Ahead of the Curve – Emerging CF Therapies 2009: Pathophysiology and Therapeutic Targets

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Disclosure

Principal Investigator: Gilead, GlaxoSmithKline, Inspire Pharmaceuticals, PTC Therapeutics, Inc., Vertex Pharmaceuticals

Consultant: Aridis Pharmaceuticals, Arriva Pharmaceuticals, Inc., Genentech, Inc., Inspire Pharmaceuticals, Johnson & Johnson, Lantibio, Inc./AOP Orphan Pharmaceuticals AG, MPEX Pharmaceuticals, Novartis Pharmaceuticals, PTC Therapeutics, Inc., Vertex Pharmaceuticals

Pathogenesis of CF Lung Disease

Defective CF Gene Product

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Defective Ion Transport

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Airway Surface Liquid Depletion

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Defective Mucociliary Clearance

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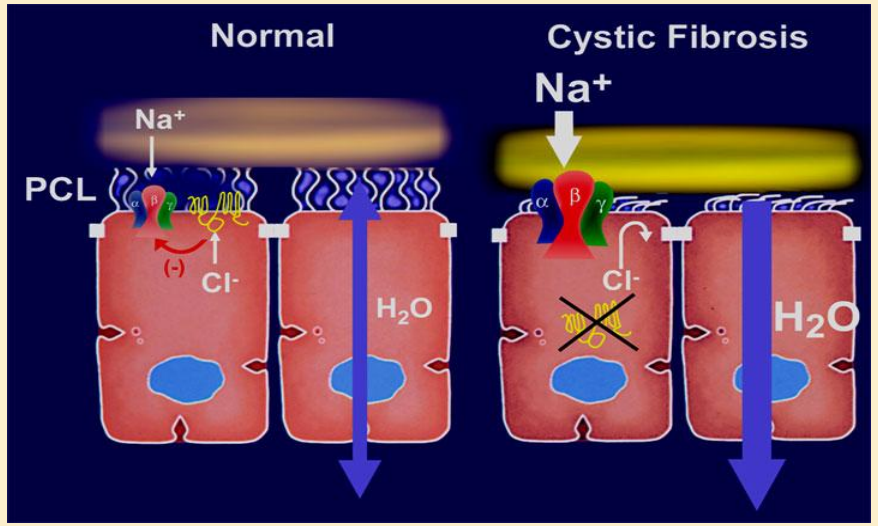
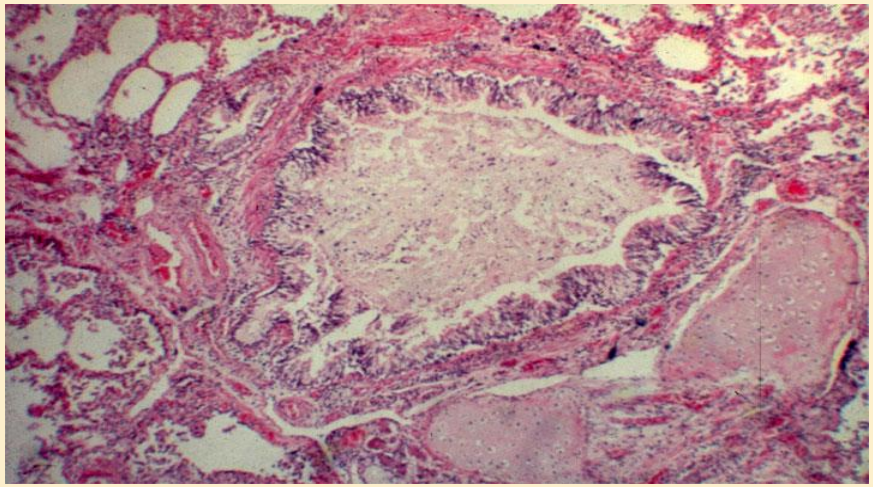
Obstruction

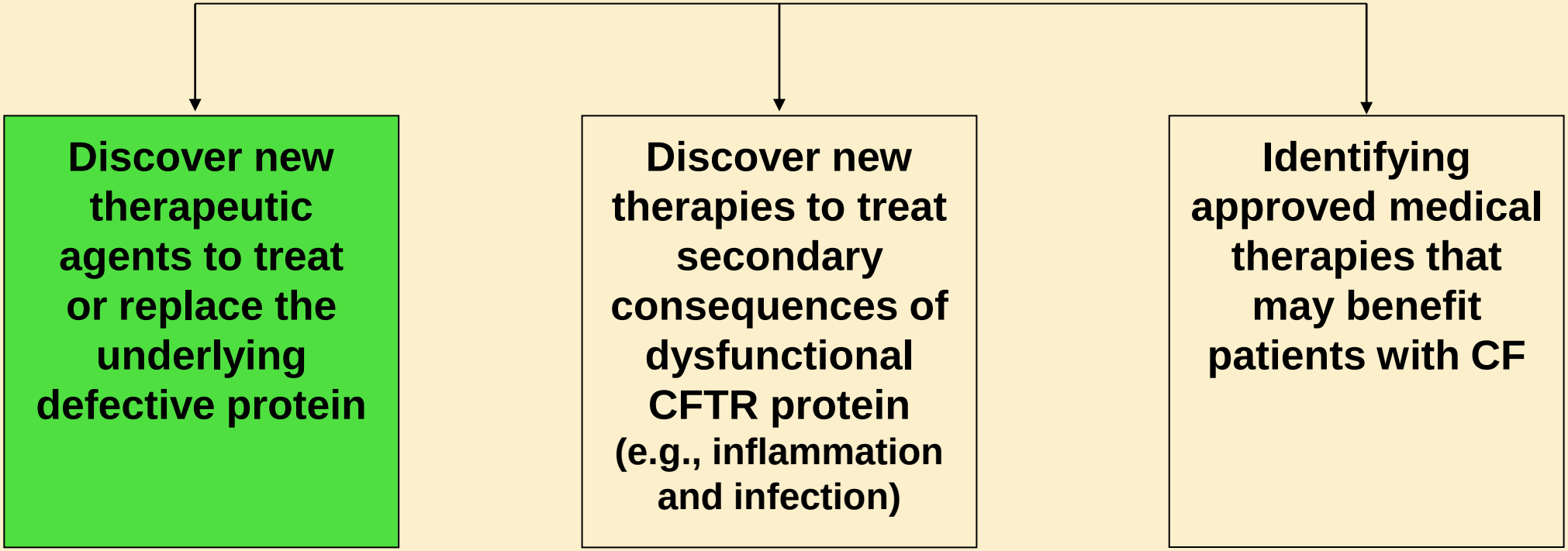
Infection

Inflammation





Three-Pronged Approach to Drug Discovery



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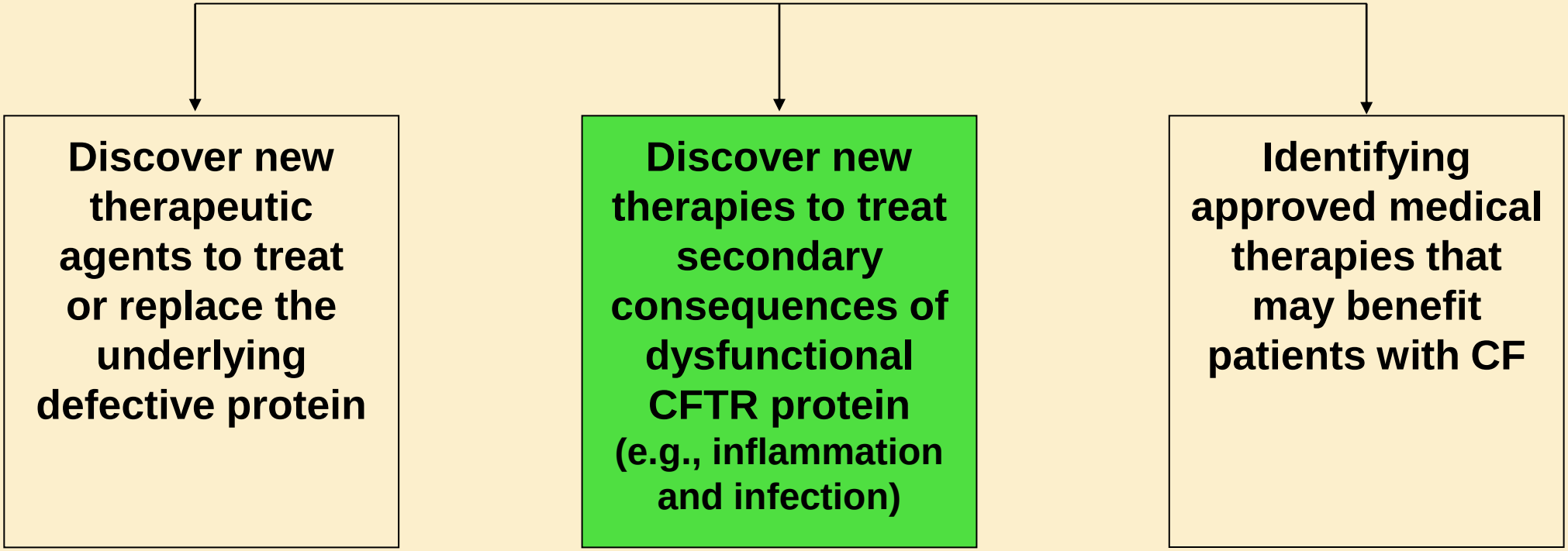

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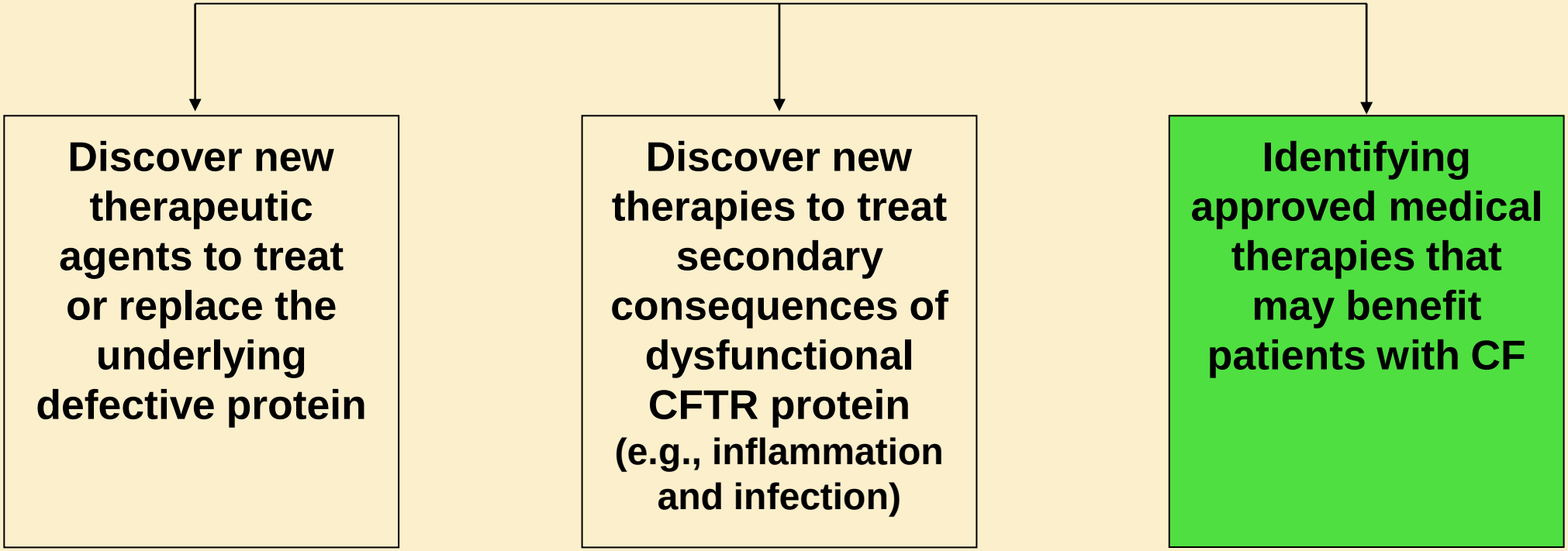
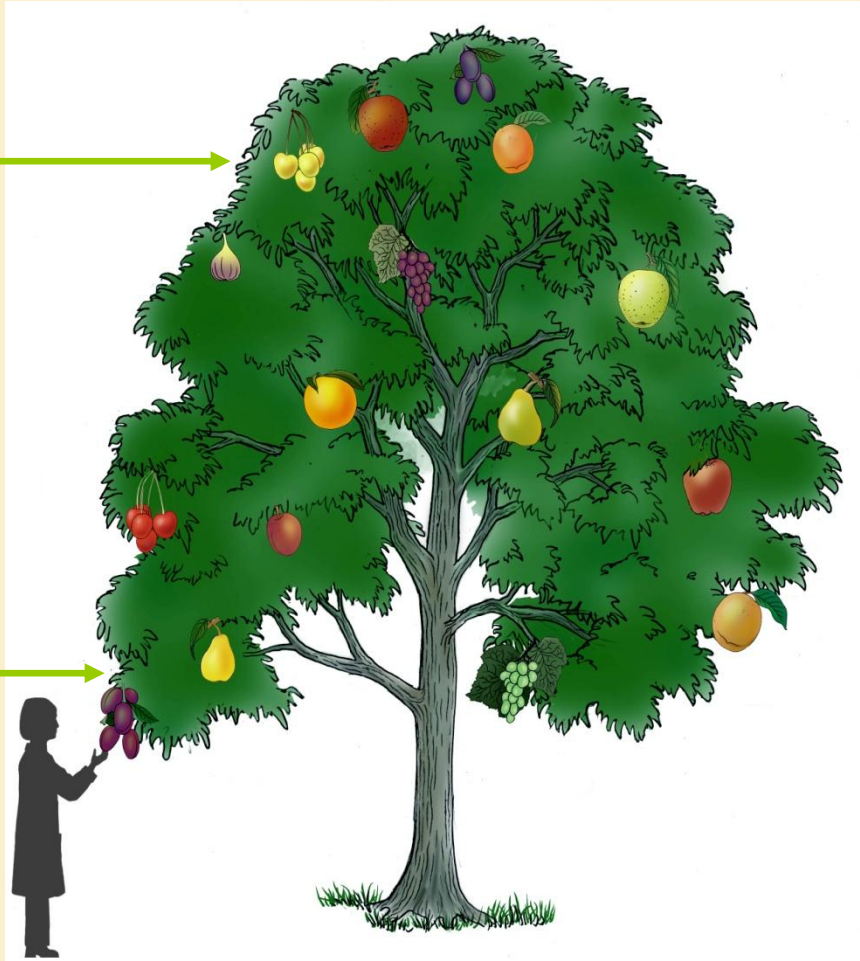


‘Low-Hanging Fruit’ Approach to CF Clinical Trials

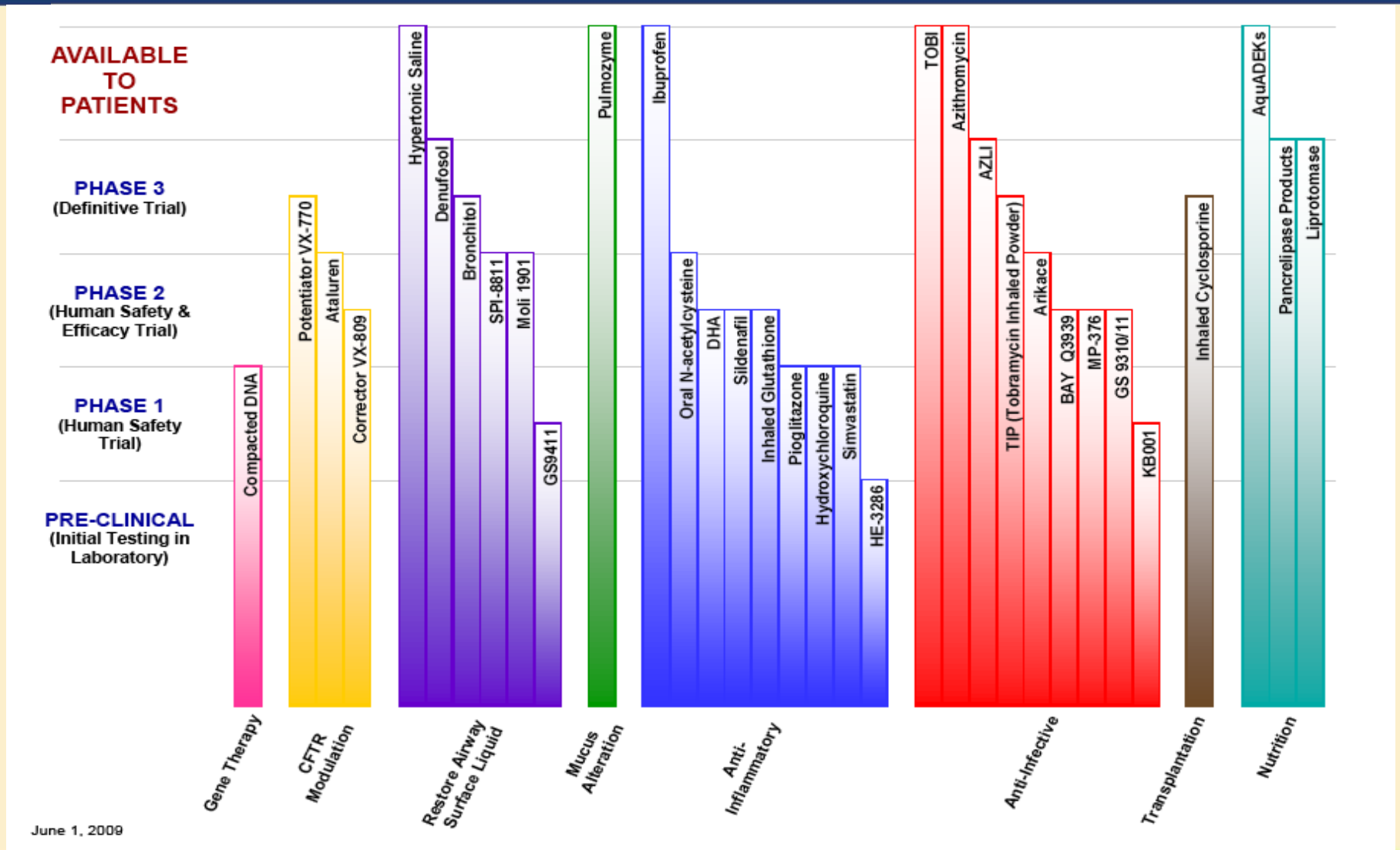
Develop New Drugs

Bringing Approved Drugs to CF

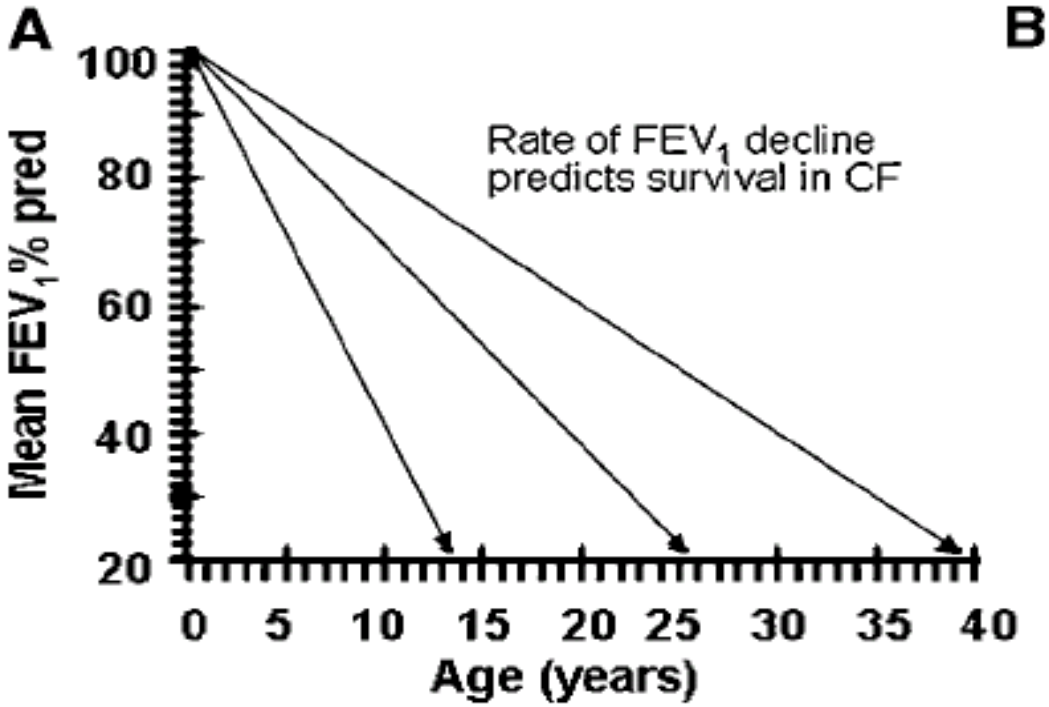


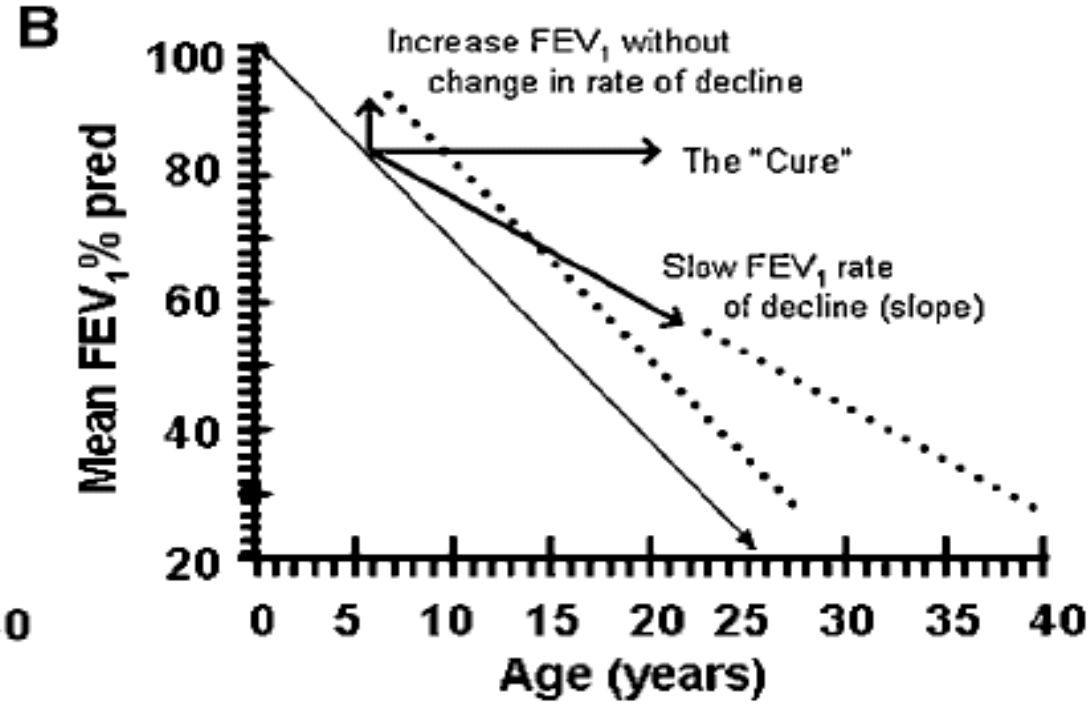
- Advantages
  - Faster
  - Cheaper
  - Immediately available to patients
  - Low risk for industry
  - Well defined safety profile
- Examples
  - Ibuprofen
  - Azithromycin
  - Hypertonic Saline

Cystic Fibrosis Foundation Therapeutics Pipeline



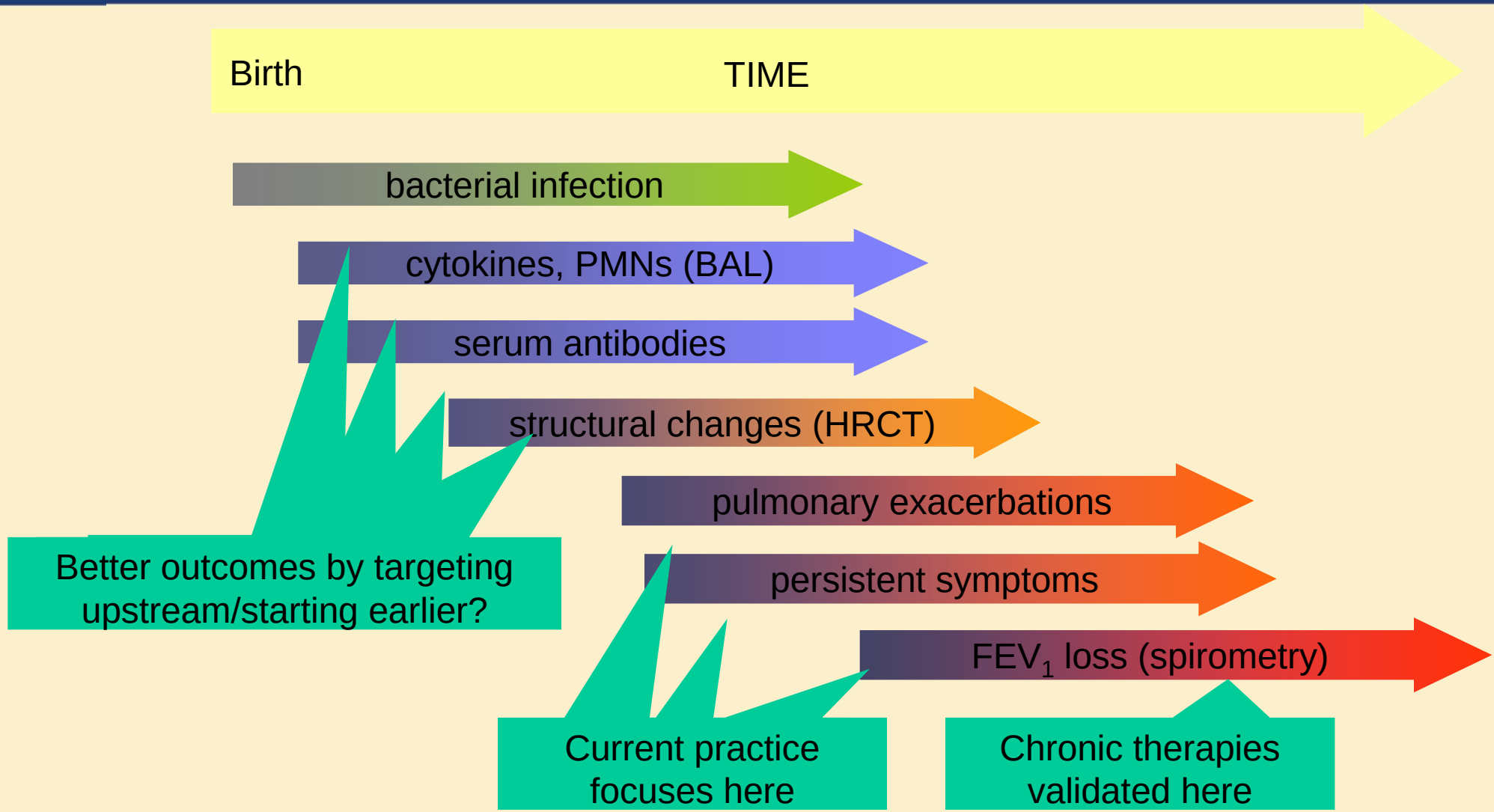
Our Goal: "Disease Modification" – Slowing or Stopping the Rate of Lung Function Decline



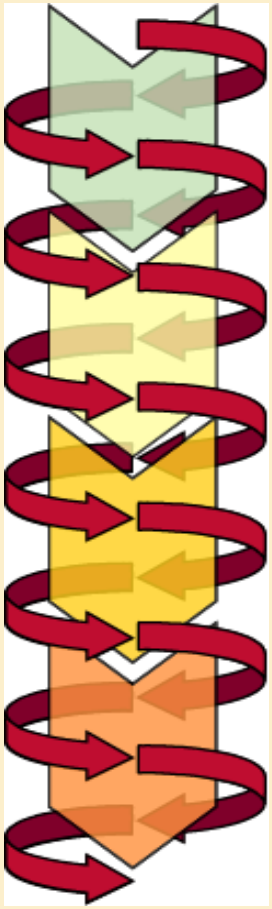


Konstan., *Pediatr Pulmonol.,* 2008. 43, S24-28

CF lung disease begins before loss of FEV_1



Targeting of Interventions



Obstruction

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Early structural lung damage

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Signs/Symptoms

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Spirometric loss

CFF Consensus Guidelines

Experimental Therapies

- CFTR potentiators
- Gene therapy
- Ion channel agents
- CFTR correctors

inhaled tobramycin

ibuprofen

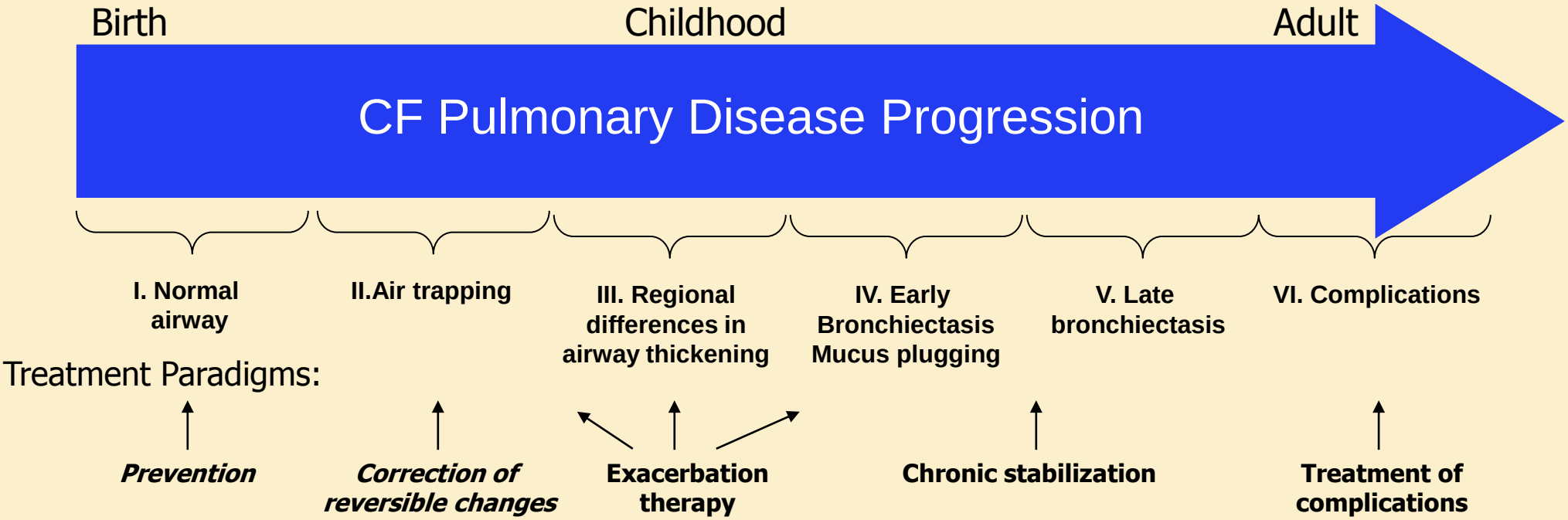
hypertonic saline

β_2-agonists

Guidelines

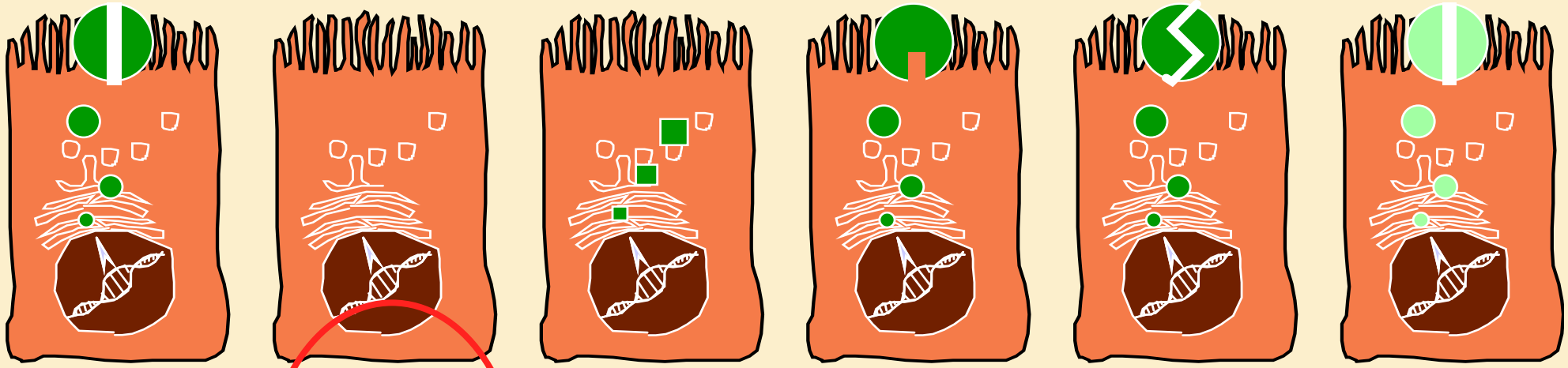
- macrolides (azithromycin)
- ibuprofen
- β_2-agonists

Defining CF Patient Populations for Therapeutic Interventions: Staging Structural Damage



Brody A et al, *AJRCCM* 2005;172:1246

Molecular Consequences of CFTR Mutations



Normal	I	II	III	IV	V
	No synthesis	**Block in processing**	**Block in regulation**	**Altered conductance**	**Reduced synthesis**
	Nonsense G542X	Missense	Missense G551D	Missense R117H	Missense A455E
	Frameshift 394delTT	AA deletion ΔF508			Alternative Splicing 3849+10kbC–>T
	Splice junction 1717-1G–>A				

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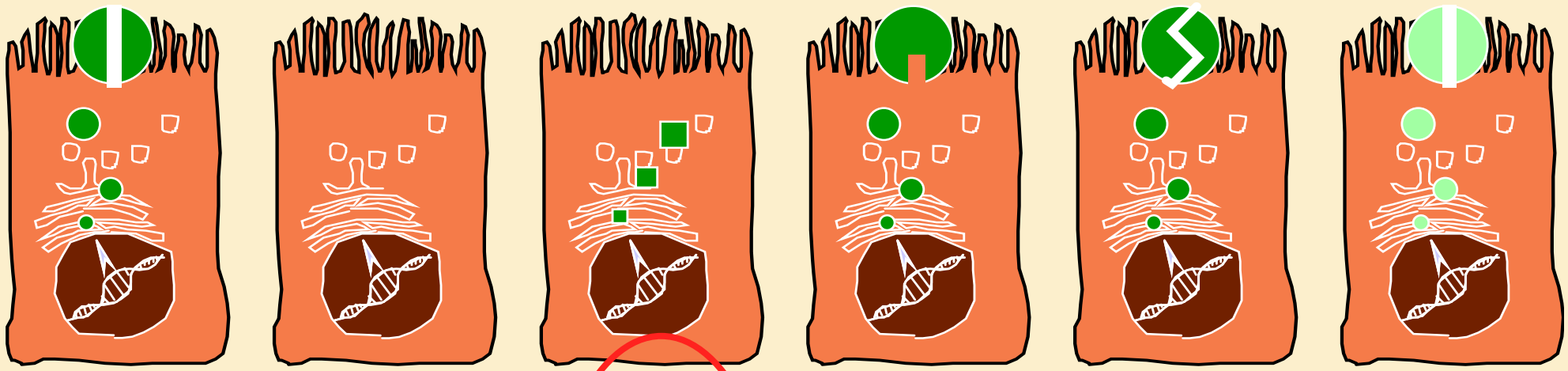

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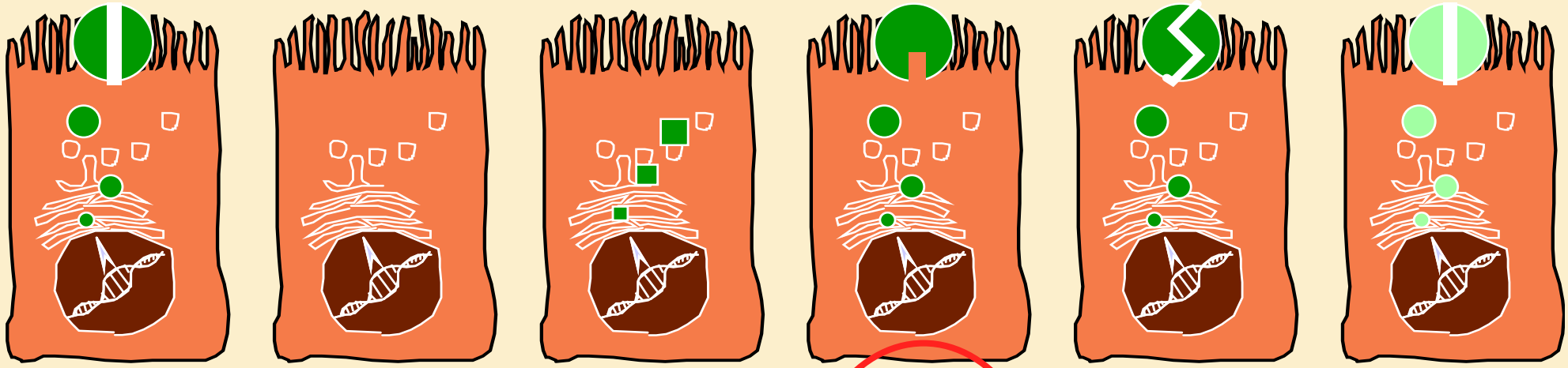

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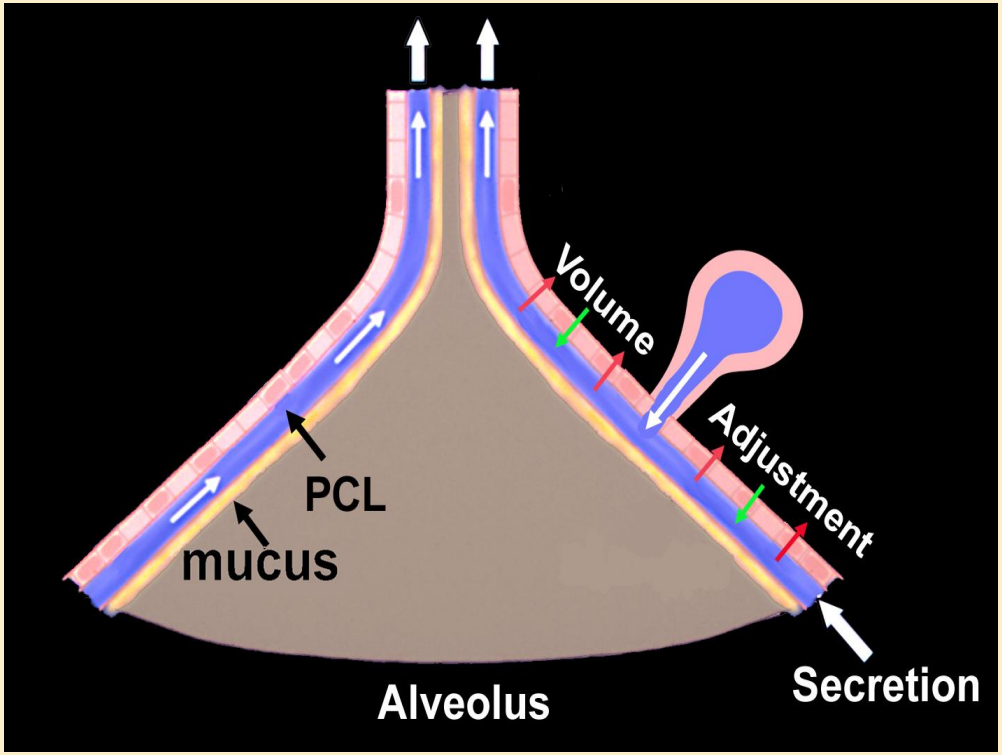
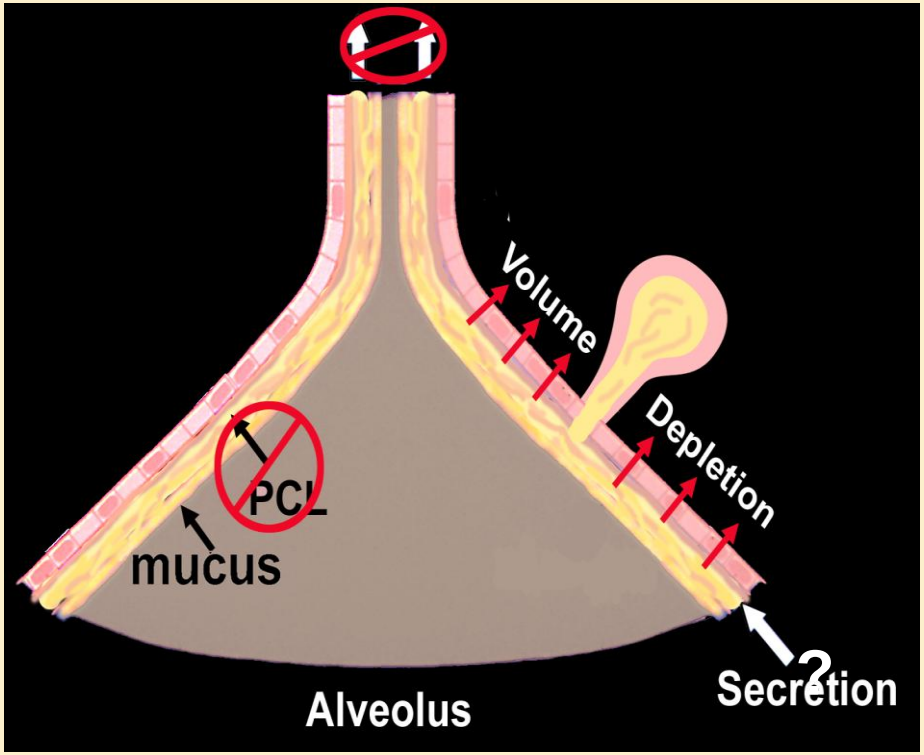
Mucus Clearance Is a Key Component of Normal Lung Defense, Depends on Adequate Surface Liquid Volume, and Is Defective in CF

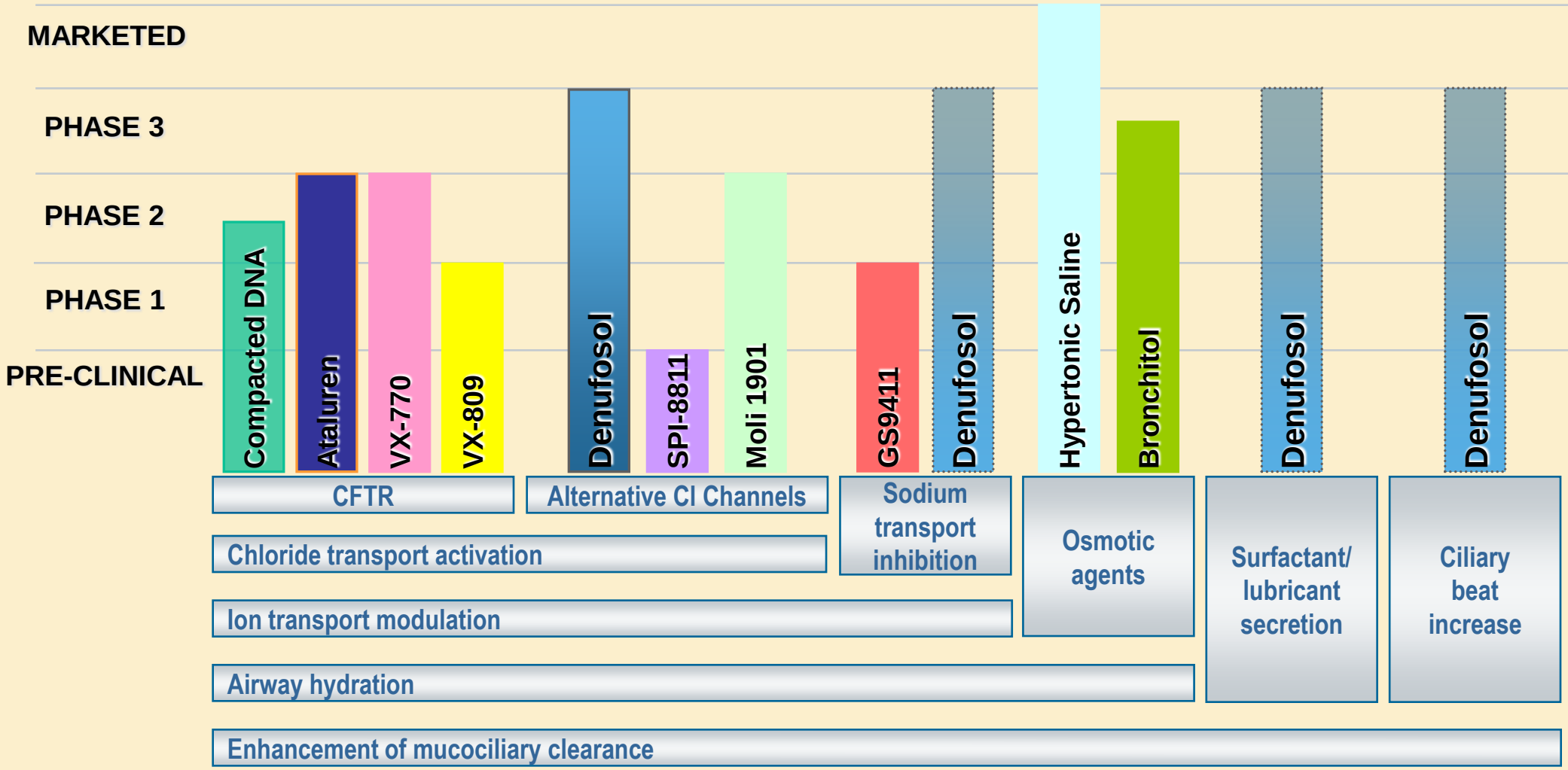


Normal

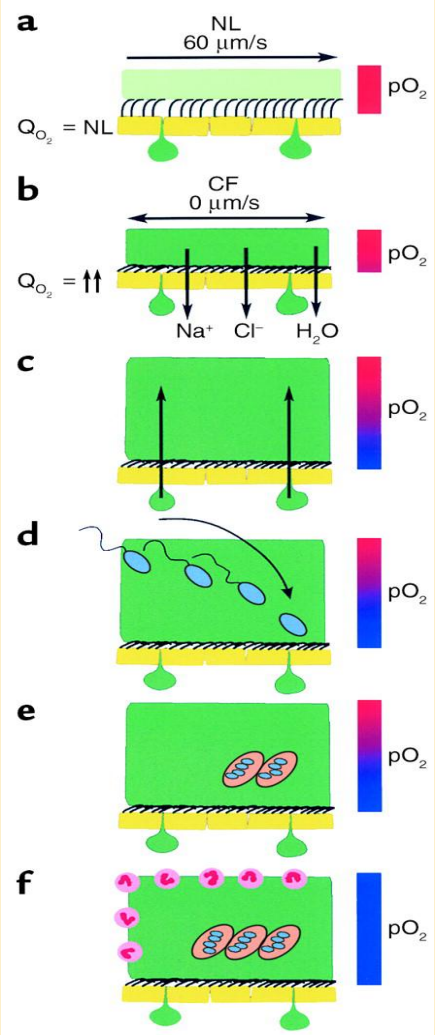


CF

Potential Enhancers of Mucociliary Clearance by Mechanism of Action



Pathogenesis of Cystic Fibrosis lung disease



Normal = adequate ASL, well-hydrated mucus, effective mucociliary clearance, normal O_2 consumption

Mutant CFTR = inadequate ASL, dehydrated mucus, paralyzed mucociliary clearance, elevated epithelial O_2 demand

Mucus plugs and plaques, hypoxic microenvironment

CF pathogen colonization

Vaccines

CF pathogen macro-colonies/biofilms, permanent infection

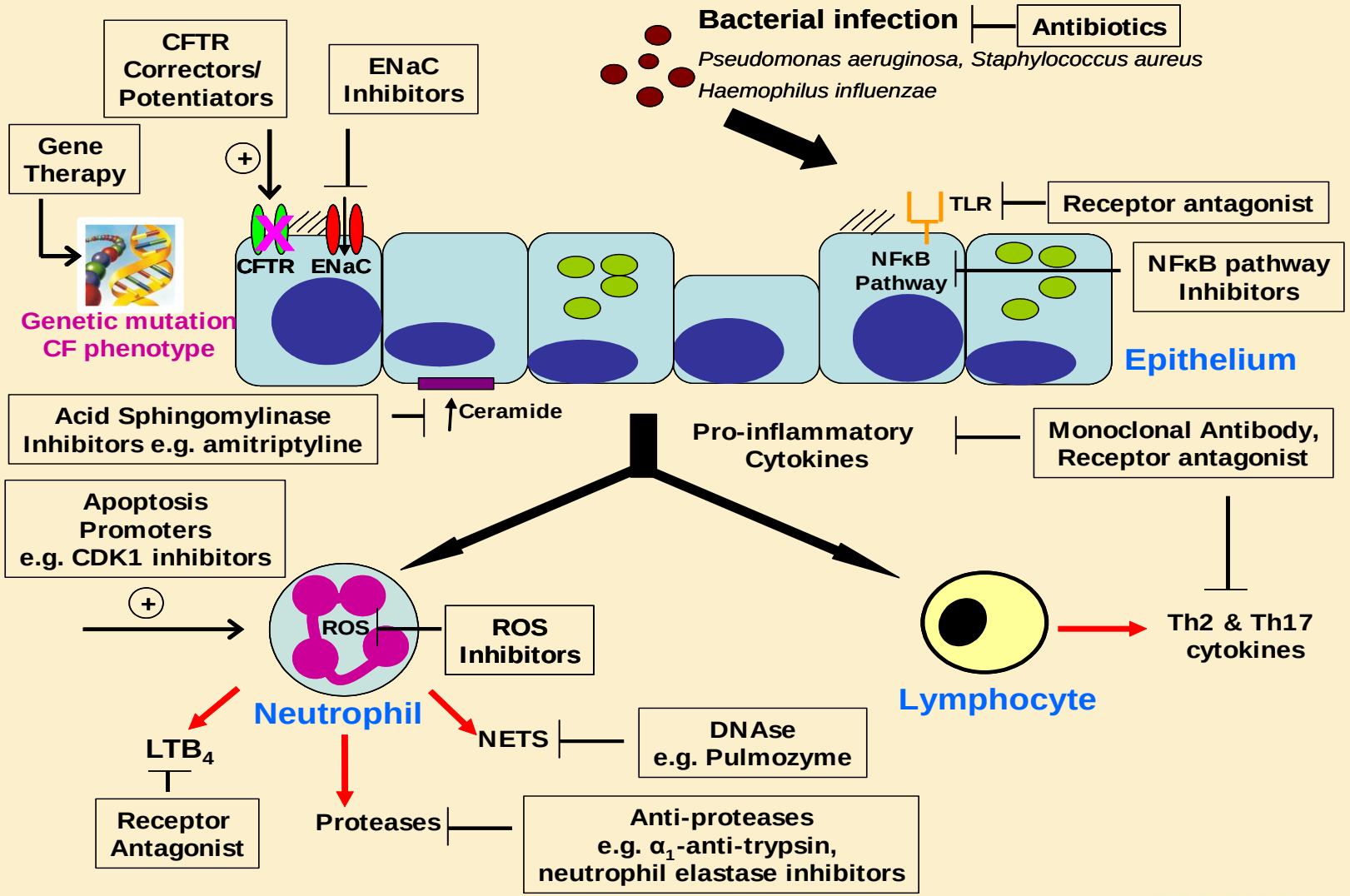
Antibiotics

Ineffective host defense/ excessive inflammation

Anti-inflammatories

Worlitzsch et al., *J Clin Invest* 109;317, 2002

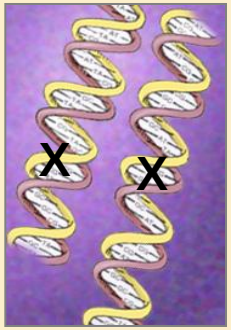
Potential Anti-Inflammatory Strategies for the Treatment of CF



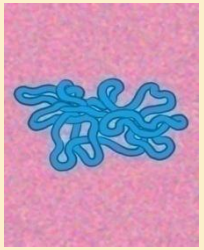
KH Banner et al, *JCF* 2009;8:1-8

Therapeutic Approaches to CF

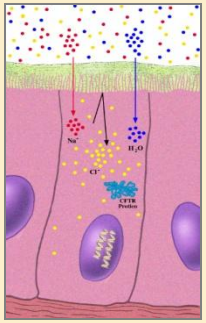
Abnormal Genes



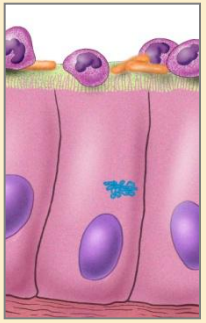
Abnormal CFTR Protein



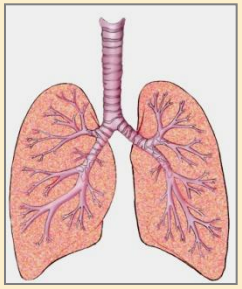
Altered Ion Transport Abnormal Mucus Secretion



Infection & Inflammation Tissue Destruction



Organ Destruction Respiratory Failure



Current:

Nutritional Support and Airway Clearance Techniques

Abnormal Genes	Abnormal CFTR Protein	Altered Ion Transport Abnormal Mucus Secretion	Infection & Inflammation Tissue Destruction	Organ Destruction Respiratory Failure
None	None	rhDNase Hypertonic Saline Physiotherapy	Anti-Inflammatories Anti-Infectives Bronchodilators	Transplantation (Lung, Liver)

In Development:

Abnormal Genes	Abnormal CFTR Protein	Altered Ion Transport Abnormal Mucus Secretion	Infection & Inflammation Tissue Destruction	Organ Destruction Respiratory Failure
Gene Therapy Modifier Genes	Protein rescue “Correction”	Proper Ion Transport “Potentiation”	Anti-Inflammatories Anti-Infectives	Stem Cells