Fibrosis Quística
Reto multidisciplinar para todos

Amparo Solé Jover,
Unidad FQ Adultos y Trasplante Pulmonar
Hospital la Fe

Visión del médico

¿Qué es la FQ?

Etiopatogenia

RETO Manifestaciones clínicas

Enfermedad cambiante: Según edad, mutación y grado de función CFTR... posteriormente trasplante

Etapas más críticas impacto en QOL y evolución: adolescencia, embarazo y trasplante

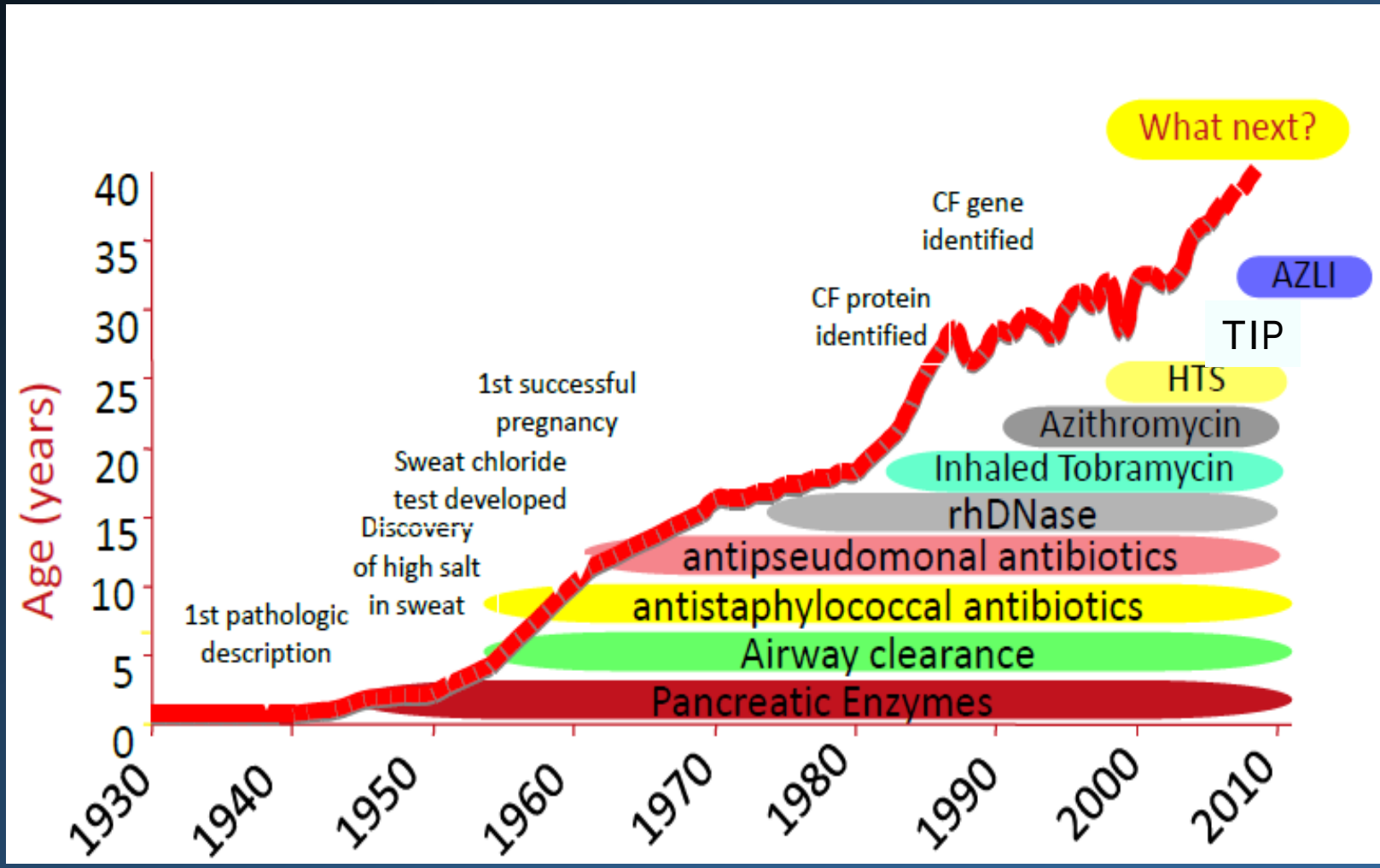
Difícil diagnostico

Seguimiento

Tratamiento (nuevas estrategias y terapia sintomática)

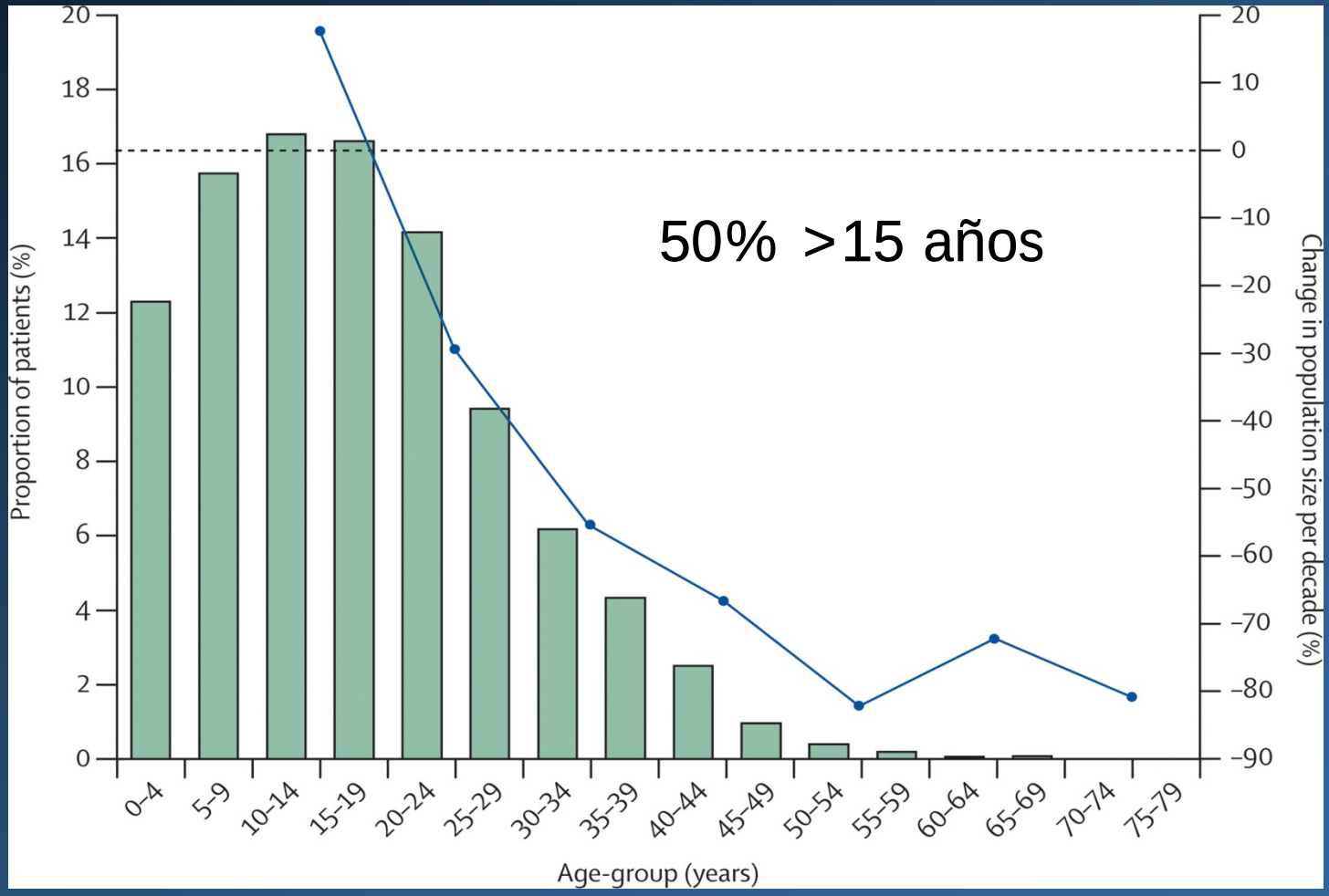
Hitos en el manejo de la FQ… supervivencia

VERTEX, nuevos ATB…..



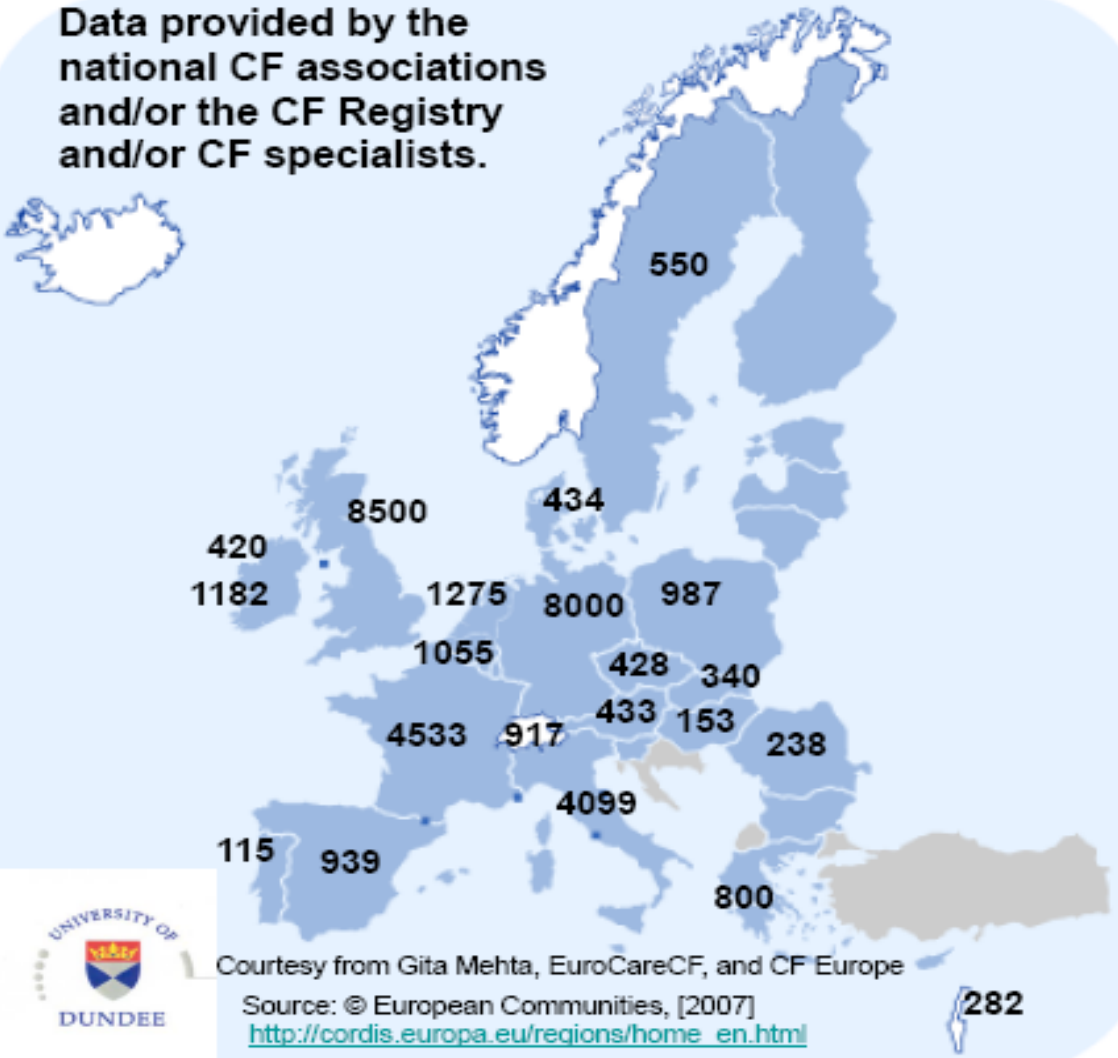
CONSECUENCIAS....
Demografía de la FQ en Europa

29,000 patients from 35 European countries



McCormick ***et al*** *Lancet* ***2010***

Data provided by the national CF associations and/or the CF Registry and/or CF specialists.



- Austria
- Belgium
- Czech R
- Denmark
- France
- Germany
- Greece
- Hungary
- Ireland
- Israel
- Italy
- Netherlands
- Poland
- Portugal
- Romania
- Slovakia
- Spain
- Sweden
- Switzerland
- UK

Total: 34,619

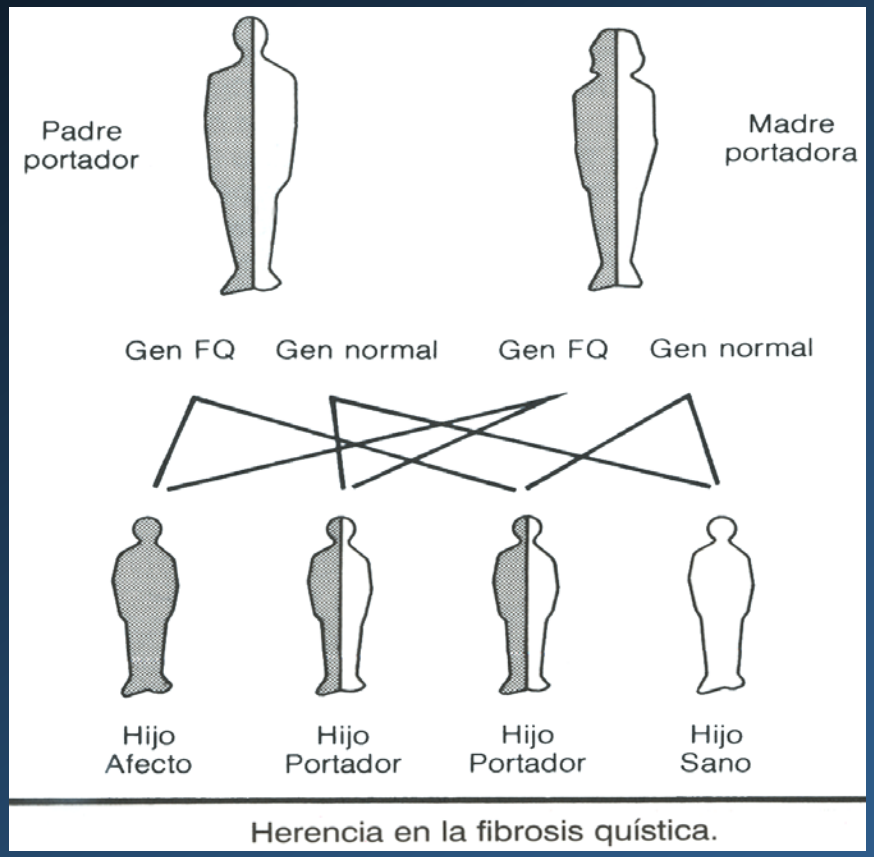
Courtesy from Gita Mehta, EuroCareCF, and CF Europe

Source: © European Communities, [2007]
http://cordis.europa.eu/regions/home_en.html

UNIVERSITY OF DUNDEE

EuroCareCF

FQ Enfermedad rara…?



Herencia en la fibrosis quística.

Herencia recesiva más frecuente caucásica

1/3000-4000 nacimientos (EU)

1/25 -40 portador una mutación

≠ Mutaciones en un gen que codifica CFTR (brl CR7)

>1800

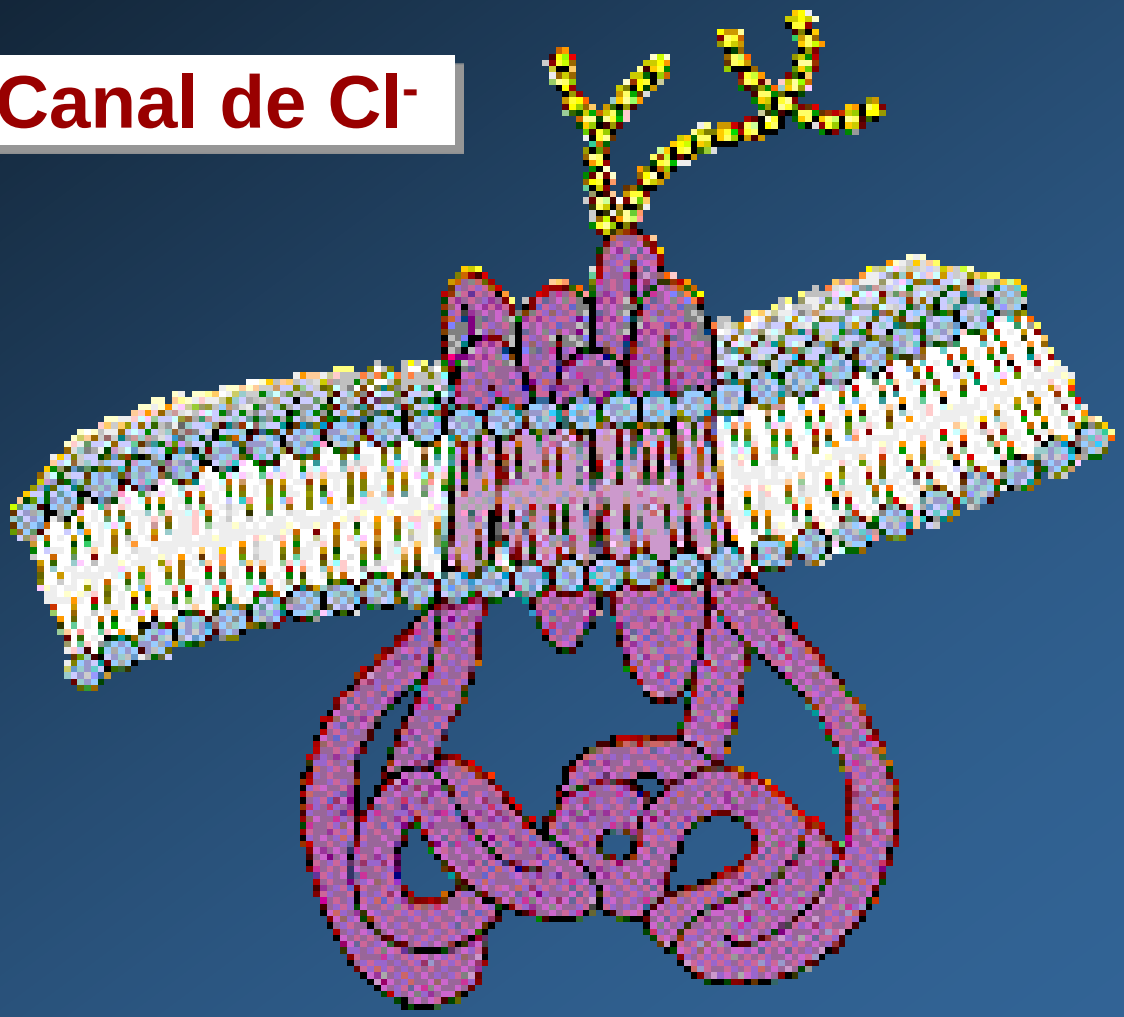
CFTR, alteración cels. epitelial

Secreciones espesas ≠ Cl/Na

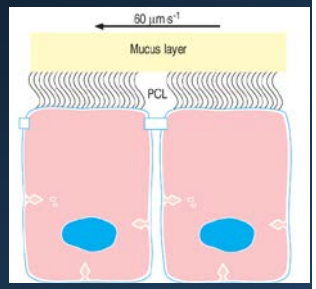
Expect vida 30-39 años (EU)

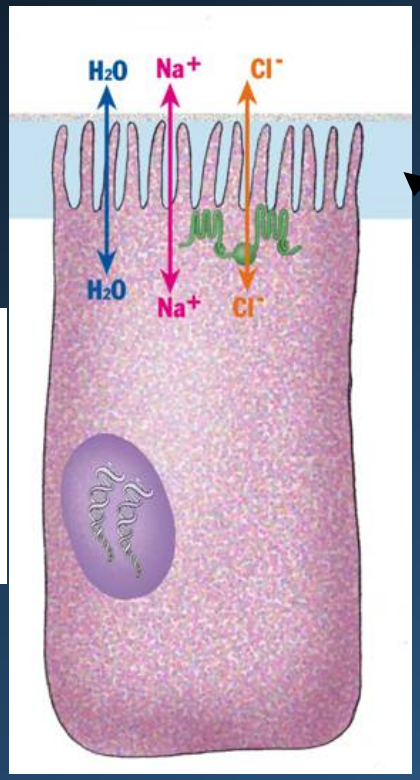
Proteína CFTR

Canal de Cl^-

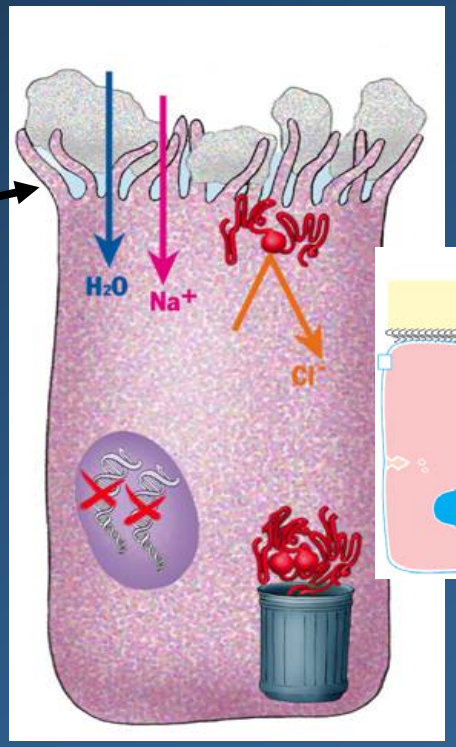


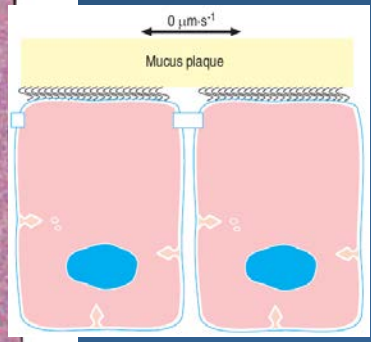
CFTR: modula secreción de CL





ASL



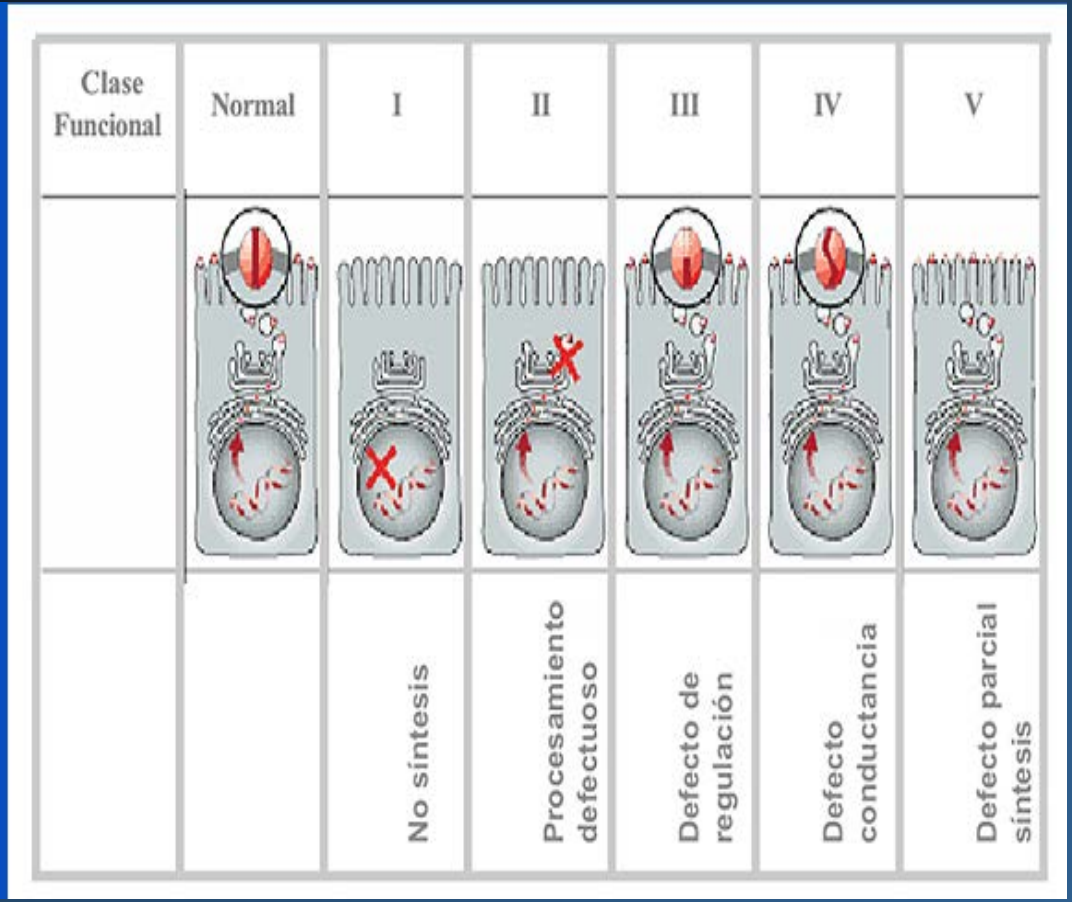


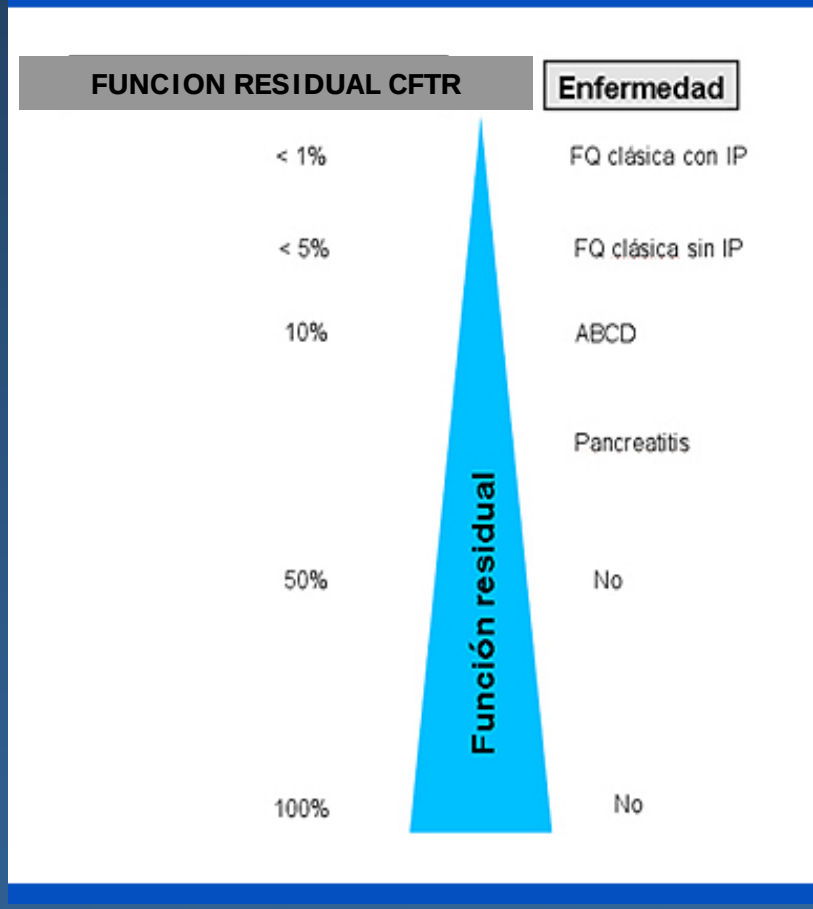
Normal **CF**

CFTR defecto: reducida la secreción de ion CLORO, incremento absorción de Na y agua

deshidratación de las secreciones, desaparición del LPC

CFTR: regulador canal de CL





Spanish CF common mutations

F508del	51.7
G542X	7.7
N1303K	2.9
1811+1,6kbA>G	1.8
R334W	1.8
L206W	1.6
711+1G>T	1.6
Q890X	1.4
R1162X	1.3
R1066C	1.2
2789+5G>A	1.2
I507del	1.0
1609delCA	1.0

712-1G>T	0.9
3272-26A>G	0.9
G85E	0.8
2869insG	0.8
W1282X	0.8
2183AA>G	0.8
V232D	0.7
2184insA	0.6
K710X	0.6
A1006E	0.6
621+1G>T	0,5
1078delT	0.5

(Alonso et al. *Ann Hum Genet* 2007)

Donde esta CFTR?

Superficie células epiteliales:

Pulmón, tracto intestinal, páncreas,

También expresión:

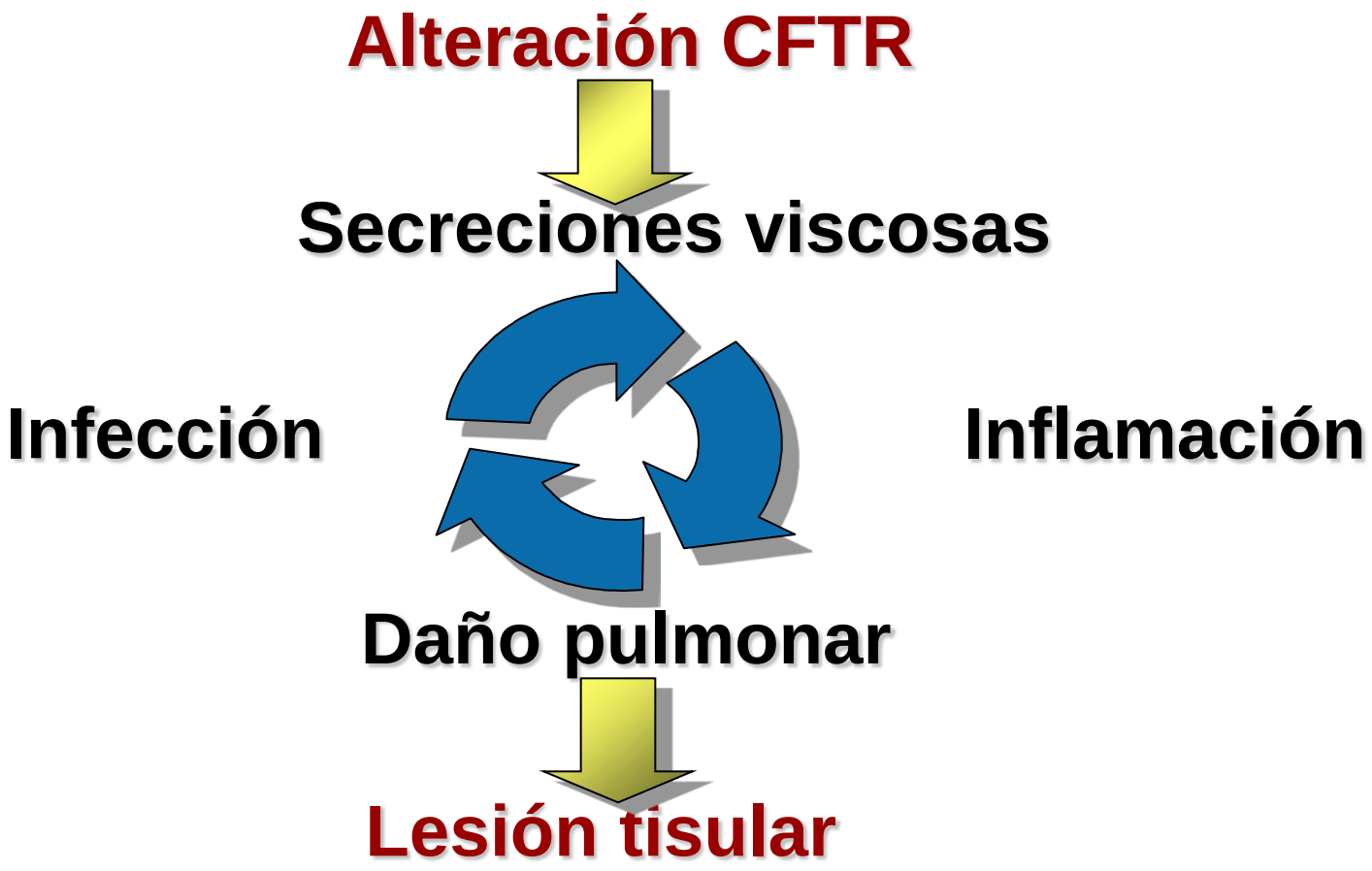
Tracto reproductor

Glándulas sudoríparas

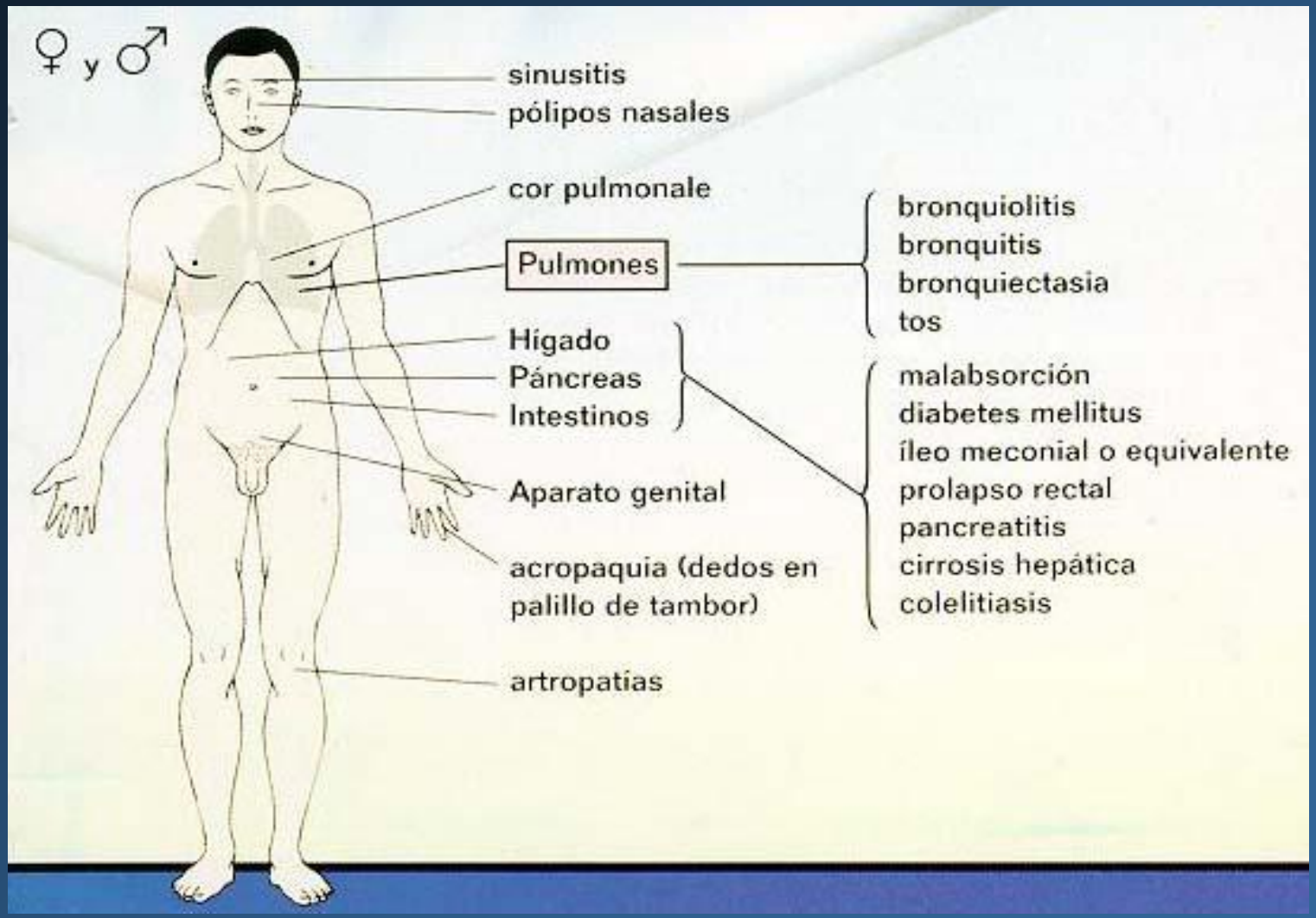
Hígado y tracto biliar

Senos paranasales

Afectación respiratoria mayor impacto en morbi-mortalidad



Clínica de la FQ



FORMAS OLIGOSINTOMÁTICAS

Tos productiva que mejora con antibióticos

Tos productiva con gérmenes poco habituales en el esputo: *S.aureus, Ps.aeruginosa*

Asma con bronquiectasias

Pólipos nasales

Sinusitis crónica

Pancreatitis aguda / recidivante

Diagnóstico de Fibrosis Quística

-Test del sudor positivo (Cl^- > 60 mmol/L)

y/o

- Presencia de dos mutaciones en el estudio genético

31 FQ mutaciones; Nivel de detección (76%)
2º 108 mutaciones analisis genético (97 %)

- Más cualquiera de los siguientes hallazgos:

- Cribado neonatal positivo
- Historia familiar de FQ
- Manifestaciones clínicas compatibles

J Pediatr 1998; 132:589-595

Manejo del paciente con FQ

-Unidades especializadas

-Equipos multidisciplinarios entrenados

-Enfermera especialista FQ

- Control clínico: 1-2 meses, revisión de Farmacia

-Controles evolutivos: Función respiratoria.RHB
Radiológicos/microbiológicos
Otros:Nutrición, endocrino, gine , fertilidad....

ELSEVIER

Journal of Cystic Fibrosis 4 (2005) 7–26

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Standards of care for patients with cystic fibrosis: a European consensus

Eitan Kerem*, Steven Conway, Stuart Elborn, Harry Heijerman

For the Consensus Committee[1]

Department of Pediatrics and CF center, Mount Scopus, Jerusalem 91240, Israel

Equipos multidisciplinares

E. Kerem et al. / Journal of Cystic Fibrosis 4 (2005) 7–26

Seguimiento: Pruebas funcionales. Cadencia según demanda

- **Función pulmonar: Espirometría.**

  Valor pronóstico (FEV1<30%: esperanza de vida a los 2 años del 50%)

  - Evaluación de la hiperreactividad bronquial

- **Gases en sangre fases avanzadas**
  - Disminuye la PaO_2 y aumenta la $PaCO_2$

Seguimiento: pruebas funcionales

- **Función pancreática:**

  Determinación de grasa en heces recogida durante 3 días

  Determinación de tripsina, quimotripsina o elastasa en heces

  Determinación enzimática de jugo duodenal

  Controles de hemoglobina glicosilada a partir de 10 años (DM)

Seguimiento: radiología y cultivo

- **Hallazgos radiológicos pulmonares:** Tomografía computarizada de alta resolución es mas sensible y específica que la Rx

  - Atrapamiento aéreo
  - Neumonias
  - Bronquiectasias
  - Fibrosis pulmonar

- **Hallazgos radiológicos sinusales:** Opacificación de los senos paranasales

- **Microbiología:** cultivo de esputo cada 1-2 meses y en las reagudizaciones respiratorias

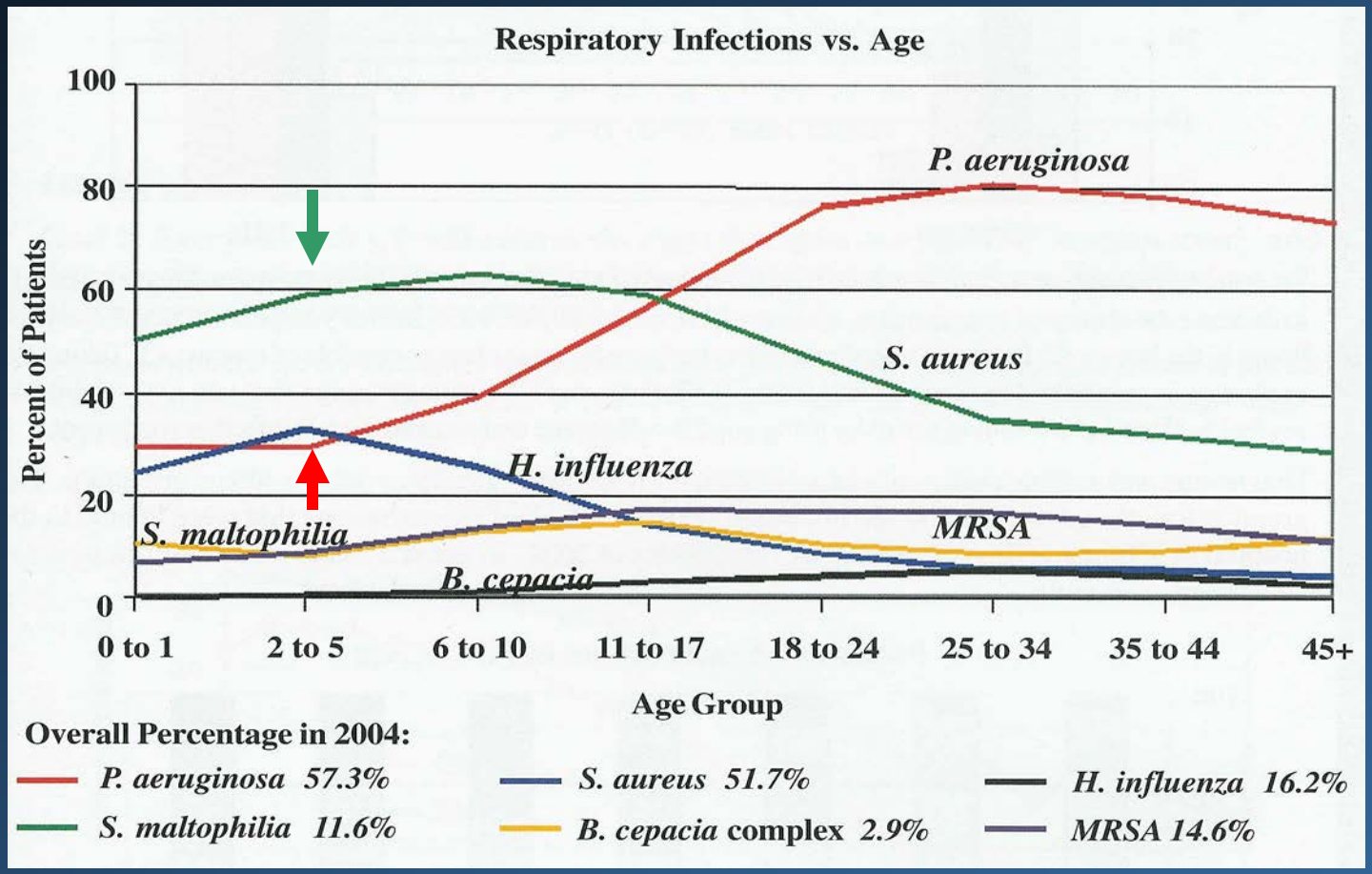
Tratamiento

El tratamiento actualmente no es curativo, aunque ya se han iniciado los pasos con la terapia proteica

Objetivos:

- Detener la progresión de la enfermedad:
  - Insuficiencia pancreática
  - Infección bronquial crónica
- Mejorar la calidad de vida del paciente

Incidencia por edades de los principales patógenos de las vías respiratorias en FQ

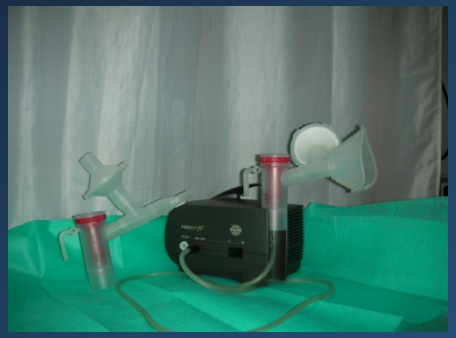


Patient registry 2004. Cystic Fibrosis Foundation

TRATAMIENTO DE LA COLONIZACIÓN CRÓNICA POR P. A.

Antibióticos nebulizados

- ↑ Concentración mucosa bronquial
- ↓ niveles séricos
- ↓ toxicidad sistémica
- Efectos clínicos beneficiosos
  - mejoría función pulmonar
  - ↓ exacerbaciones respiratorias
  - mejoría calidad de vida
- Efectos adversos: broncoconstricción
  - sulfitos y fenoles
  - osmolaridad
  - propio medicamento



- Colimicina Tobramicina

Colimicina, Tobramicina en polvo

eFlow

i-neb AAD

Amikacina SLIT (liposoma inhalada)

Antibióticos administrado por via inhalatoria en nebulizador electrónico

Tratamiento pulmonar farmacológico

- **Broncodilatadores:** agonistas betadrenérgicos (salbutamol…)
- **Antiinflamatorios:** azitromicina, ibuprofeno
- **Mucolíticos:** DNAsa
- **Hidratación de la vía aérea:** suero salino hipertónico
- **ANTIBIÓTICOS:** punto principal del tratamiento para controlar la progresión de la enfermedad

Tratamiento pulmonar no-farmacológico

- **Fisioterapia:** Técnicas para el aclaramiento de la vía aérea:
  - Percusión y drenaje postural (convencional)
  - Dispositivos de presión positiva espiratoria
  - Técnicas de respiración de ciclo activo
  - Dispositivos de compresión de la pared torácica
  - Drenaje autógeno
- **Ejercicio**
- **Terapia postural**
- **O_2** (en fases avanzadas)

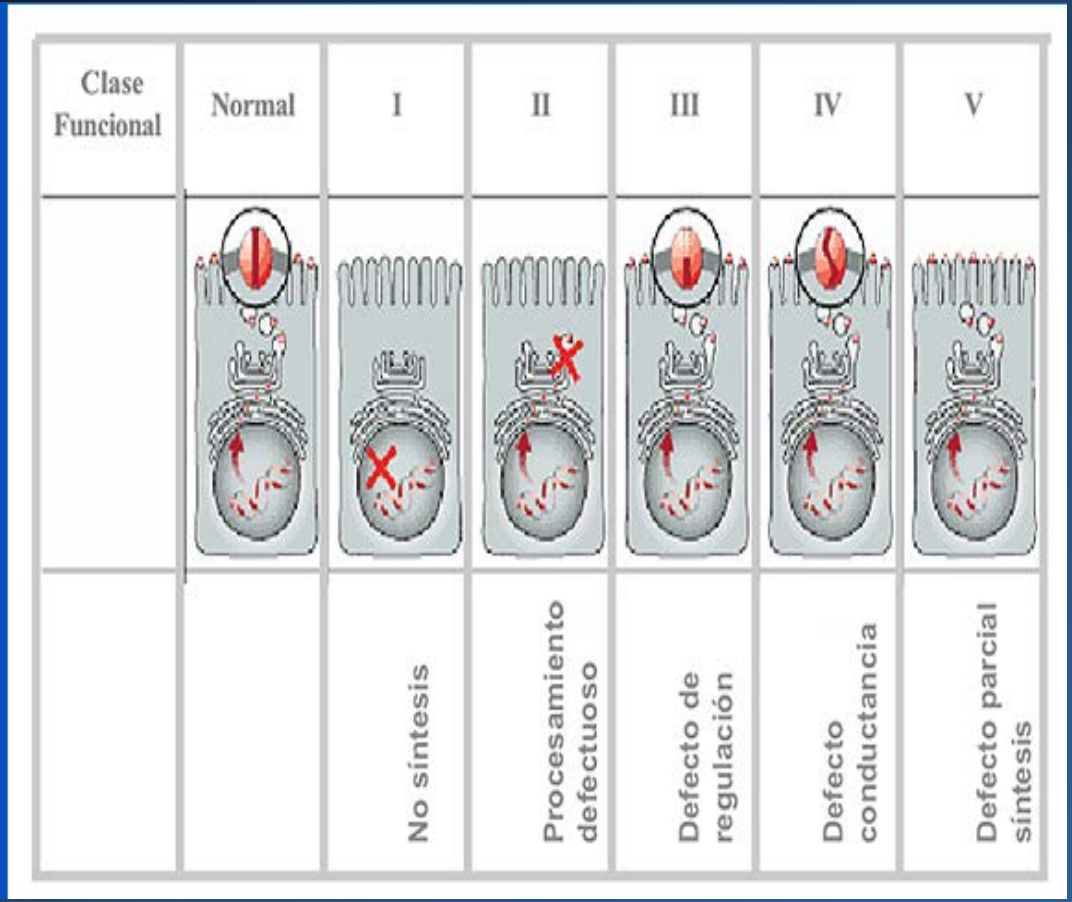
Tratamiento nutricional

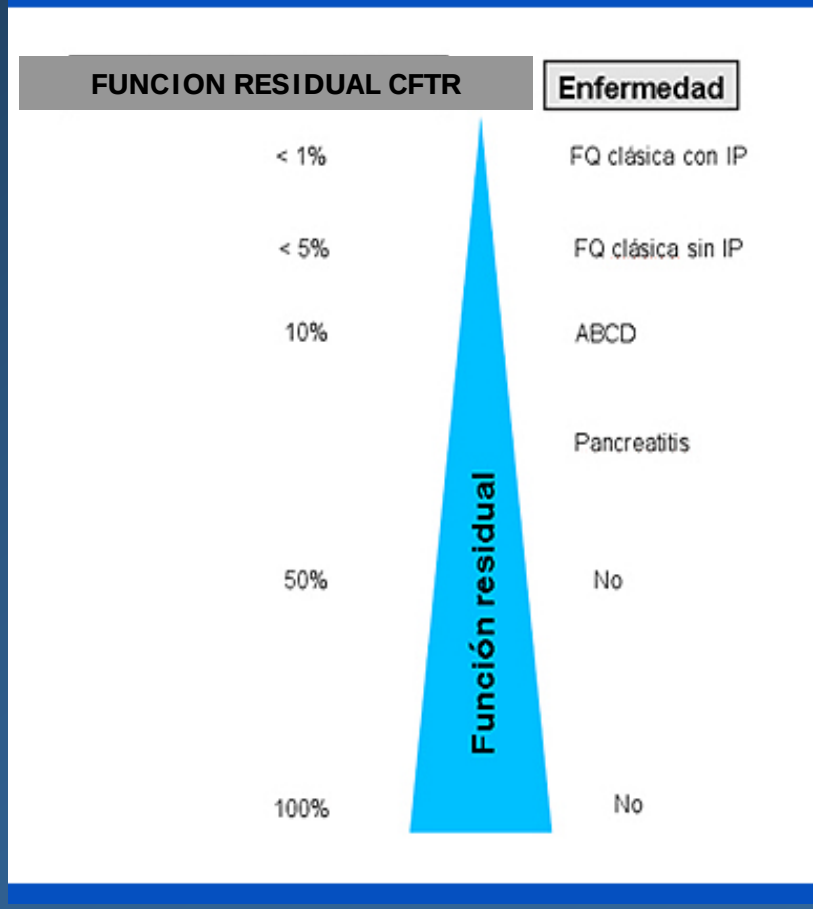
Existe una correlación importante entre el estado nutricional y la función pulmonar:

- **Ajuste de la dieta:** rica en calorías, proteínas y grasas “buenas”
- **Enzimas pancreáticas:** 30.000-40.000 UI
- **Suplementos vitamínicos** (A, D, E, K)
- Suplemento con ácidos grasos omega 3
- **Suplemento de sal** durante el verano o en enfermedad febril

TERAPIA PROTEICA

CFTR: regulador canal de CL



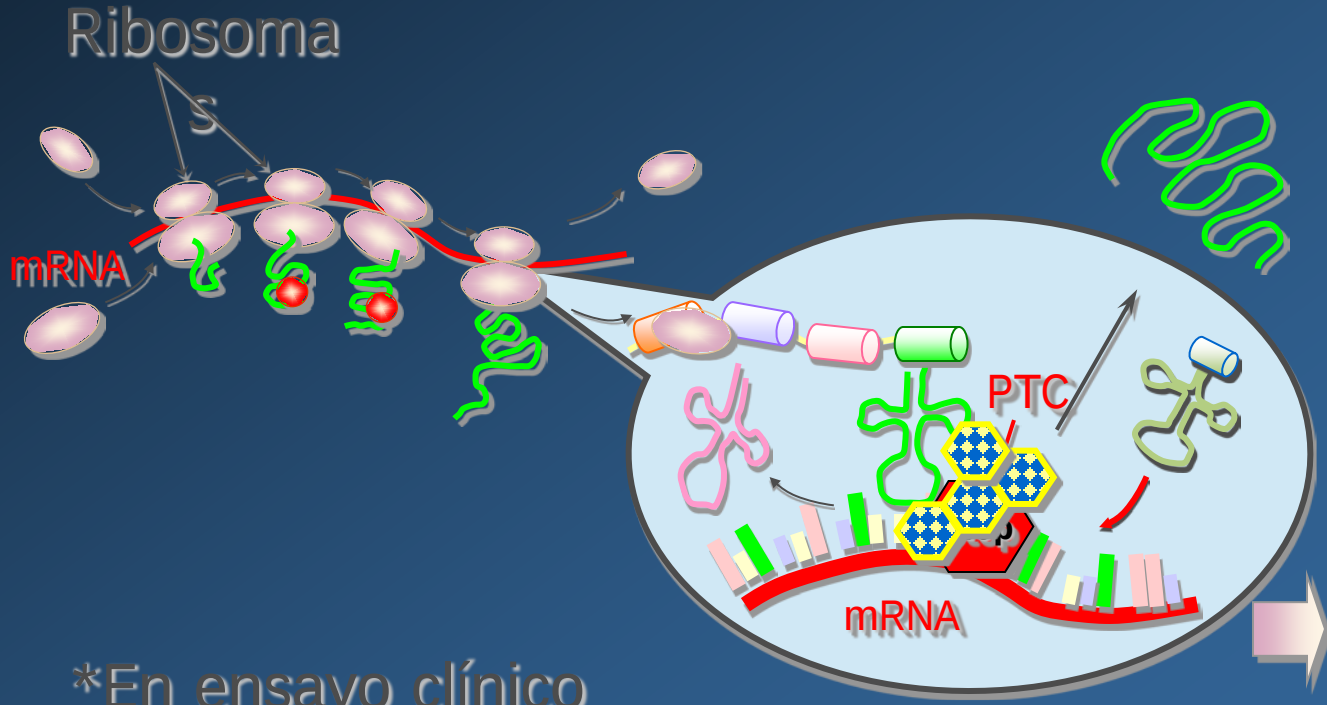


Clase I Mutaciones : Nuevas Terapias

Supresión de Codóns Stop Prematuros (PTCs)

Traducción de mRNA en proteína

Ex: Ataluren (PTC-124)*
Gentamicina

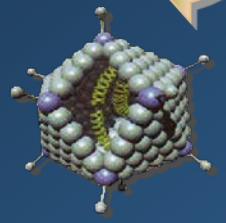


*En ensayo clínico

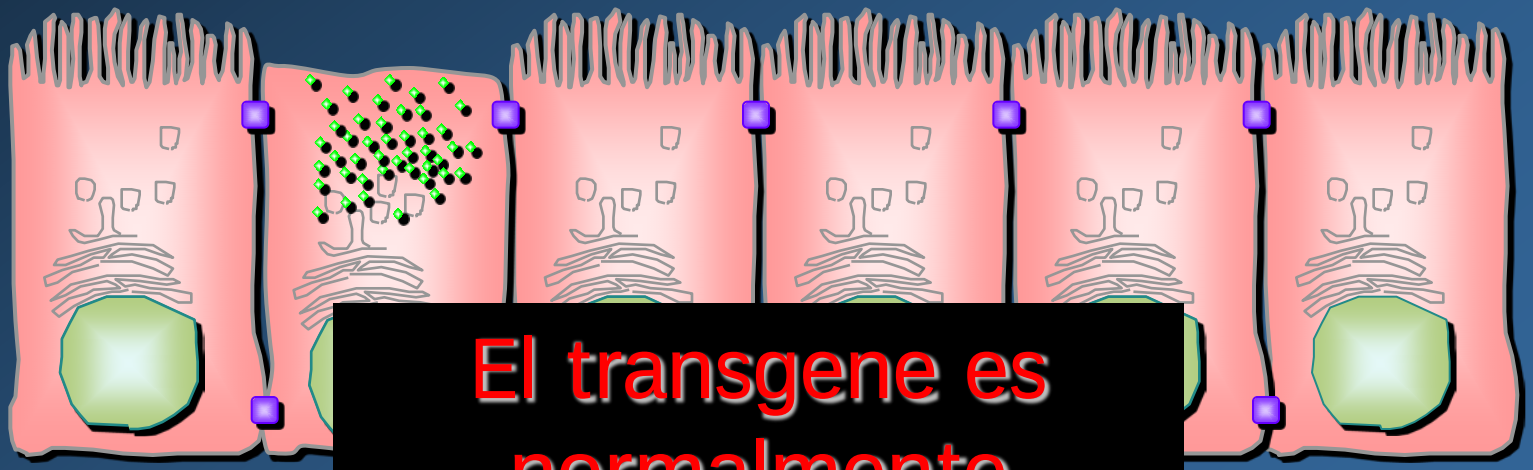
Terapia Génica

cDNA CFTR

Liposomas



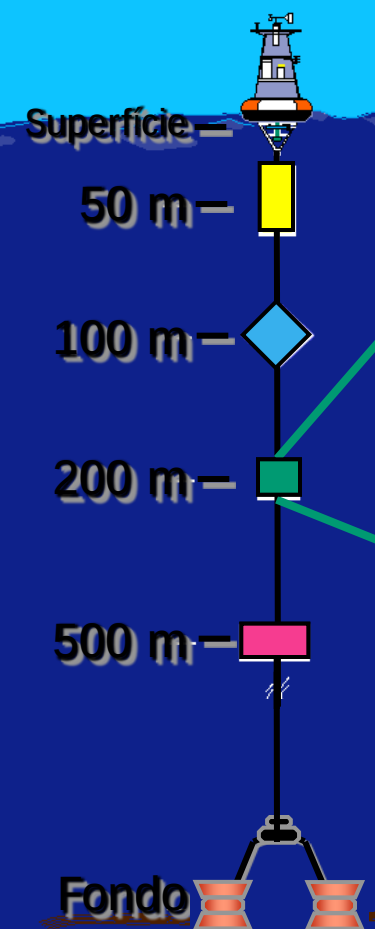
Vectores Virales



El transgene es normalmente silenciado!

- No-toxic
- Baja eficie
- Alta eficiencia
- Imunogénicos

Mutaciones de Clase II
Tráfico Defectuoso



Ejemplos:

- F508del
- A561E
- N1303K
- R1066C

Cómo Rescatar F508del-CFTR para Fuera de lo RE?

1. Aumentando su "folding"

2. Alterando el Controlo de Calidad del RE

3. Por "bypass" de lo Controlo de Calidad

Rescate de la F508del-CFTR con Corrector y Potenciador (VX-809 + VX-770)

VERTEX

Interim Phase 2 Data Showed a Combination of VX-770 and VX-809 Improved Function of the Defective Protein that Causes Cystic Fibrosis in People With the Most Common Form of the Disease

-13.17 mmol/L reduction in sweat chloride in one arm supports further evaluation of a combination approach to treating the root cause of cystic fibrosis-

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced interim results from the first part of a Phase 2 study designed to evaluate multiple combination regimens of VX-770 and VX-809, Vertex's lead medicines in development that aim to treat the defective protein that causes cystic fibrosis (CF). That protein, known as the cystic fibrosis transmembrane conductance regulator (CFTR), is responsible for regulating the flow of chloride across the cell surface to help hydrate and clear mucus from the airways. The first part of the study enrolled and randomized 62 people with two copies of the most common mutation in the CF gene, known as the F508del mutation. In people with the F508del mutation, the CFTR protein does not reach the cell surface in normal amounts, resulting in a buildup of mucus and other complications that can lead to lung damage. VX-809, known as a CFTR corrector, is designed to help the protein reach the cell surface, while VX-770, known as a CFTR potentiator, aims to help the protein function more normally once it reaches the cell surface. VX-770 and VX-809 were advanced into development with support from Cystic Fibrosis Foundation Therapeutics, Inc., the nonprofit affiliate of the Cystic Fibrosis Foundation. Vertex retains worldwide rights to develop and commercialize these potential medicines.

The first part of the study met its two primary endpoints: (1) safety and tolerability of the combination regimen and (2) the effect of the combination of VX-770 and VX-809 on CFTR function as measured by sweat chloride, a key measure of the function of the CFTR protein. There were no serious adverse events reported, and the adverse event profile during the combination-dosing portion of the study (Day 14 to Day 21) was similar to that during the VX-809 monotherapy-dosing portion (Day 0 to 14). In the arm that evaluated VX-809 (200 mg) followed by dosing of VX-770 (250 mg) in combination with VX-809, a statistically significant reduction in sweat chloride of -13.17 mmol/L ($p<0.001$) was observed from baseline (Day 0) through Day 21. In this arm, a -9.10 mmol/L ($p<0.001$) reduction was observed after VX-770 (250 mg) was added to VX-809 (200 mg) for seven days (Day 14 to 21). Vertex intends to initiate the second part of this study in the fourth quarter of 2011 after the completion of further analyses of data from Part 1.

http://investors.vrtx.com/releasedetail.cfm?releaseid=583683

Rescate de la F508del-CFTR con Corrector de Segunda Generación (VX-661)

VERTEX

Vertex and Cystic Fibrosis Foundation Therapeutics to Collaborate on Discovery and Development of New Medicines to Treat the Underlying Cause of Cystic Fibrosis

-Expanded collaboration supports development of a second corrector, VX-661, and accelerated discovery and development of next-generation correctors-

-Phase 2 study of VX-661 planned for 2011 in people with CF who have the F508del mutation-

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) and Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) today announced they will collaborate on the continued discovery and development of new medicines known as correctors that aim to treat the underlying cause of cystic fibrosis (CF) in people with the most common form of the disease. The expanded collaboration will support development activities for VX-661, Vertex's second corrector to enter clinical development, and the accelerated discovery and development of next-generation correctors. Vertex plans to begin the first study of VX-661 by the end of 2011 in people with CF who have the F508del mutation.

Vertex and CFFT, a nonprofit drug discovery and development affiliate of the CF Foundation, began their collaborative research and development efforts in 1998, and to date, three potential new medicines, known as CFTR modulators, have resulted from the collaboration — the potentiator VX-770 and the correctors VX-809 and VX-661. Correctors and potentiators are medicines in development that aim to treat the underlying cause of CF by improving the function of the defective protein known to cause the disease. Vertex retains worldwide rights to develop and commercialize these potential medicines.

http://investors.vrtx.com/releasedetail.cfm?releaseid=563453

Nuevos Correctores que Rescatan la F508del-CFTR

Chemistry & Biology
Volume 18, Issue 2, 25 February 2011, Pages 231-242

doi:10.1016/j.chembiol.2010.11.016 | How to Cite or Link Using DOI

[redacted]

Article

Identification of a NBD1-Binding Pharmacological Chaperone that Corrects the Trafficking Defect of F508del-CFTR

[redacted]

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Received 26 August 2010; revised 9 November 2010; accepted 29 November 2010. Published: February 24, 2011. Available online 24 February 2011.

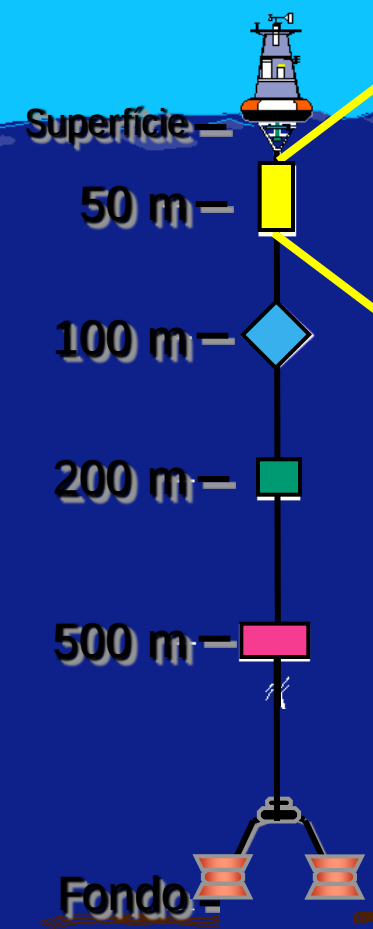
Summary

Most cases of cystic fibrosis (CF) are attributable to the F508del allele of CFTR, which causes the protein to be retained in the endoplasmic reticulum (ER) and subsequently degraded. One strategy for CF therapy is to identify corrector compounds that help traffic F508del-CFTR to the cell surface. Pharmacological chaperones, or correctors that bind specifically to F508del-CFTR and restore function, would be the most promising drug development candidates, but few pharmacological chaperones exist for F508del-CFTR. Using differential scanning fluorimetry (DSF), we have surveyed corrector compounds and identified one, RDR1, which binds directly to the first nucleotide binding domain (NBD1) of F508del-CFTR. We show that RDR1 treatment partially rescues F508del-CFTR function in both cells and in an F508del-CF mouse model. Thus, RDR1 is a pharmacological chaperone of F508del-CFTR and represents a novel scaffold for drug development.

Highlights

► DSF was used to identify pharmacological chaperones for F508del-CFTR ► RDR1 stabilizes F508del-NBD1 at low micromolar doses ► RDR1 treatment partly rescues F508del-CFTR function in cells and a CF mouse model

Mutaciones de Clase III/IV Regulación ó Conductancia Defectuosos



Ejemplos:

- G551D (III)
- R334W (IV)
- R117H (IV)

Potenciando la CFTR Que ya Está en la Membrana (G551D)

VERTEX

Phase 3 STRIVE Study of VX-770 Showed Durable Improvements in Lung Function (FEV1) and Other Measures of Disease Among People With a Specific Type of Cystic Fibrosis

- Complete data presented at ECFS showed improvements in lung function and reductions in sweat chloride observed at week two of treatment were sustained through 48 weeks -

- Vertex also announces that 48-week data from the ENVISION study of VX-770 among children ages 6 to 11 years are consistent with previously announced 24-week results -

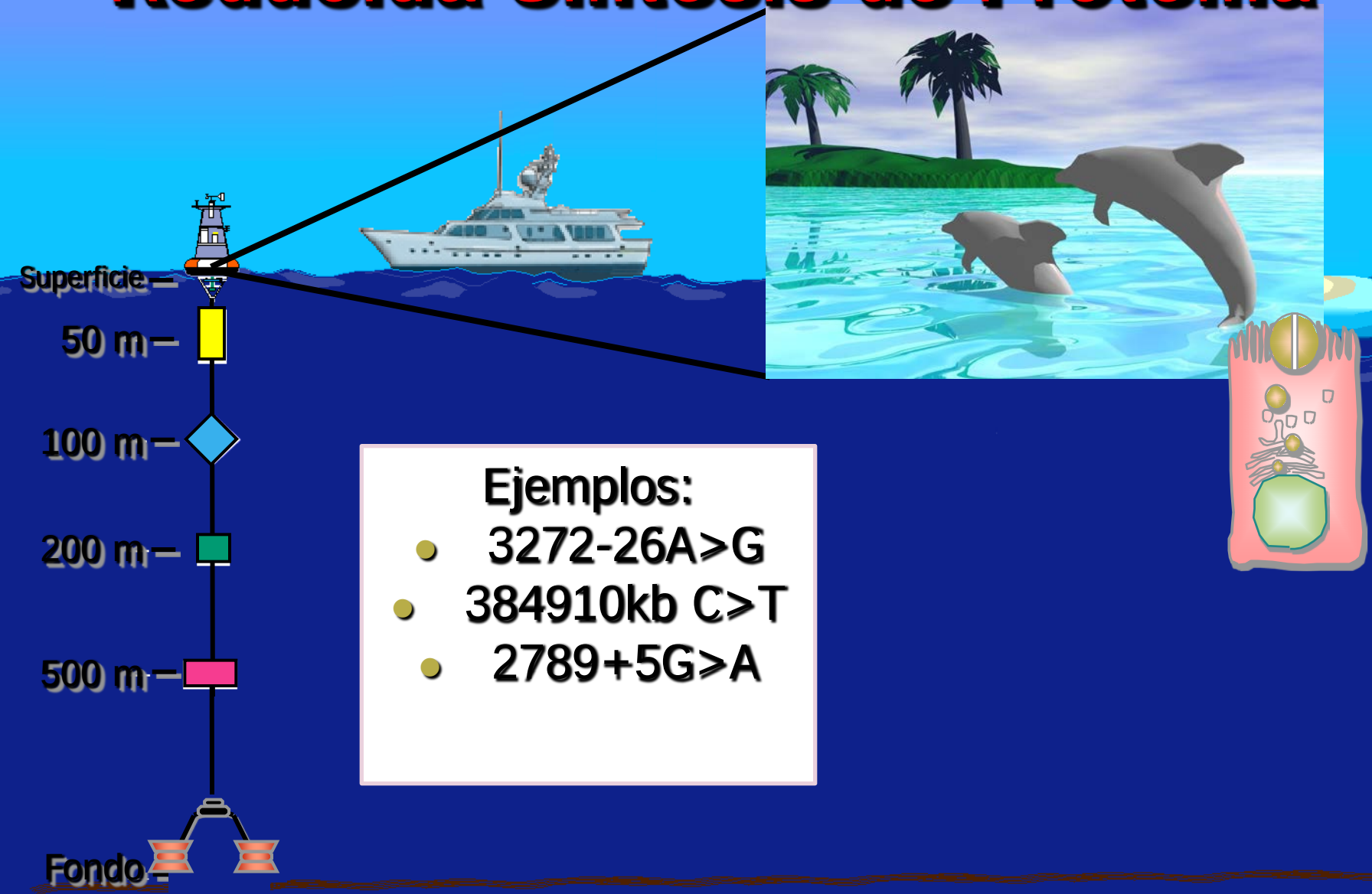
HAMBURG, Germany--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq:VRTX - News) today announced the final results from its pivotal Phase 3 STRIVE study that evaluated VX-770, a medicine in development that targets the defective protein that causes cystic fibrosis (CF). STRIVE was designed to evaluate VX-770 among 161 people 12 years or older with a mutation known as G551D in the CF gene. Approximately 4 percent of people with CF have at least one copy of the G551D mutation.

Data from the study showed rapid improvements in lung function (FEV_1) that were sustained through 48 weeks among those who received VX-770, compared to those treated with a placebo. Significant improvements in all key secondary endpoints were observed among people who received VX-770 compared to placebo. Adverse events that occurred more frequently among those treated with VX-770 compared to placebo were headache, upper respiratory tract infections, nasal congestion, rash, dizziness and bacteria in the sputum. These data were presented today at the 34^{th} European Cystic Fibrosis Society (ECFS) Conference in Hamburg, Germany.

The results of STRIVE showed a mean absolute improvement in lung function of 10.6 percent through week 24 (primary study endpoint) and 10.5 percent through week 48 (secondary study endpoint) among those treated with VX-770 (n=83). The mean relative improvement from baseline in lung function among people treated with VX-770 compared to placebo (n=78) was 16.9 percent through week 48. Absolute and relative changes in lung function are being reported in today's announcement. Phase 3 results and product labeling for currently available CF medicines generally describe relative improvements in lung function.

http://investors.vrtx.com/releasedetail.cfm?releaseid=583934

Mutaciones de Clase V
Reducida Síntesis de Proteína



Ejemplos:

- 3272-26A>G
- 384910kb C>T
- 2789+5G>A

Pacientes 3272-26A>G/F508del: FQ Más Suave

Menos Proteína Normal → Cuanta?

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Five Percent of Normal Cystic Fibrosis Transmembrane Conductance Regulator mRNA Ameliorates the Severity of Pulmonary Disease in Cystic Fibrosis

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+

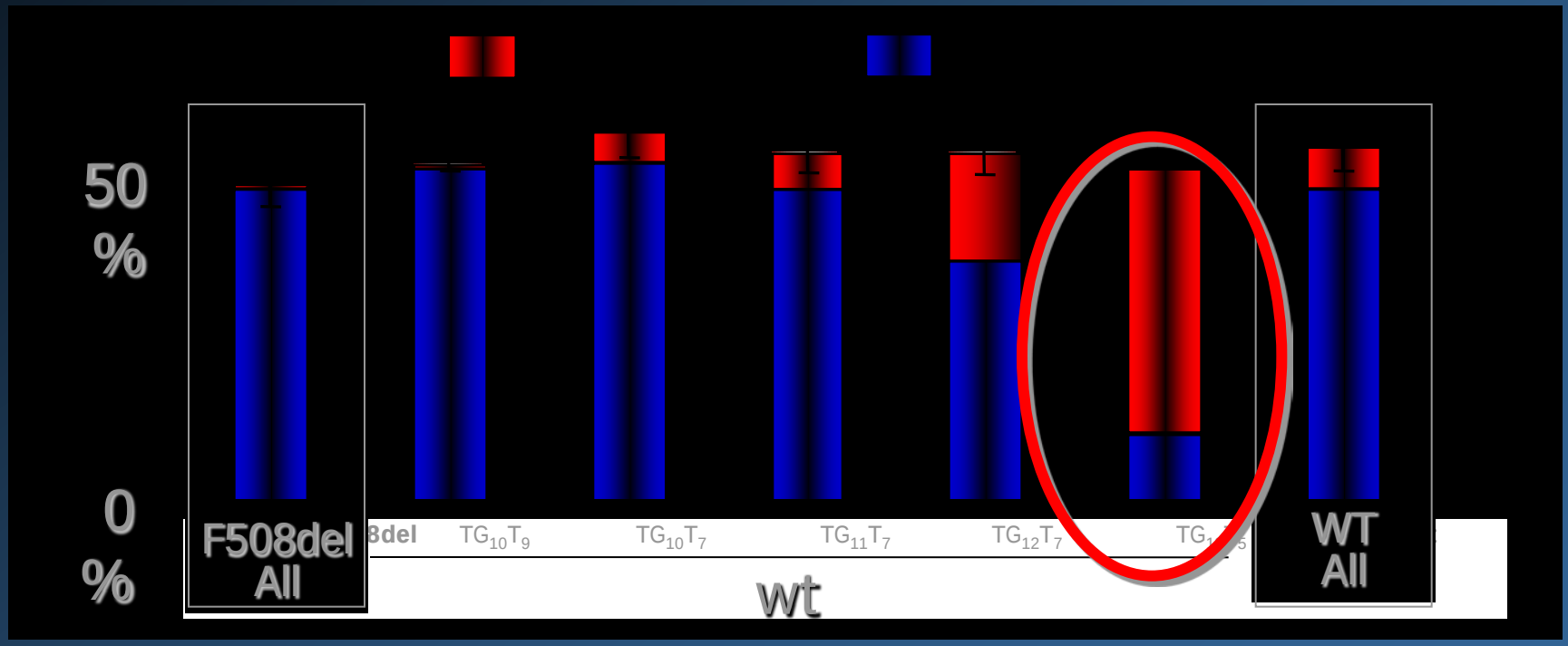
% Transcritos Normales?

4.7% ± 0.45

Ramalho *et al* (2002) AJRCMB **27**, 619-627

Estudio de Portadores F508del (n = 39)

Cuantificación de "skipping" del exon 9



Anabela Ramalho

Un individuo asintomático tiene ~10% de mRNA CFTR normal → valor suficiente para evitar la FQ?

Perspectivas de Terapias Reparadoras de la CFTR

- Todavía sabemos *algo* sobre los mecanismos básicos de la FQ → pero aunque necesitamos validarlos en células/ tejidos nativos

- Tenemos compuestos correctoras de la CFTR:
  - PTC124 → Clase I (mutaciones Stop);
  - VX809 → Clase II/V (correctores de tráfico de la CFTR);
  - VX770 → Clase III/IV/V (potenciadores de la CFTR);
  - Terapia Génica → Todas las clases de mutaciones
  - Nuevos compuestos → saliendo de la "pipeline"
- Probablemente 10% de corrección es suficiente para no tener FQ

Trasplante pulmonar

- Supervivencia post trasplante a los 5 años: alrededor del 70%

- Se estudian para trasplante con:
  - %FEV1 < 30% de la predicha
  - Deterioro rápido de la función pulmonar
  - Desnutrición resistente a una intervención nutricional
  - Cor pulmonale
  - Hipoxemia (pO_2< 55mmHg) y/o hipercapnia (pCO_2 > 50 mmHg)
  - Aumento progresivo de la resistencia antimicrobiana de los patógenos pulmonares

Fibrosis Quística resumiendo….

- FQ principalmente afecta los pulmones con infección crónica….Trasplante pulmonar
- Insuficiencia pancreática es el segundo reto (malaabsorción)
- Nutrición y fisioterapia son aspectos en ocasiones descuidados en el manejo de estos pacientes
- Diabetes, osteoporosis y enfermedad hepática son los frecuentes de los adultos
- Infertilidad, relaciones sociales y empleo …son materias muy importante…,

Mensaje....

Enfermedad de adultos

Mas complicada

Precisa de equipos bien formados, principalmente en el área de adultos

Ejemplo de colaboración

Visión esperanzadora

MUCHAS GRACIAS

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