La ricerca in Fibrosi Cistica: dalla teoria alla pratica

Daniela De Stefano
European Institute for Research in Cystic Fibrosis (IERFC)

LEGA ITALIANA FIBROSI CISTICA - ONLUS

Parma, 17 Maggio 2015

Istituto Europeo per la Ricerca in Fibrosi Cistica

IERFC Fondazione Onlus

IERFC: strategia di ricerca

Network

University of Naples Federico II

University of Rome
Tor Vergata

Hadassah Medical Center
Jerusalem

IERFC Labs

University of Dundee

University of
Southampton
Cancer Sciences
Division

INSERM Gustave Roussy

DIBIT
HSR, Milan

Sickkids Hospital
Toronto

IERFC's lab

Fondazione
Centro San Raffaele

Eleonora Ferrari

Ilenia Sana

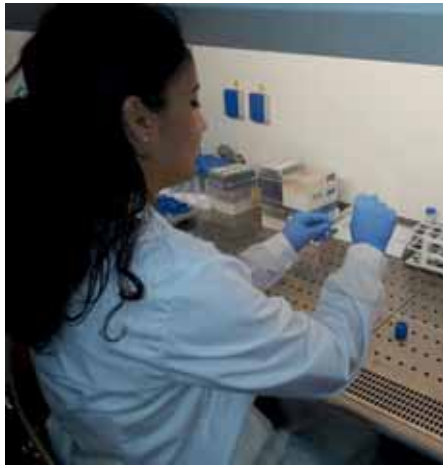
Romina Monzani

Andrea Venerando

Luigi
Maiuri

Candida
Bonelli

Marika Barbareschi



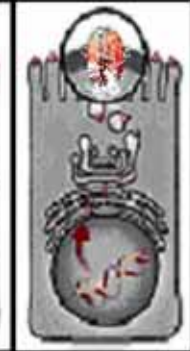
Speranza Esposito

Giorgio Cozza

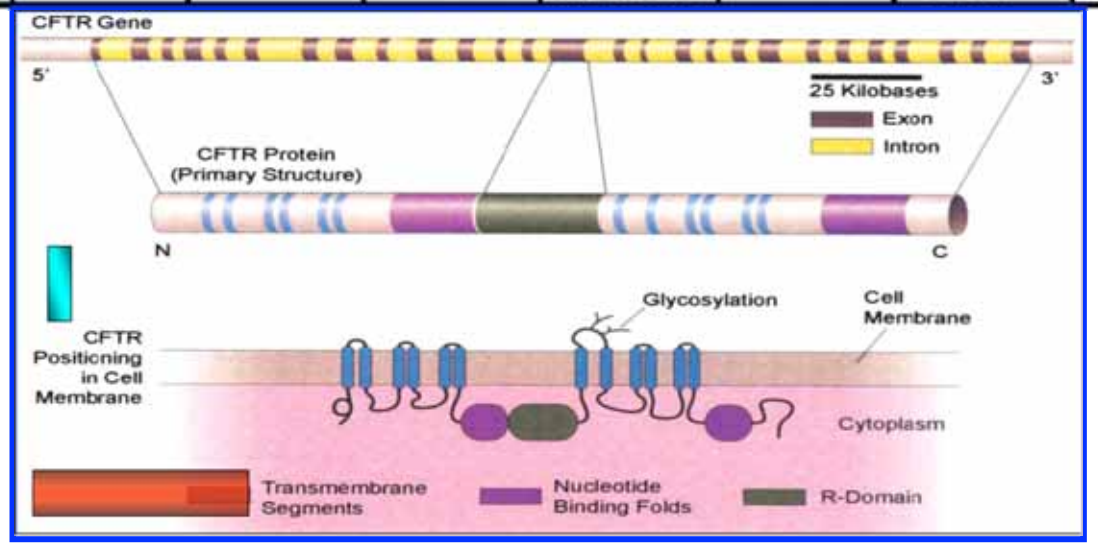
Daniela De Stefano

Mutazioni del gene CFTR

"Severe mild"

CLASSE	NORMALE	I	II	III	IV	V	VI
							
EFFETTO		No Sintesi	Mancato Processam.	Blocco Regolazione	Alterata conduttanza	Ridotta Sintesi	Instabil. Metabolica

>1900 variazioni di sequenza

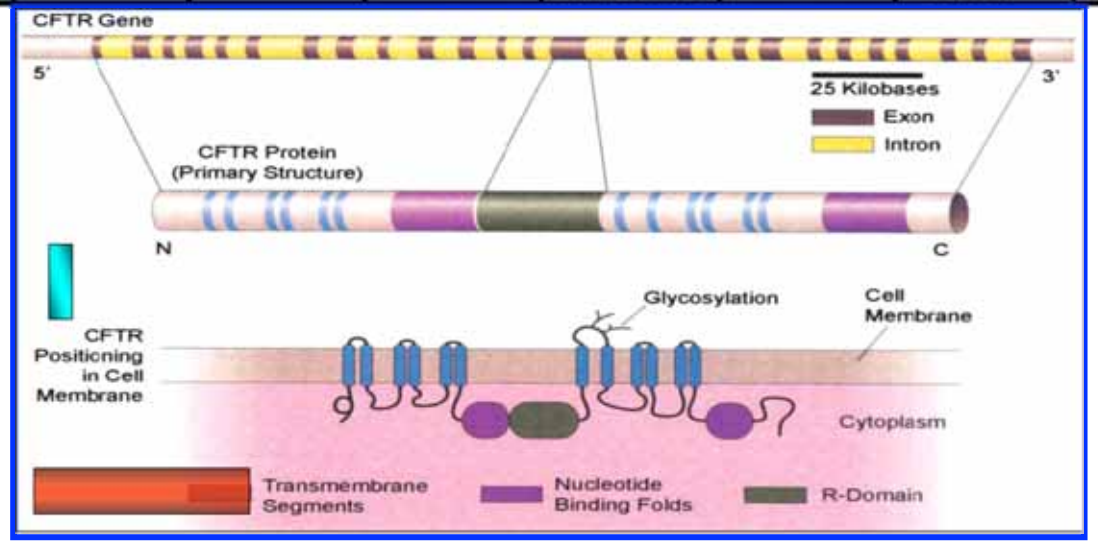


La ΔF508- CFTR

"Severe mild"

CLASSE	NORMALE	I	II	III	IV	V	VI
							
EFFETTO		No Sintesi	Mancato Processam.	Blocco Regolazione	Alterata conduttanza	Ridotta Sintesi	Instabil. Metabolica

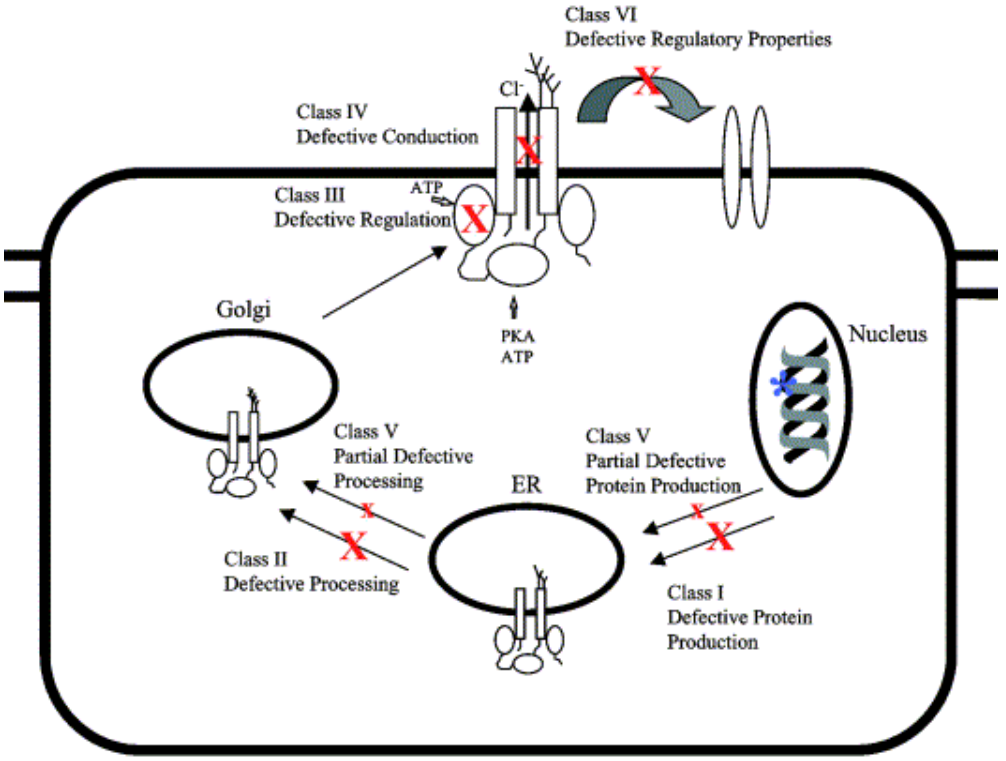
>1900 variazioni di sequenza



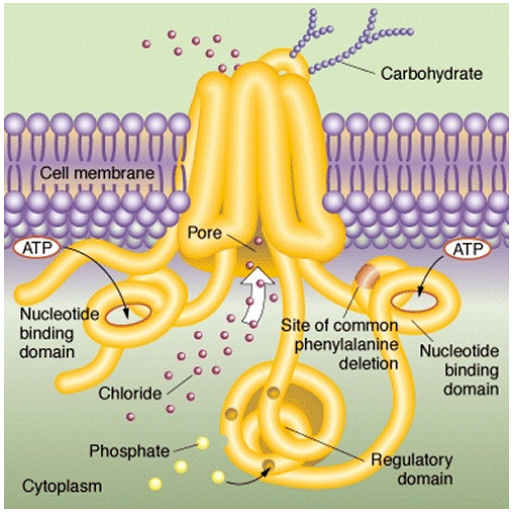
Mutazioni del gene CFTR

Panel 2: Functional classification of CFTR alleles

Class	Functional effect of mutation	Allele
I	Defective protein production	G542X, R553X, W1282X, [illegible], 1717–1G→A, 1078ΔT, 3659ΔC
II	Defective protein processing	ΔF508, ΔI507, N1303K, [illegible]
III	Defective protein regulation	G551D, R560T
IV	Defective protein conductance	R117H, R334W, G85E, R347P
V	Reduced amounts of functioning CFTR protein	3849+10KbC→T, 2789+5G→A, A455E
Unknown		711+1G→T, 2184DA, 1898+1G→A

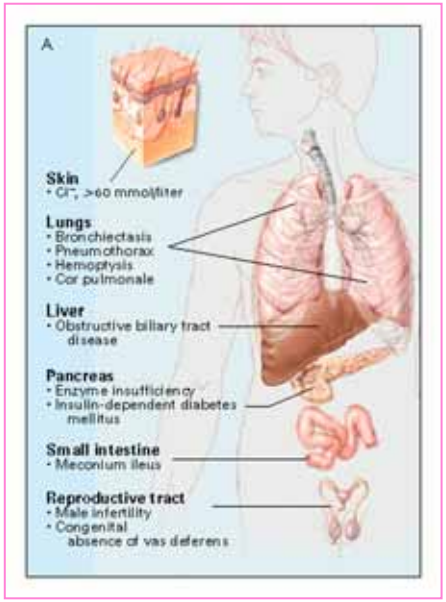


La teoria per …. la pratica



Dalla CFTR

al paziente



Oltre agli ambiti di ricerca “clinica”

Molte aree di ricerca “di base” per curare i sintomi

esempio:

infiammazione, infezione, etc…

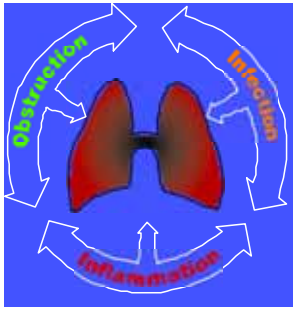
Molti candidati farmaci “nuovi e vecchi rivisitati…”

esempio:

“nuovi” anti-infiammatori

“nuovi” antibatterici

Sostituire la CFTR che “non funziona”



Circolo vizioso FC

Stem cells

Problemi:

- Colonizzazione delle cellule dei tessuti bersaglio
- Integrazione funzionale

Terapia genica

Problemi:

- Efficienza di trasferimento genico
- Efficacia nella correzione del difetto di canale
- Persistenza transitoria dell’espressione

Riparare la CFTR che "non funziona"

Correttori e potenziatori

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

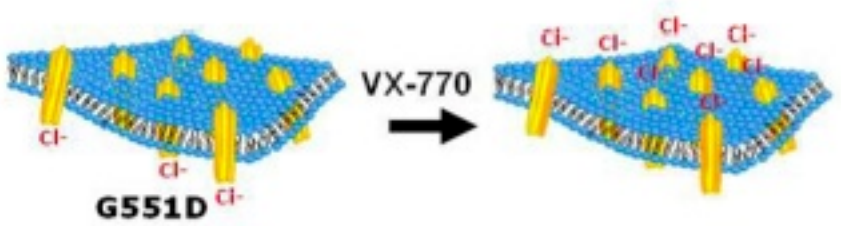
Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, Ph.D., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

Necessità dei correttori per la ΔF508- CFTR

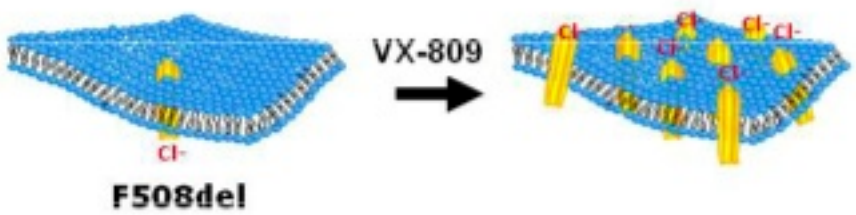
CFTR Modulator Program Goals (Corrector and Potentiator Drugs)

- Orally bioavailable drugs
- Two targets:

Potentiators:
Increase opening (gating) of CFTR channels



Correctors:
Increase number and function of CFTR channels at the cell surface



Perché i correttori hanno un razionale?

- ***La ΔF508-CFTR non raggiunge la membrana ma può funzionare (anche se parzialmente)***

- ***E' sufficiente un recupero di funzione di circa il 20% per ottenere effetti sul fenoitipo***

- ***Esistono strategie in vitro che possono correggere il difetto di "folding" e "trafficking" della ΔF508-CFTR (esempio: bassa temperatura)***

Necessità dei correttori per la ΔF508- CFTR

Correctors:
Increase number and function of CFTR channels at the cell surface

Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809

Fredrick Van Goor[a], Sabine Hadida[a], Peter D. J. Grootenhuis[a], Bill Burton[a], Jeffrey H. Stack[a], Kimberly S. Straley[a], Caroline J. Decker[a], Mark Miller[a], Jason McCartney[a], Eric R. Olson[b], Jeffrey J. Wine[c], Ray A. Frizzell[d], Melissa Ashlock[e], and Paul A. Negulescu[a,1]

Efficacia dimostrata in vitro

Come sono identificate queste molecole (correttori e potenziatori) ?

Screening fra migliaia di molecole con test in vitro

Top-down approach

La ricerca per …. la cura

ORIGINAL ARTICLE

Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the *F508del-CFTR* mutation

?

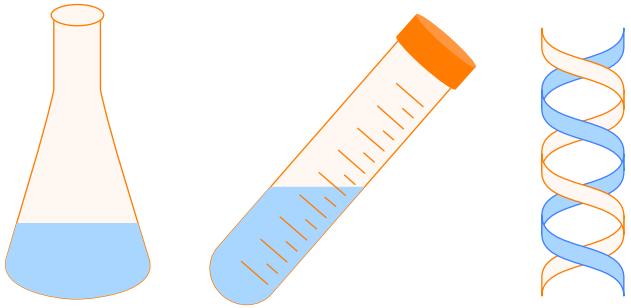
TROVARE "CORRETTORI" PIÙ POTENTI ?

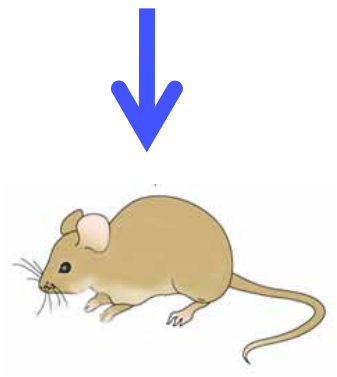
Principi strategici di ricerca IERFC

Facilities

Dai modelli in vitro alla ricerca pre-clinica

- Modelli in vitro
- Modelli ex vivo
- Modelli in vivo





Paziente

Principi strategici di ricerca IERFC

Facilities

Dai modelli in vitro alla ricerca pre-clinica

Modelli in vitro

Linee cellulari epiteliali respiratorie

- **FC** con mutazioni CFTR F508del

  strategia: "normalizzare l'epitelio FC"

  studio di markers basali e dopo inibizione di pathways specifiche

- ***Isogeniche corrette***

  Non-FC

  strategia: "rendere FC una cellula normale"

  Knock down CFTR gene

  Transfection con GFP-F508del-CFTR

  Inibizione funzionale CFTR

  studio di markers basali e dopo inibizione di pathways specifiche

Linee cellulari epiteliali intestinali con espressione di CFTR

Principi strategici di ricerca IERFC

Facilities

Dai modelli in vitro alla ricerca pre-clinica

Modelli ex vivo

Coltura di mucosa di polipo nasale di pazienti FC e controlli e brushing nasale

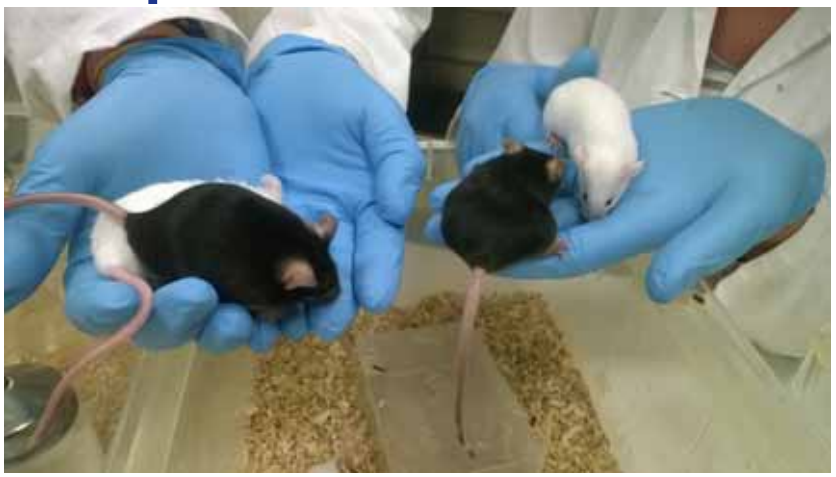
- correlazioni con genotipo
- studio delle popolazioni cellulari epiteliali e cellule infiammatorie

- studio di markers basali e dopo inibizione di pathways specifiche
- studio del recruitment intraepiteliale di neutrofili

IERFC research strategy

Facilities

Dai modelli in vitro alla ricerca preclinica

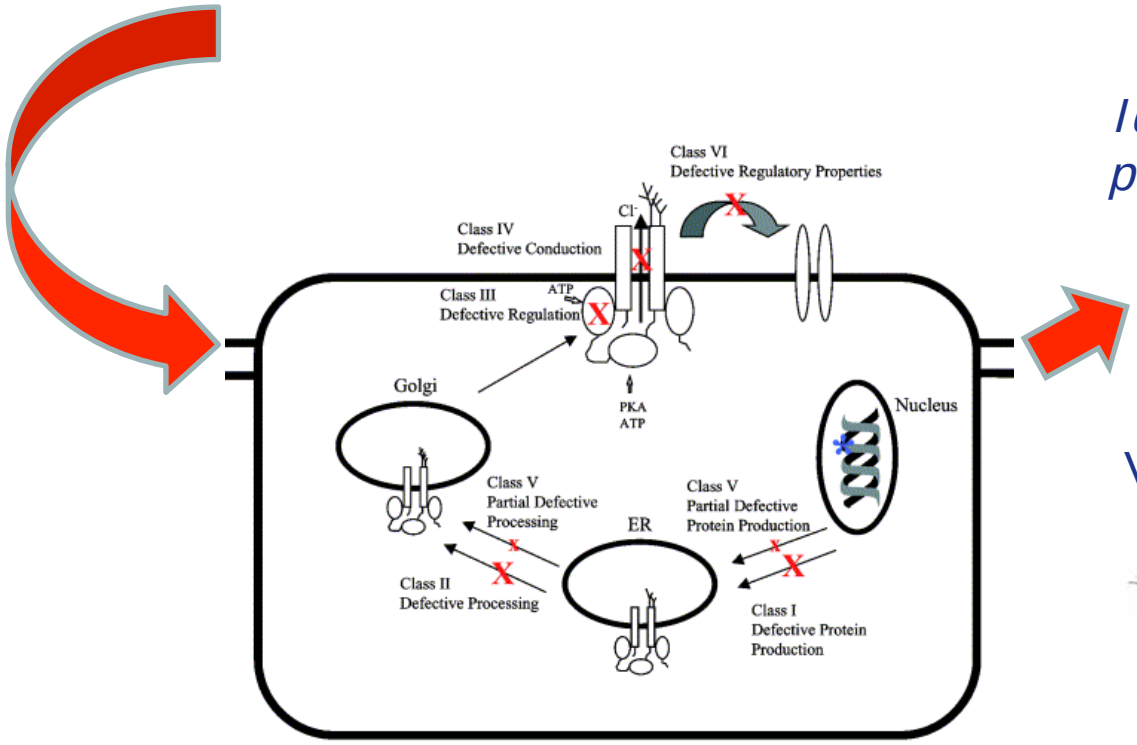


In vivo models

Modelli FC

1. CFTR-F508del homozygous mice
2. *Scnn 1b* transgenic mice (β-ENaC)
3. CFTR-KO mice
4. CFTR-KO/CFTR-F508del mice
5. CFTR-F508del homozygous cross-bred with TG2 KO mice
6. CFTR-F508del homozygous mice cross-bred with Beclin-1 haploinsufficient mice

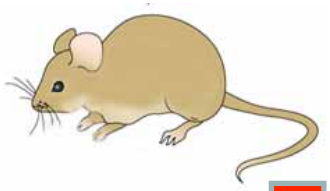
La strategia bottom up



Drug discovery

Identificazione di nuove pathways infiammatorie e loro modulazione

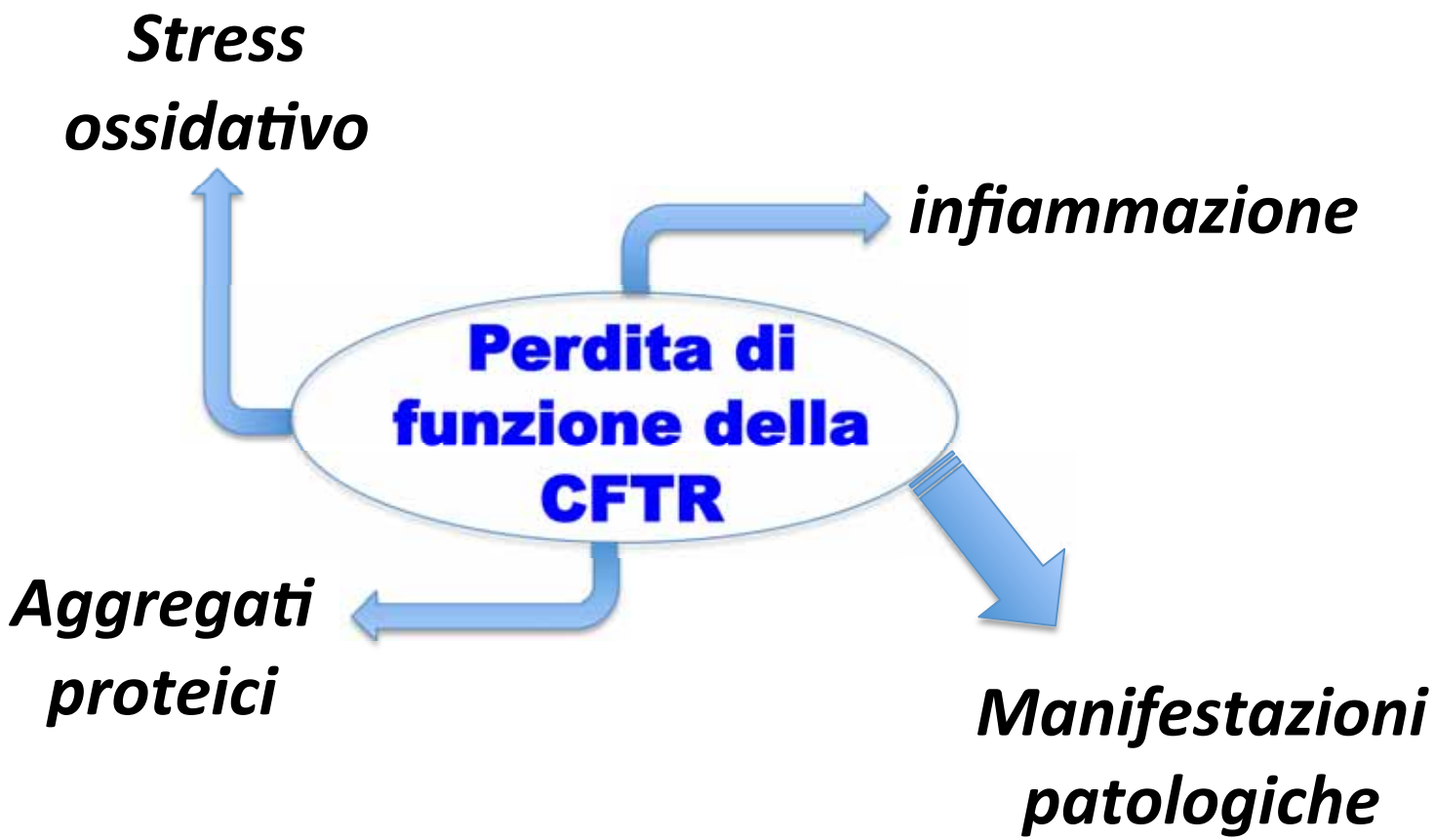
Validazione pre-clinica



Sperimentazione clinica

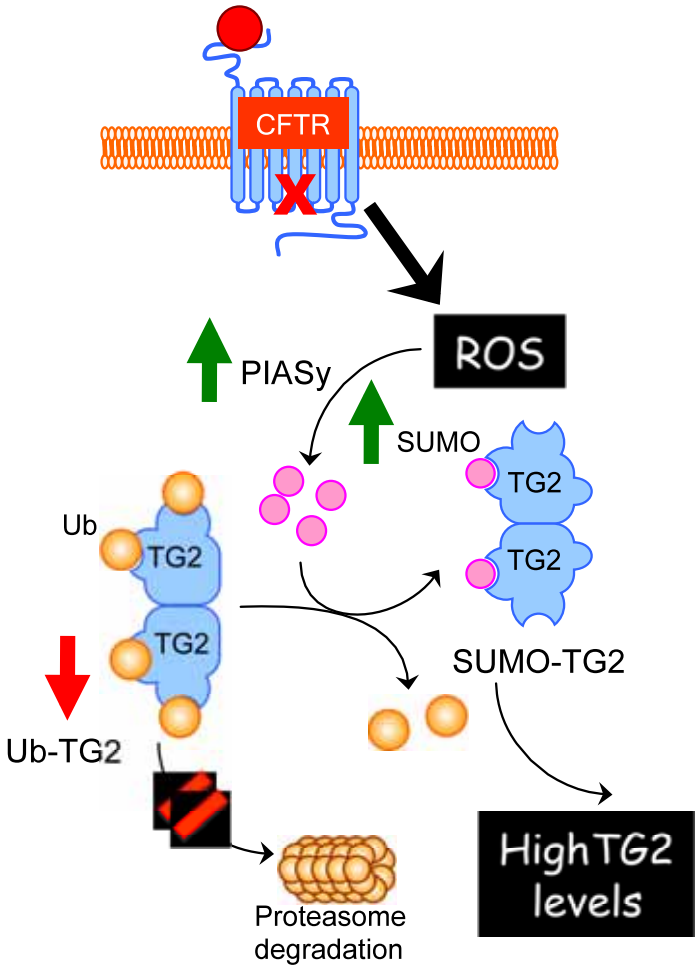
Progetto globale: comprendere per curare

L’anello mancante in CF



Transglutaminasi tissutale (TG2): il link che manca?

I radicali liberi attivano l'enzima TG2



Difetto di CFTR

↓

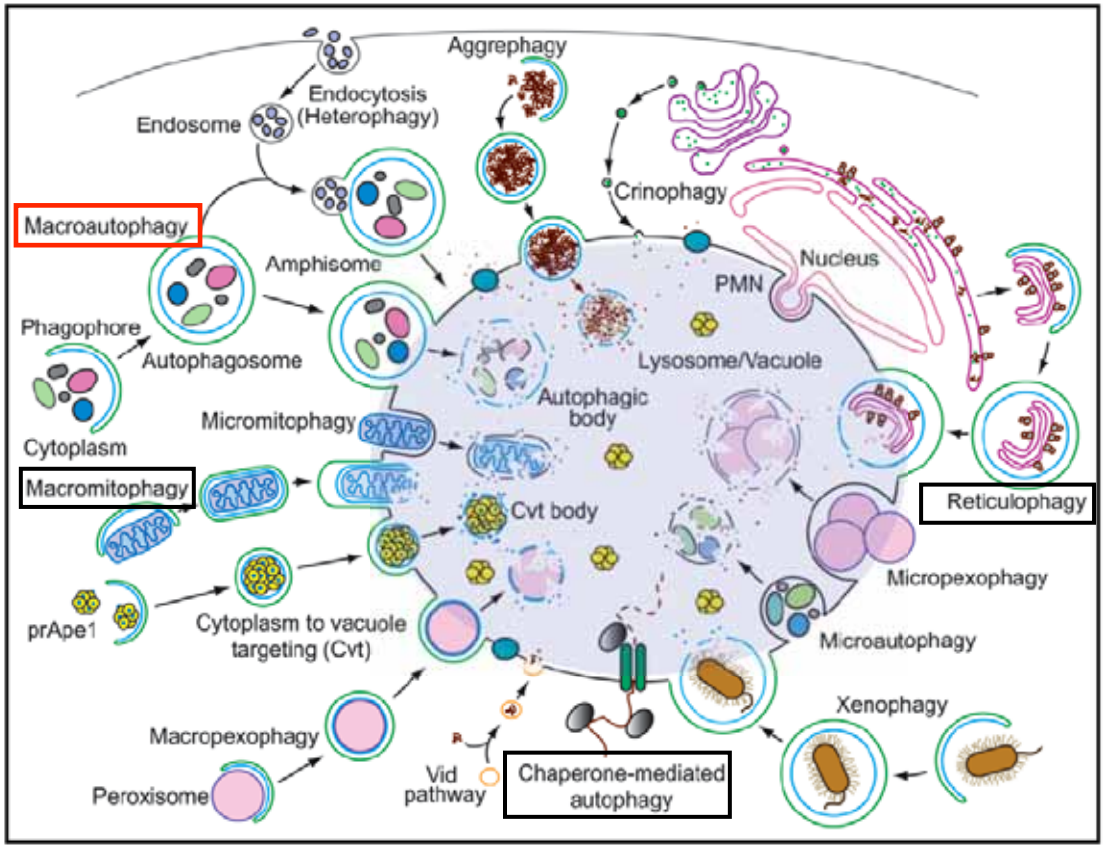
Accumulo di ROS = stress ossidativo

↓

Attivazione della TG2

Luciani A, J Immunol, 2009

Autofagia: un meccanismo che le cellule adottano in risposta a differenti stimoli e condizioni di stress

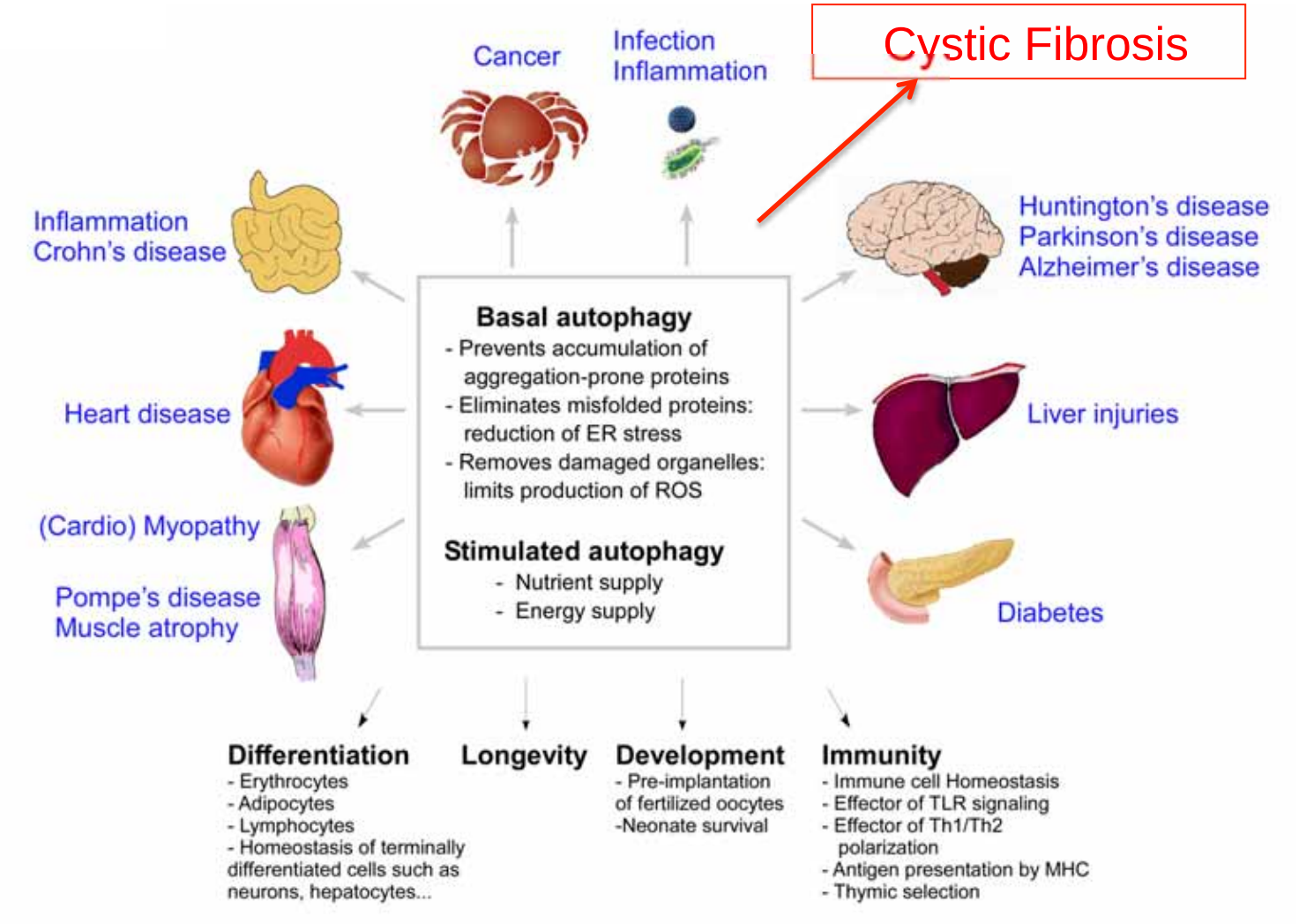


stress ossidativo

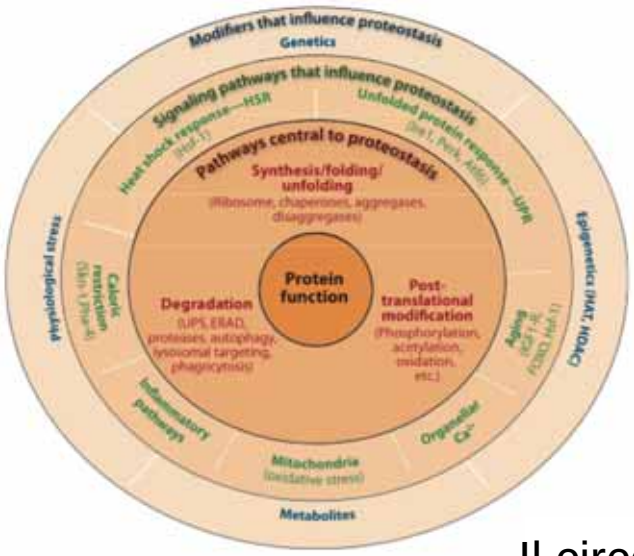
challenge batterico

accumulo di proteine con difetto di folding

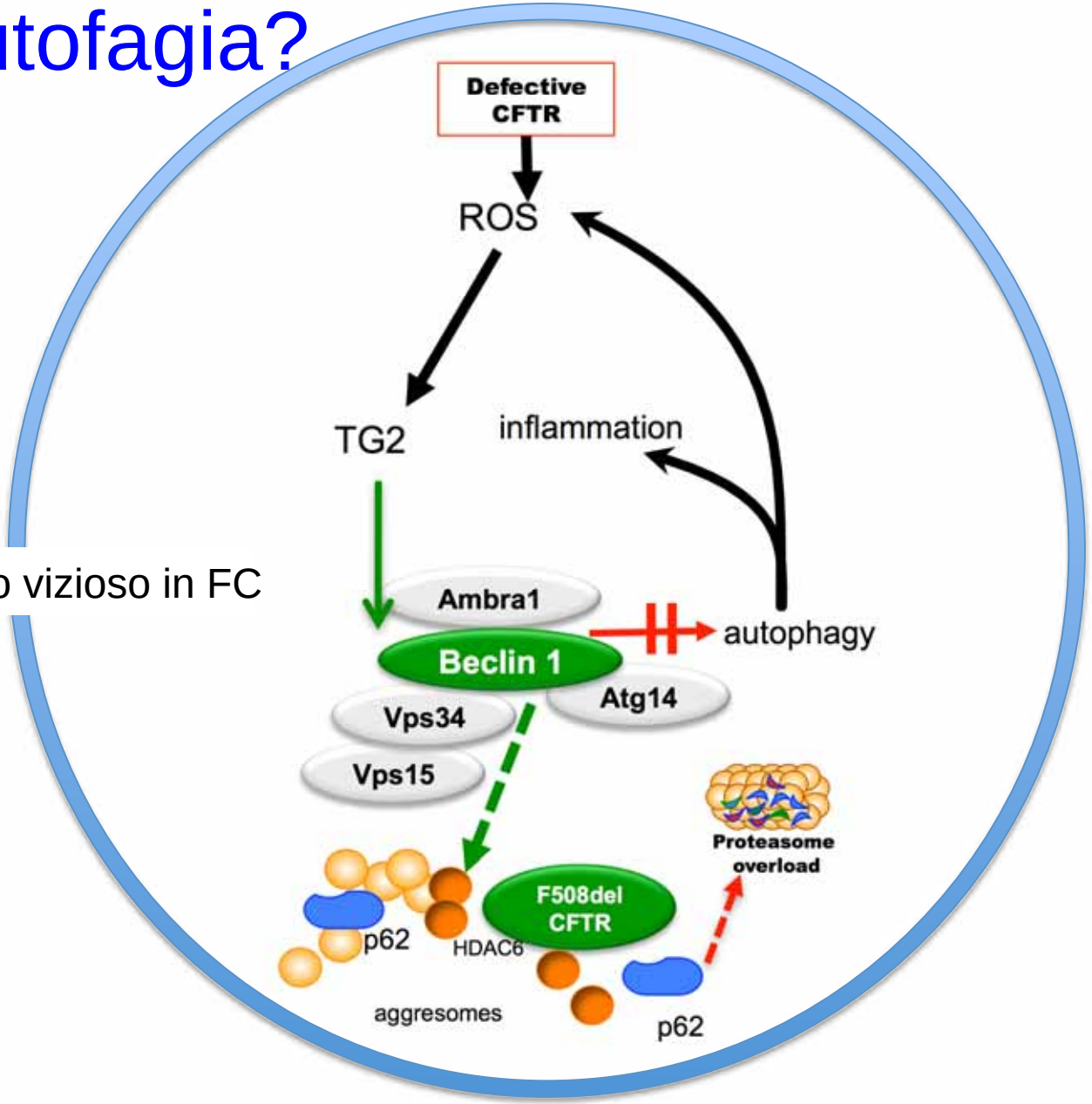
FC:una patologia con difetto di autofagia?



FC:una patologia con difetto di autofagia?

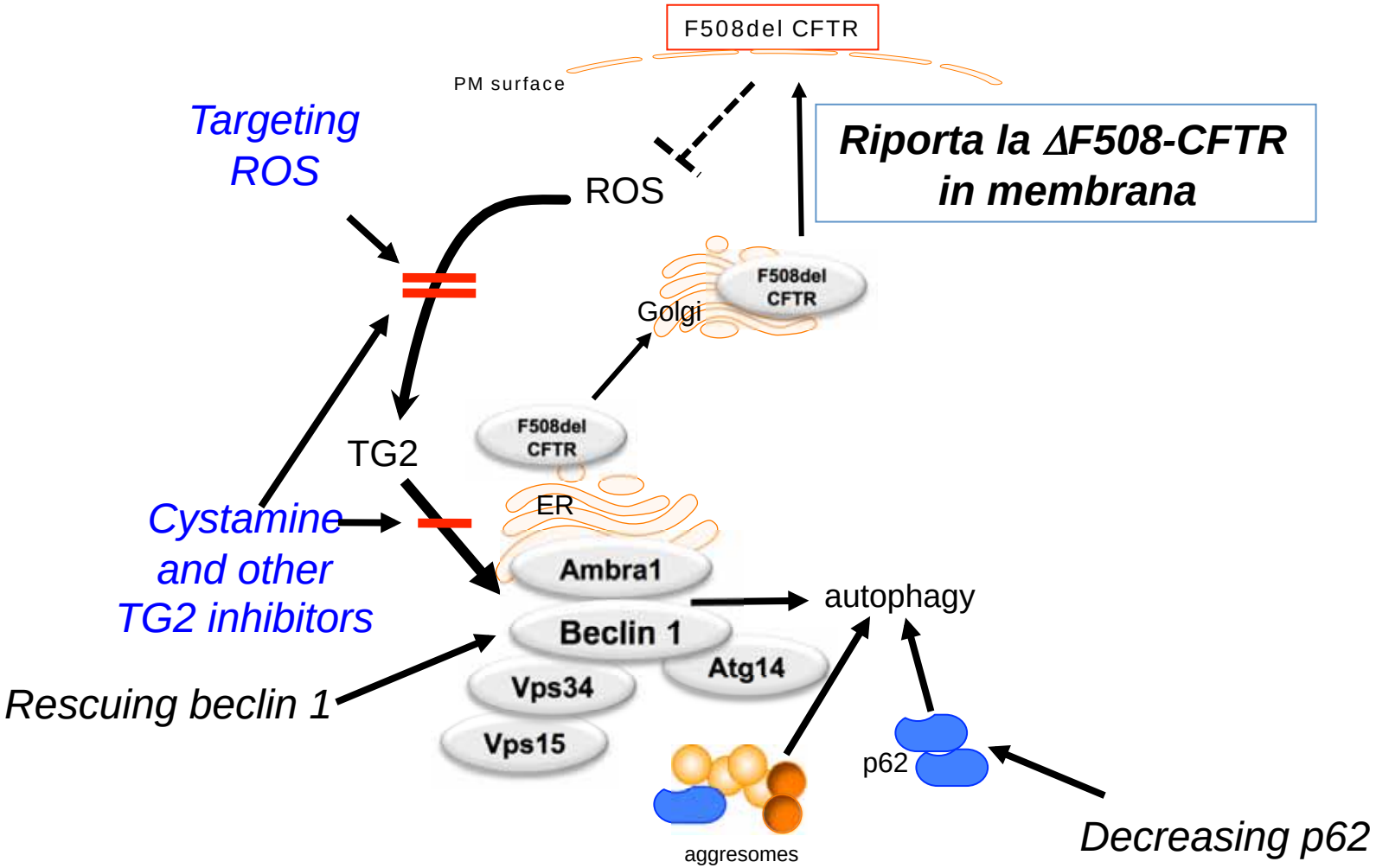


Il circolo vizioso in FC



A. Luciani, Autophagy, 2011

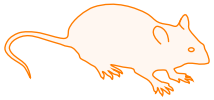
Cystic Fibrosis: Proteostasis Regulators as a new therapeutic option

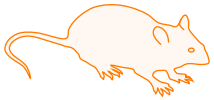


A. Luciani, Autophagy, 2011

In quali modelli lo abbiamo dimostrato?

In vitro

In vivo su due modelli di topi FC 



CFTR^{F508delCFTR} mouse

Scnn 1b-Tg mouse

In biopsie di polipo nasali umane
da pazienti con ΔF508/ΔF508

Towards a rational combination therapy of cystic fibrosis

How cystamine restores the stability of mutant CFTR

Valeria R. Villella,[1] Speranza Esposito,[1] Maria Chiara Maiuri,[1,2] Valeria Raia,[3,4] Guido Kroemer[5,6,7,8,9] and Luigi Maiuri[10,11]
[1]European Institute for Research in Cystic Fibrosis; Division of Genetics and Cell Biology; San Raffaele Scientific Institute; Milan, Italy;
[2]Department of Experimental Pharmacology; School of Biotechnological Sciences; Federico II University; Naples, Italy; [5]INSERM, U848; Villejuif, France;
[3]Cystic Fibrosis Unit; Department of Pediatrics; Federico II University; Naples, Italy; [6]Université Paris Descartes; Paris, France; [7]Metabolomics and Cell Biology Platforms; Institut Gustave Roussy; Villejuif, France; [8]Equipe 11 Labellisée Ligue contre le Cancer; Centre de Recherche des Cordeliers; Paris, France;
[9]Pôle de Biologie; Hôpital Européen Georges Pompidou; Assistance Publique Hôpitaux de Paris; Paris, France; [4]Institute of Pediatrics; University of Foggia; Foggia, Italy

Cell Death and Differentiation (2013) 20, 1101–1115

1350-9047/13
www.nature.com/cdd

Disease-relevant proteostasis regulation of cystic fibrosis transmembrane conductance regulator

Villella[1], S Esposito[1], EM Bruscia[1,2], M Vicinanza[3], S Cenci[4], S Guido[5], M Pettoello-Mantovani[6], R Carnuccio[7], De Matteis[3], A Luini[3,8], MC Maiuri[7,9], V Raia[4,10], G Kroemer[4,9,11,12,13,14] and L Maiuri[4,1,8]

Reduced caveolin-1 promotes hyper-inflammation due to abnormal heme oxygenase-1 localizationin LPS challenged macrophages with dysfunctional CFTR

Ping-Xia Zhang[¶,*], **Thomas S. Murray**[†,*], **Valeria Rachela Villella**[‖], **Eleonora Ferrari**[‖], **Speranza Esposito**[‖], **Anthony D'Souza**[*], **Valeria Raia**[#], **Luigi Maiuri**[‖,**], **Diane S. Krause**[*,‡], **Marie E. Egan**[¶,§], and **Emanuela M. Bruscia**[¶,‖,††]
[¶]Department of Pediatrics, 333 Cedar Street, Yale University School of Medicine, New Haven

frontiers in
PHARMACOLOGY

REVIEW ARTICLE
published: 21 January 2013
doi: 10.3389/fphar.2013.00001

Targeting the intracellular environment in cystic fibrosis: restoring autophagy as a novel strategy to circumvent the CFTR defect

Valeria Rachela Villella[1], Speranza Esposito[1], Emanuela M. Bruscia[1,2], Maria Chiara Maiuri[3,4], Valeria Raia[5], Guido Kroemer[4,6,7,8,9] and Luigi Maiuri[1,10]**

TRANSLATIONAL RESEARCH PAPER

Autophagy 8:11, 1655–1672, November 2012; © 2012 Landes Bioscience

Targeting autophagy as a novel strategy for facilitating the therapeutic action of potentiators on ΔF508 cystic fibrosis transmembrane conductance regulator

Alessandro Luciani,[1,2,†] Valeria Rachela Villella,[1,†] Speranza Esposito,[1,2] Manuela Gavina,[1] Ilaria Russo,[1] Marco Silano,[4] Stefano Guido,[1] Massimo Pettoello-Mantovani,[2] Rosa Carnuccio,[5] Bob Scholte,[6] Antonella De Matteis,[7] Maria Chiara Maiuri,[1,8] Valeria Raia,[9] Alberto Luini,[7,10] Guido Kroemer[8,11,12,13,14,*] and Luigi Maiuri[1,2,*]

Pediatric Pulmonology 48:761–771 (2013)

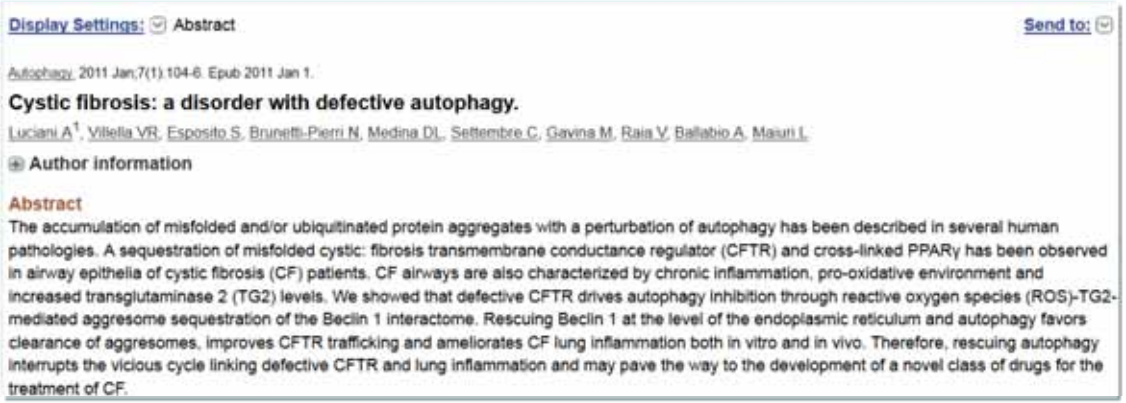
Nebulized Hyaluronan Ameliorates Lung Inflammation in Cystic Fibrosis Mice

Manuela Gavina, PhD,[1] Alessandro Luciani, PhD,[1] Valeria R. Villella, PhD,[1] Speranza Esposito,[2,3] Eleonora Ferrari,[1] Ilaria Bressani,[1] Alida Casale, MD,[4] Emanuela M. Bruscia, PhD,[1,5] Luigi Maiuri, MD,[1,2] and Valeria Raia, MD[4*]**

nature cell biology

Defective CFTR induces aggresome formation and lung inflammation in cystic fibrosis through ROS-mediated autophagy inhibition

Alessandro Luciani[1,2,11], Valeria Rachela Villella[1,11], Speranza Esposito[2,3], Nicola Brunetti-Pierri[4,5], Diego Medina[4], Carmine Settembre[4], Manuela Gavina[1], Laura Pulze[1], Ida Giardino[6], Massimo Pettoello-Mantovani[3], Maria D'Apolito[3], Stefano Guido[2], Eliezer Masliah[7], Brian Spencer[7], Sonia Quaratino[8], Valeria Raia[9,12], Andrea Ballabio[4,10,12] and Luigi Maiuri[1,3,12]



Display Settings: Abstract Send to:

Autophagy. 2011 Jan;7(1):104-6. Epub 2011 Jan 1.

Cystic fibrosis: a disorder with defective autophagy.

Luciani A[1], Villella VR, Esposito S, Brunetti-Pierri N, Medina DL, Settembre C, Gavina M, Raia V, Ballabio A, Maiuri L

Author information

Abstract

The accumulation of misfolded and/or ubiquitinated protein aggregates with a perturbation of autophagy has been described in several human pathologies. A sequestration of misfolded cystic: fibrosis transmembrane conductance regulator (CFTR) and cross-linked PPARγ has been observed in airway epithelia of cystic fibrosis (CF) patients. CF airways are also characterized by chronic inflammation, pro-oxidative environment and increased transglutaminase 2 (TG2) levels. We showed that defective CFTR drives autophagy inhibition through reactive oxygen species (ROS)-TG2-mediated aggresome sequestration of the Beclin 1 interactome. Rescuing Beclin 1 at the level of the endoplasmic reticulum and autophagy favors clearance of aggresomes, improves CFTR trafficking and ameliorates CF lung inflammation both in vitro and in vivo. Therefore, rescuing autophagy interrupts the vicious cycle linking defective CFTR and lung inflammation and may pave the way to the development of a novel class of drugs for the treatment of CF.

Uno studio clinico pilota

TRANSLATIONAL RESEARCH PAPER

Autophagy 10:11, 2053–2074; November 2014; Published with license by Taylor & Francis

Restoration of CFTR function in patients with cystic fibrosis carrying the F508del-CFTR mutation

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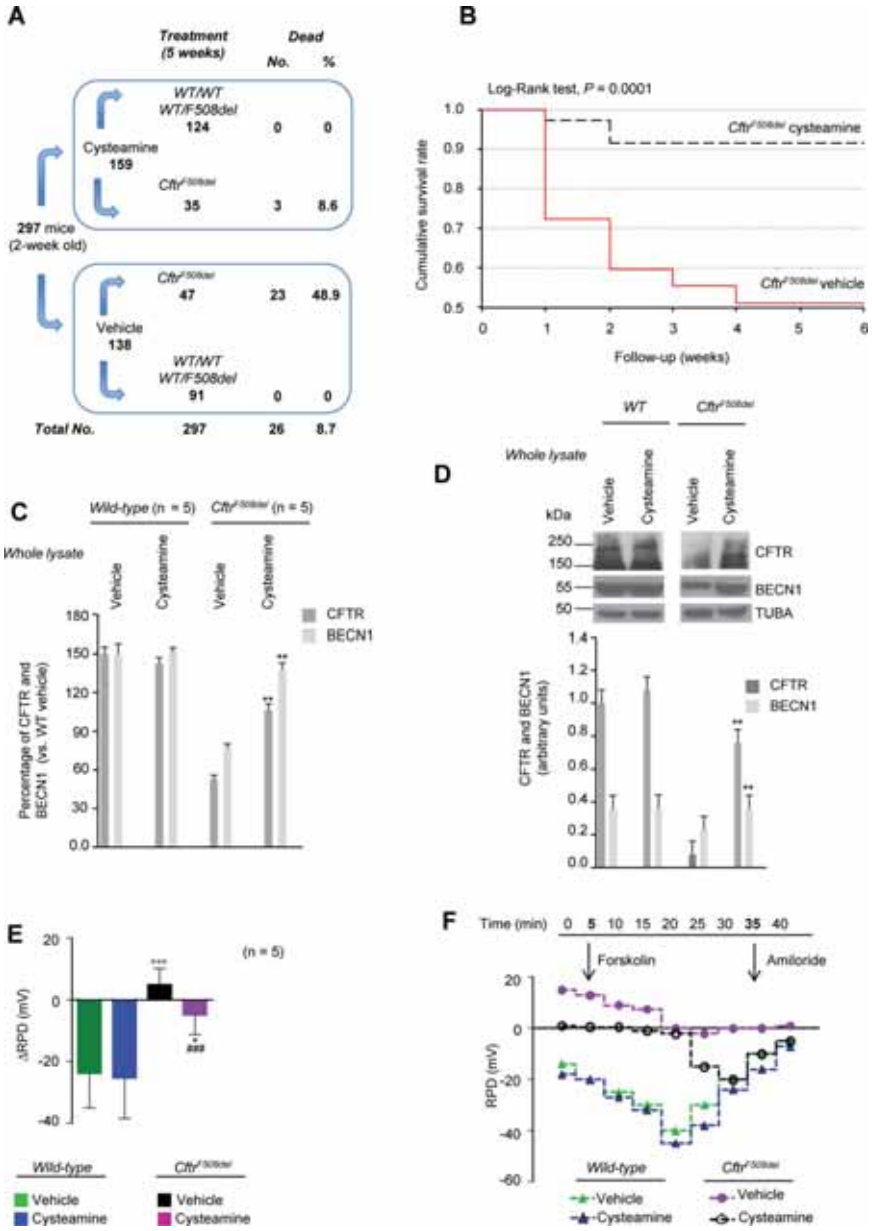
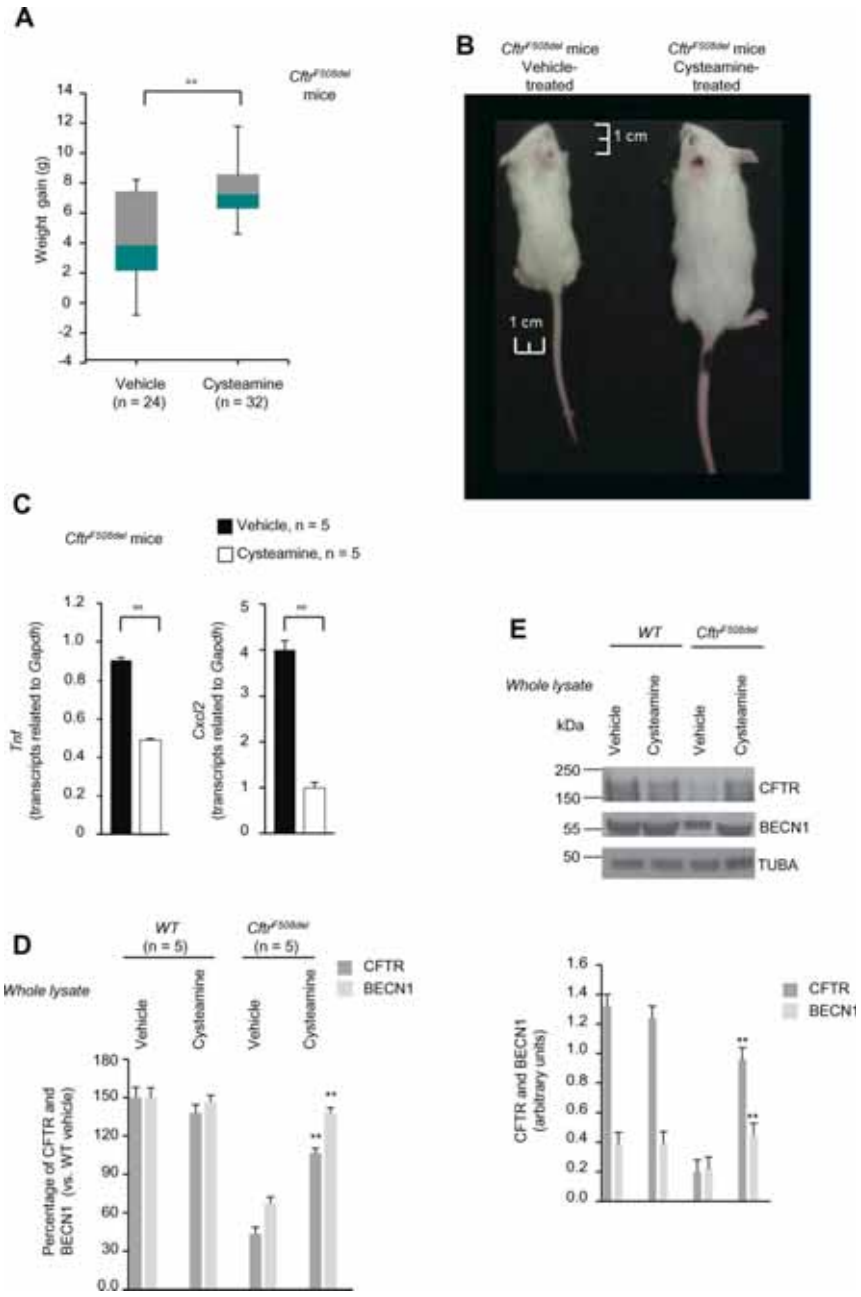
Keywords: cystic fibrosis, CFTR, autophagy, cysteamine, epigallocatechin gallate, sweat chloride

Abbreviations: BECN1/Beclin 1, autophagy-related; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CHX, cycloheximide; CSNK2, casein kinase 2; CXCL2, chemokine (C-X-C motif) ligand 2; CXCL8, chemokine (C-X-C motif) ligand 8; EGCG, epigallocatechin gallate; FEV, forced expiratory volume; PM, plasma membrane; RPD, rectal potential difference; SQSTM1, sequestosome 1; TGM2, transglutaminase 2; TNF, tumor necrosis factor.

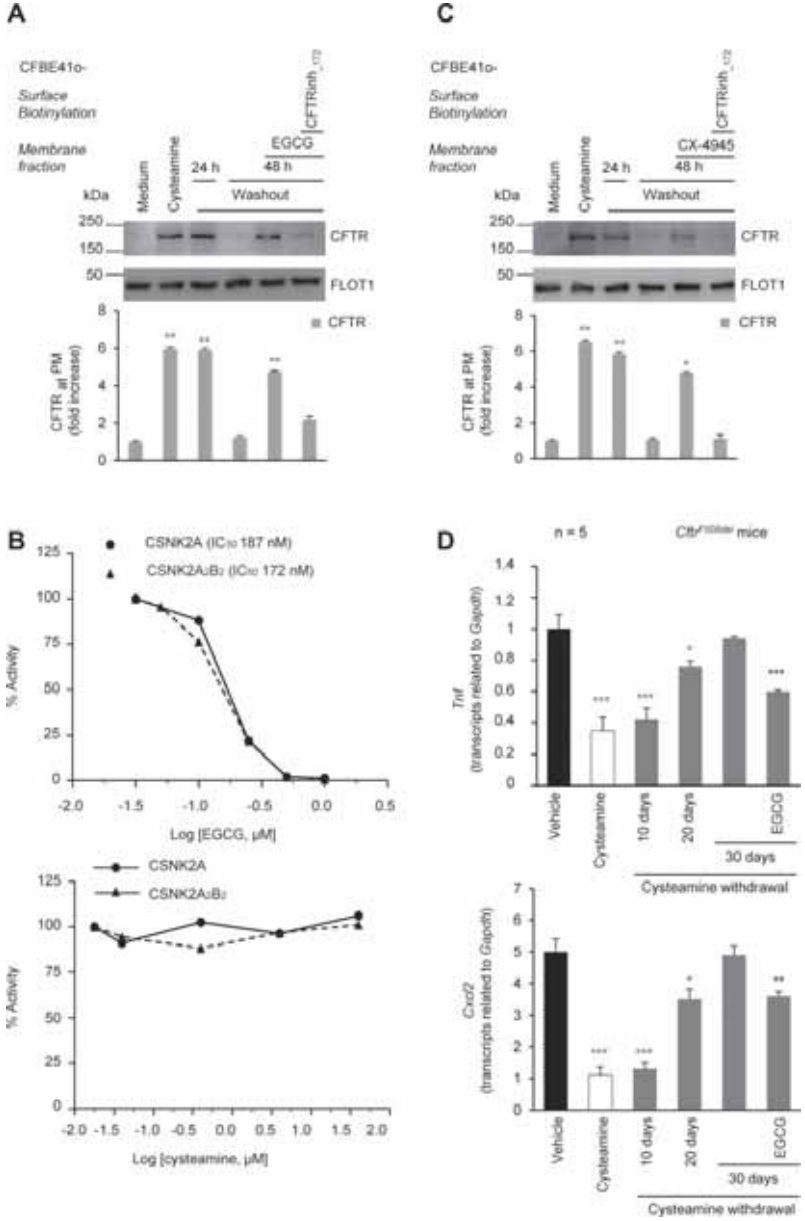
Effetti della cisteamina in vivo



Effetti della cisteamina in vivo



Effetti della cisteamina in cellule FC



Caratteristiche dei pazienti

Table 1. Baseline Characteristics of the Patients

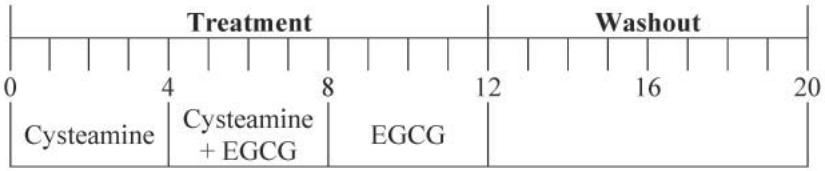
	Sex	Age (years)	Weight (Kg)	Height (cm)	BMI	*PA*	FEV_1 % predicted	FEF_{25-75} % predicted	Sweat chloride (mmol/liter)
1	M	15.8	58.2	160.0	22.73	–	103.6	50.0	71
2	M	10.7	37.3	131.0	21.70	–	75.7	39.0	88
3	F	19.8	46.2	159.0	18.27	–	81.3	28.1	76
4	F	25.0	53.0	160.3	20.62	–	74.6	29.4	84
5	M	13.6	45.8	156.0	18.82	–	95.9	53.1	115
6	F	17.7	44.1	151.0	19.34	+	89.6	52.7	113
7	F	12.0	44.6	146.5	20.80	–	113.1	105.9	67
8	F	15.6	52.5	161.3	20.18	+	109.3	62.6	100
9	F	17.8	48.0	153.5	20.37	+	77.8	24.5	74
10	M	8.6	32.6	132.5	18.57	–	101.2	42.9	153

PA, Pseudomonas aeruginosa.

Criteri di inclusione

Inclusion criteria

F508del/F508del-CFTR
≥8 years of age
Sweat chloride ≥60 mmol/liter
FEV_1 >50% predicted



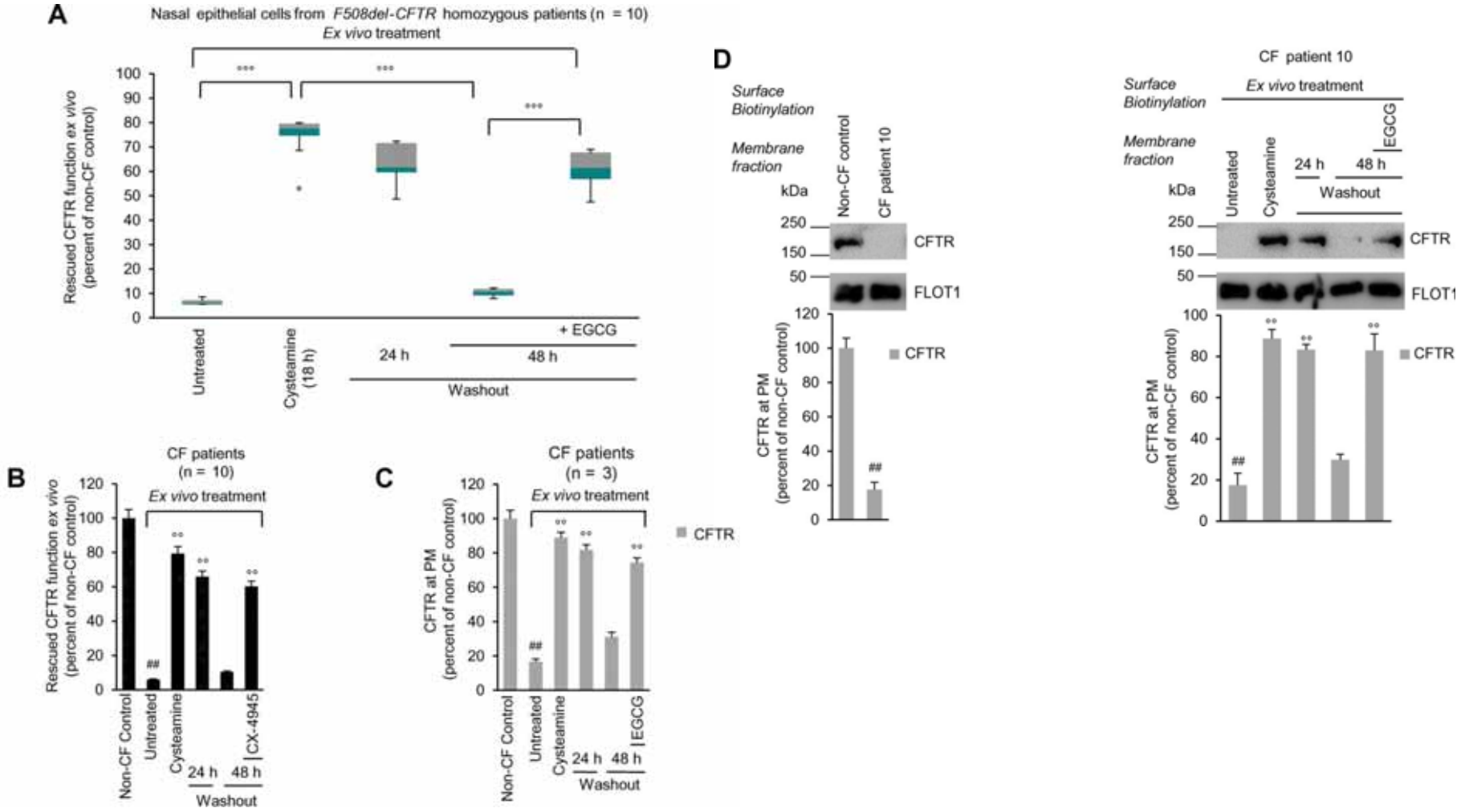
Core study measures Visit	V1	V2	V3	V4	V5	V6
Sweat Chloride	X	X	X	X	X	X
Sputum						
Inflammatory cytokines	X	X	X	X		
Clinical outcomes						
FEV_1 % predicted	X	X	X	X	X	X
FEV_{25-75} % predicted	X	X	X	X	X	X
Nasal brushing						
Chloride efflux	X	X	X	X		
Inflammatory cytokines	X	X	X	X		
Laboratory assessment						
Serum	X	X	X	X		
Plasma	X	X	X	X		

Effetti della cisteamina sui pazienti

Table 3. Treatment Effects

Core study measures	Visit (V)	Patients									
		1	2	3	4	5	6	7	8	9	10
					Sweat test						
Cl^- (mmol/l)	V1	71	88	76	84	115	113	67	100	74	153
	V2	72	90	80	70	95	79	61	97	82	89
	V3	52	76	64	74	74	51	52	104	69	37
	V4	48	42	63	76	58	55	45	51	87	93
	V5	57	70	70	66	65	53	58	61	47	87
	V6	93	96	104	54	95	102	71	104	92	83
					Nasal brushing						
I^- efflux % control	V1	7.3	8.3	7.1	7.6	8.9	6.2	7.1	10.2	12.8	10.2
	V2	9.2	18.6	8.8	29.7	28.7	20.4	10.0	13.4	14.1	29.2
	V3	20.5	25.9	27.1	31.0	29.5	31.6	27.6	14.6	20.3	54.0
	V4	16.5	29.6	28.5	29.0	28.7	30.0	33.2	18.2	15.1	17.0
					Sputum						
TNF (pg/ml)	V1	137.8	174.4	159.5	167.2	461.8	111.5	152.3	345.7	93.2	517.9
	V2	292.6	27.3	254.3	38.4	34.1	69.0	137.4	30.2	216.1	4.3
	V3	3.9	6.7	43.5	71.9	5.6	0.1	2.2	43.5	23.9	24.6
	V4	1.4	160.8	224.6	0	66.0	1.8	6.0	18.8	140.5	121.3
CXCL8 (pg/ml)	V1	1576.9	43.8	429.4	298.7	77.9	74.0	911.7	548.5	156.3	1431.7
	V2	1386.2	198.9	1153.7	37.2	0	15.9	6.2	0	2649.9	0
	V3	0	0	54.7	232.8	0	0	0	69.2	130.2	48.8
	V4	0	1820.9	1303.8	0	0	0	0	180.5	650.2	0
					Respiratory function						
FEV_1 liters	V1	3.04	1.28	2.48	2.34	2.66	2.13	2.45	3.04	1.91	1.71
	V2	2.84	1.65	2.74	2.26	2.74	2.14	2.45	2.90	2.01	1.60
	V3	3.17	1.73	2.54	2.20	2.99	2.38	2.62	2.65	1.91	1.54
	V4	2.94	1.75	2.89	2.43	2.67	2.40	2.46	2.90	2.05	1.60
	V5	3.61	2.00	2.66	2.47	2.93	2.18	2.56	3.22	1.87	1.62
FEV_1 %	V1	103.6	75.7	81.3	74.6	95.9	89.6	113.1	109.3	77.8	101.2
	V2	96.9	97.9	89.7	72.1	98.6	90.2	113.1	104.2	81.8	94.6
	V3	108.3	102.4	83.2	70.0	107.7	100.1	116.7	93.6	78.0	87.7
	V4	100.3	103.5	117.2	77.7	91.2	101.1	109.2	102.5	83.5	86.9
	V5	120.8	118.7	87.1	78.7	98.1	91.7	113.8	113.9	66.5	88.1
FEF_{25-75} liters/sec	V1	1.71	0.85	1.14	1.20	1.74	1.60	2.96	2.17	0.77	0.93
	V2	1.58	1.46	1.56	1.26	1.63	1.22	3.01	2.24	0.90	0.77
	V3	1.73	1.30	1.58	0.88	2.49	1.76	3.72	1.73	0.76	1.36
	V4	1.71	1.65	1.59	0.86	1.59	1.83	2.94	2.18	0.98	0.89
	V5	2.48	2.25	1.48	0.91	2.21	1.71	3.25	2.63	0.89	0.79
FEF_{25-75} %	V1	50.0	39.0	28.1	29.4	53.1	52.7	105.9	62.6	24.5	42.9
	V2	46.2	67.0	38.5	31.0	49.7	40.2	107.6	64.9	28.9	35.6
	V3	50.5	60.0	39.0	21.6	76.2	58.2	128.7	49.0	24.2	60.5
	V4	50.0	75.7	39.2	21.0	46.5	60.5	101.8	62.0	31.2	38.3
	V5	71.4	103.4	36.5	22.3	63.8	56.5	112.4	74.6	22.3	33.9

Effetti della cisteamina su cellule nasali di paziente



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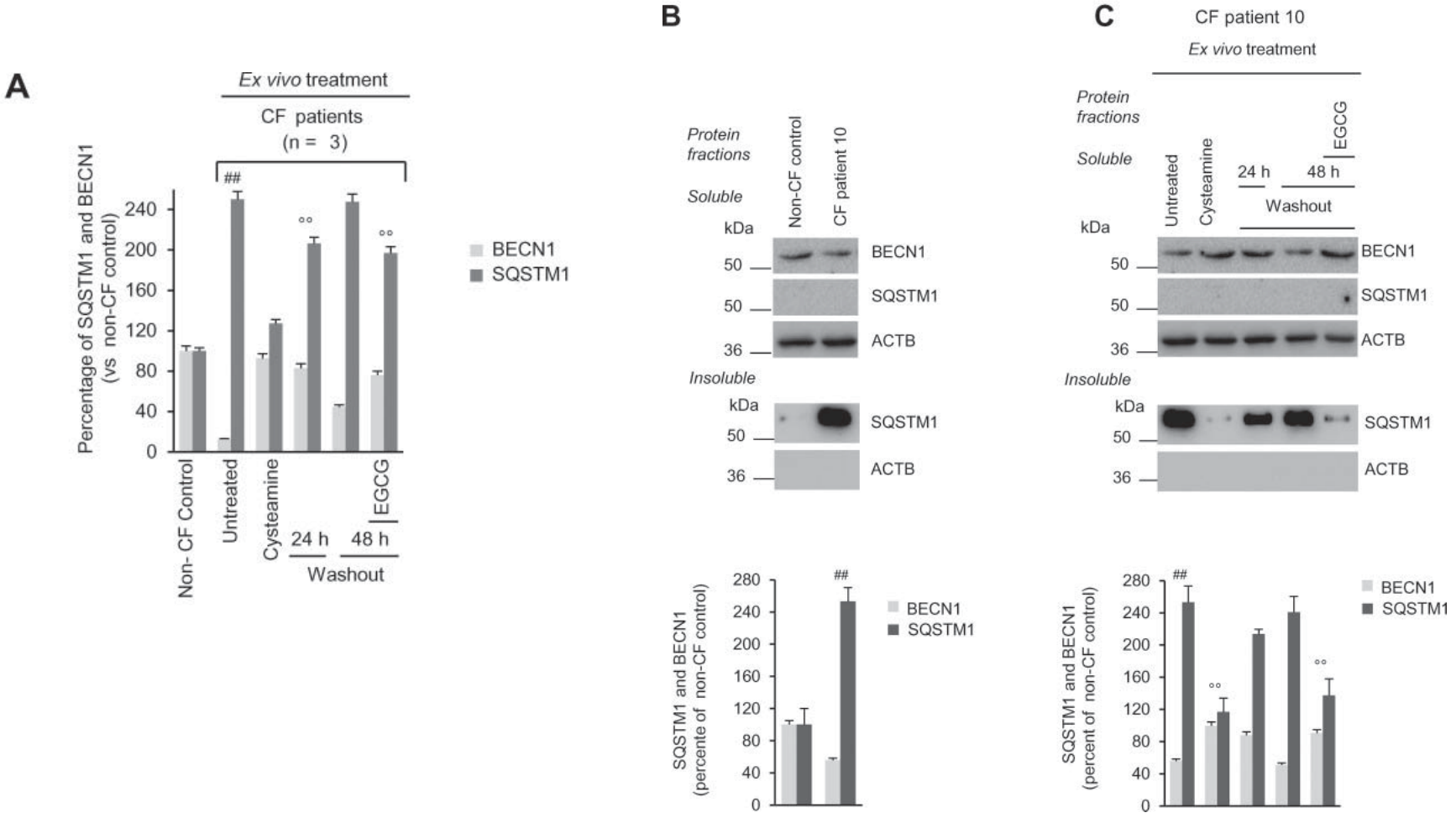

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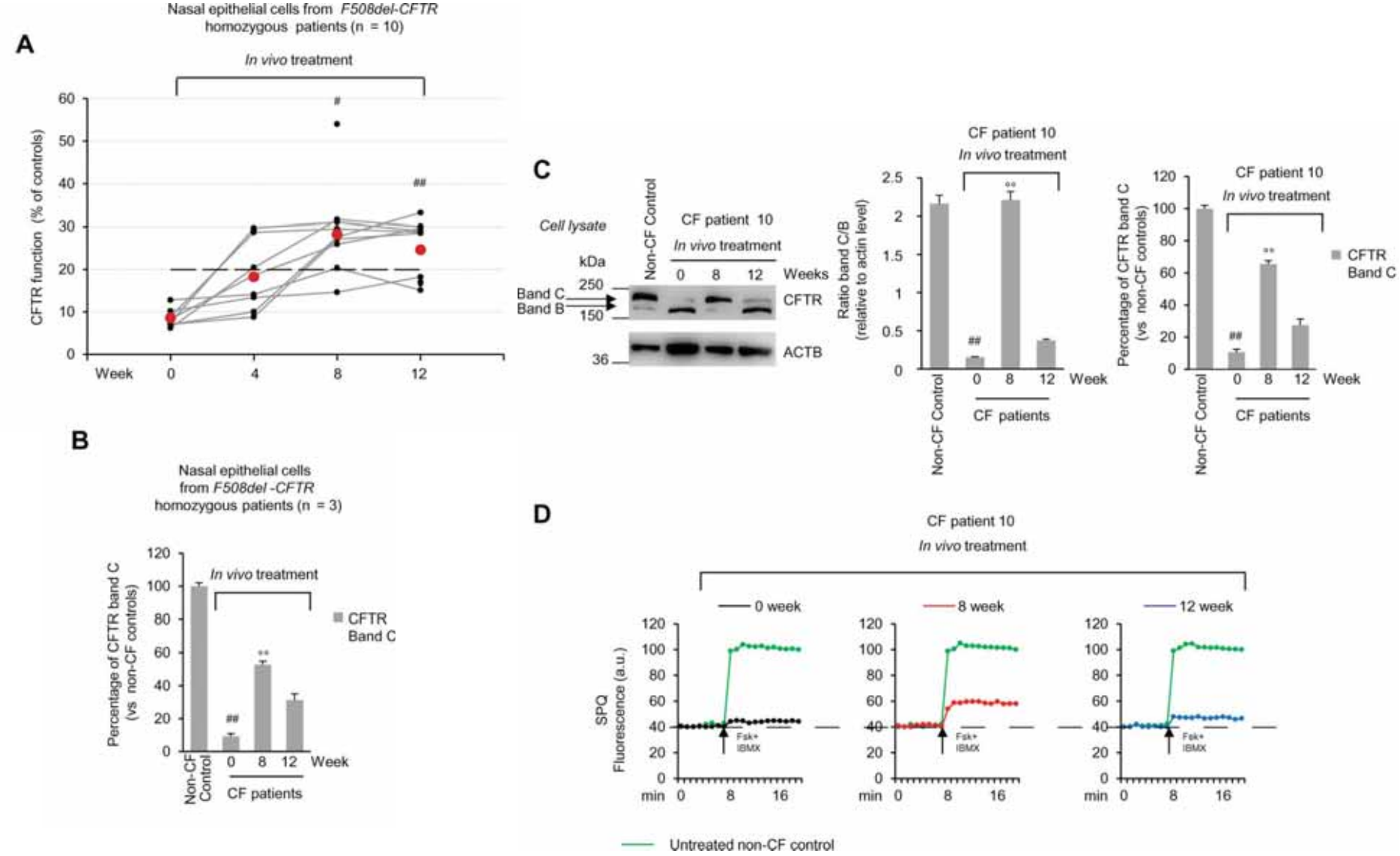

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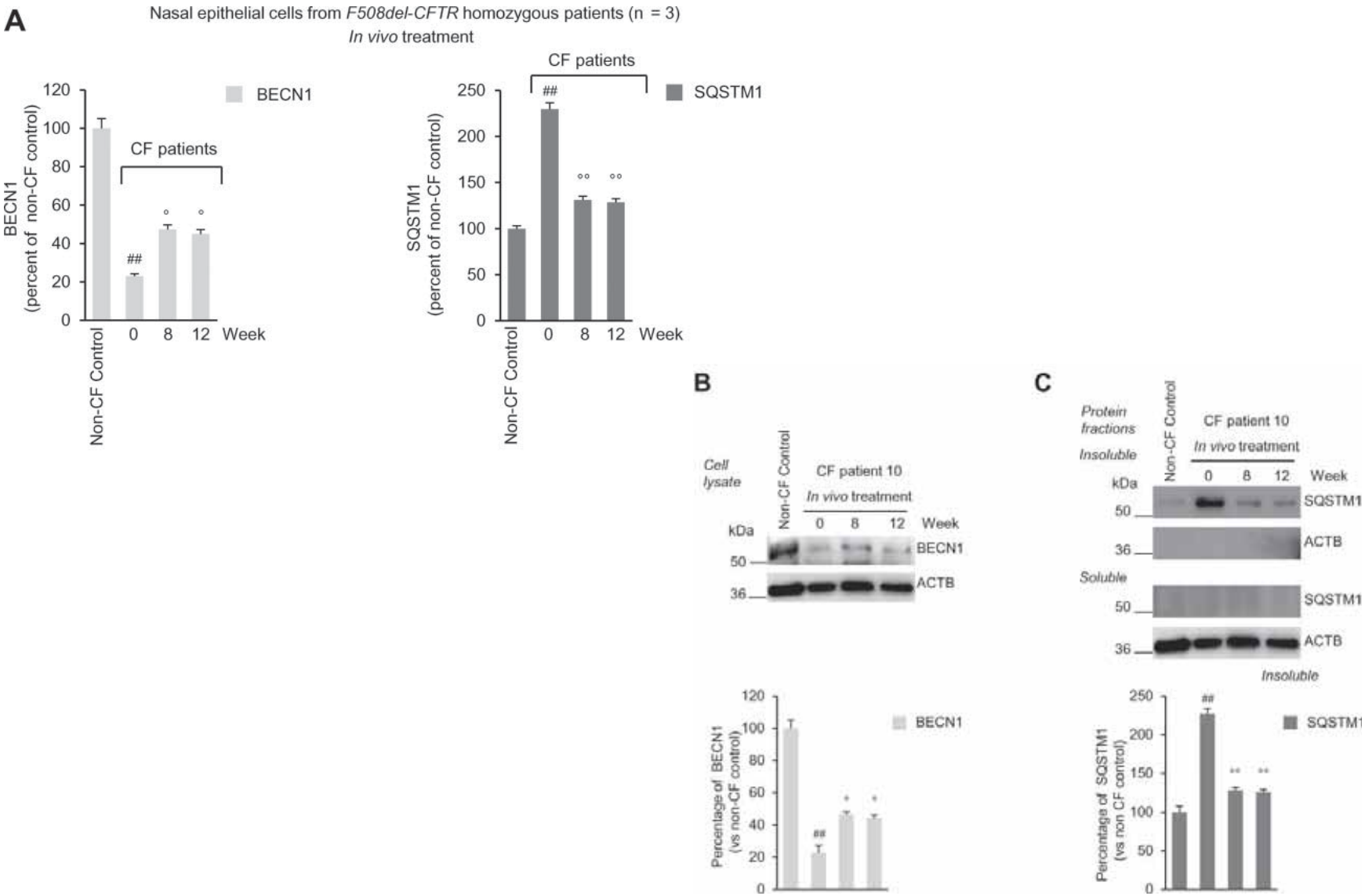
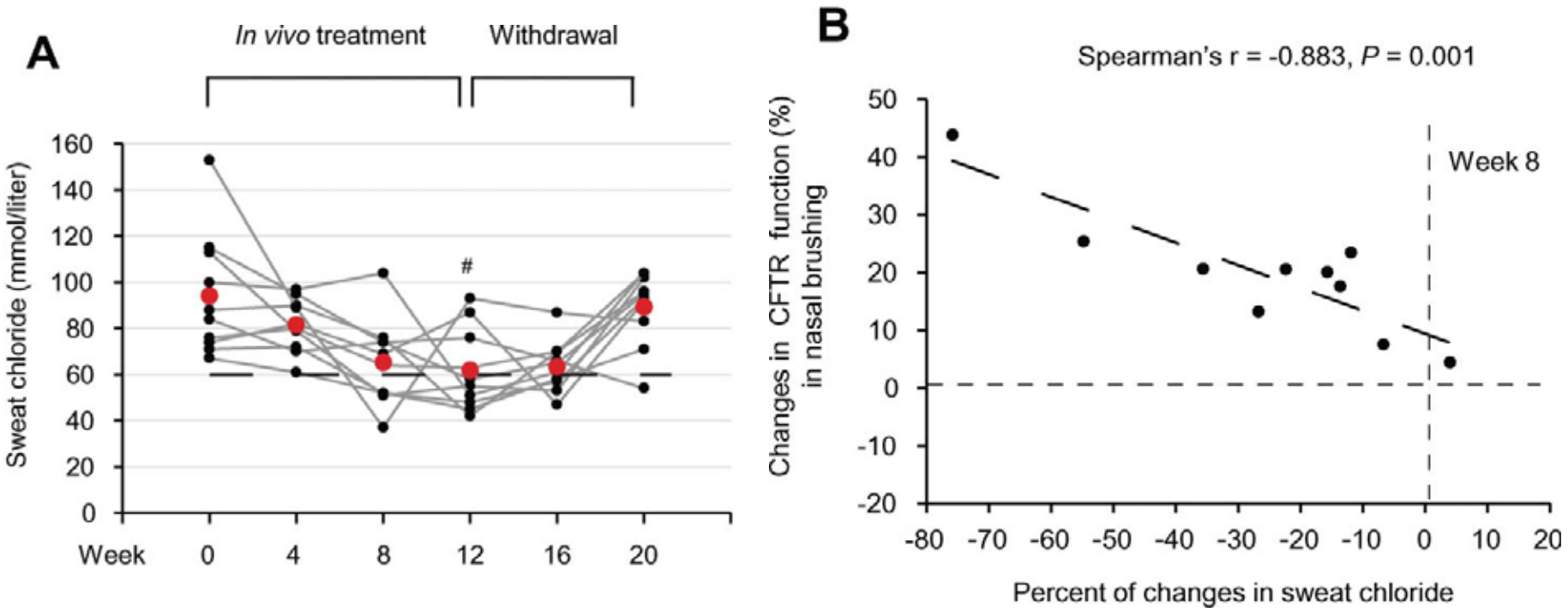
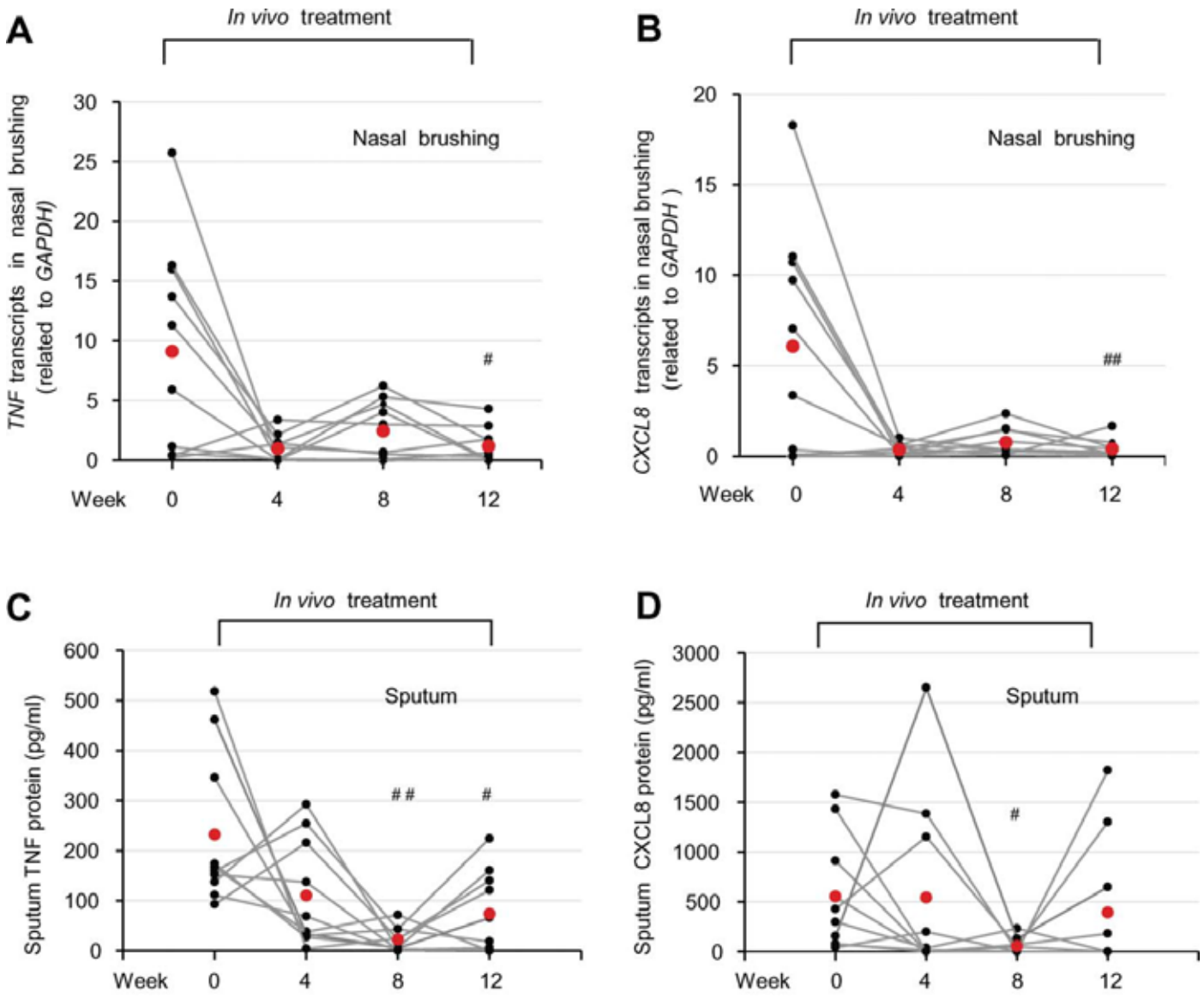


Effetti della cisteamina sul test del sudore



Effetti della cisteamina sui parametri infiammatori



una nuova strategia
NON
una nuova molecola

- Una *piccola* molecola (non obbligatoriamente anti-infiammatoria di per sè) che riduca l'infiammazione *attraverso* il recupero di funzione della CFTR.

- Una *piccola* molecola in grado di recuperare la funzione della CFTR (non obbligatoriamente un correttore) e *quindi (di conseguenza)* ridurre l'infiammazione.

FINANZIAMENTI

LIFC

TELETHON

FFC

AZIENDE

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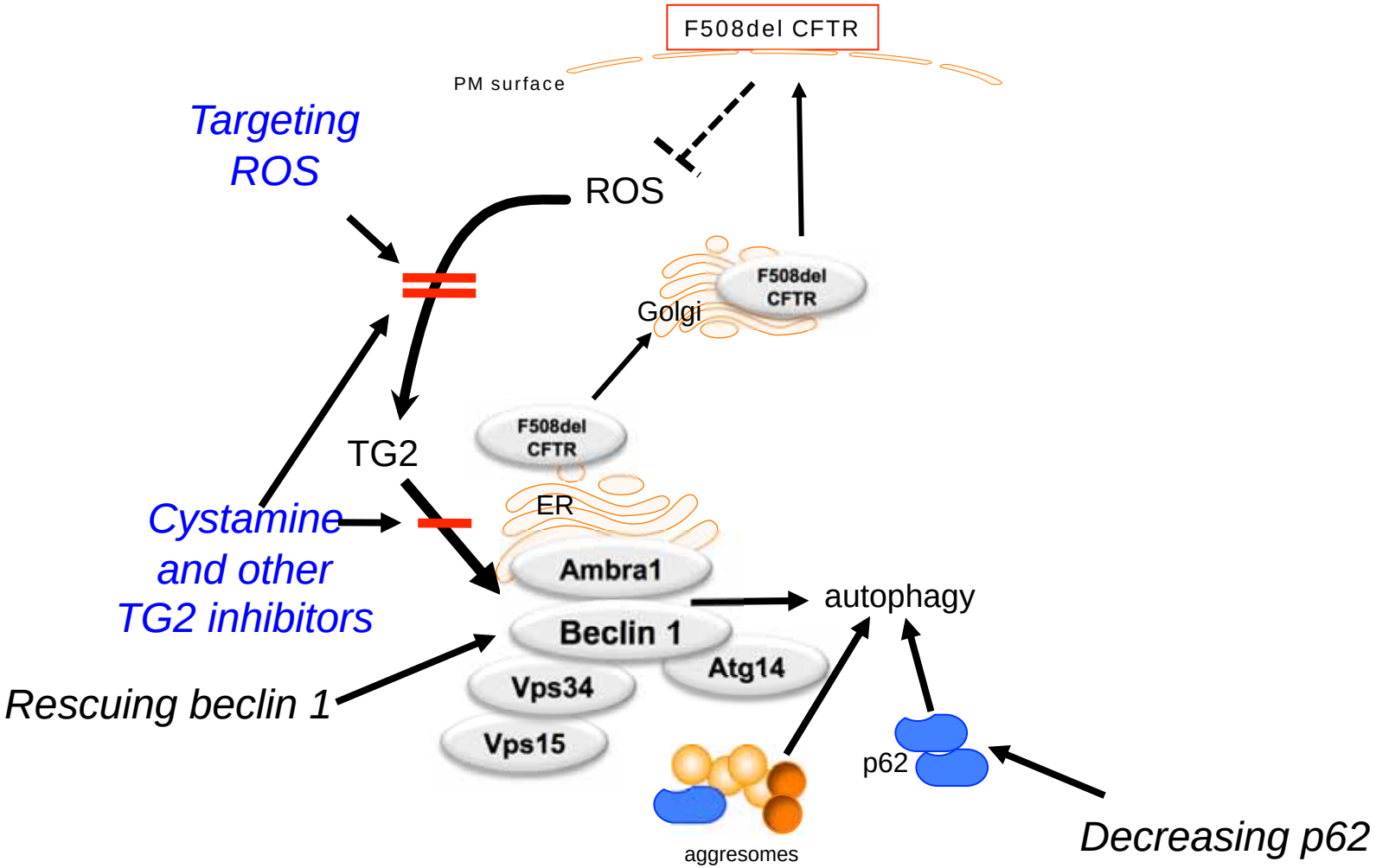
Dr.ssa Giovanna Pisi

Cystic Fibrosis: Proteostasis Regulators as a new therapeutic option



A. Luciani, Autophagy, 2011