGT GL67 clinical trial**

**Compatible with GL67 formulations**

**Acceptable droplet size for CF patients**

**Enhanced delivery efficiency**

**Acceptable delivery rate**

## Conclusions

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- **Nebuliser selection is extremely important**
- **Combination of GTA and nebuliser device is critical**
- **Need to physically measure aerosol output characteristics**
- **Optimisation of aerosol delivery for individual diseases maximises chances of success**

## Acknowledgements

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