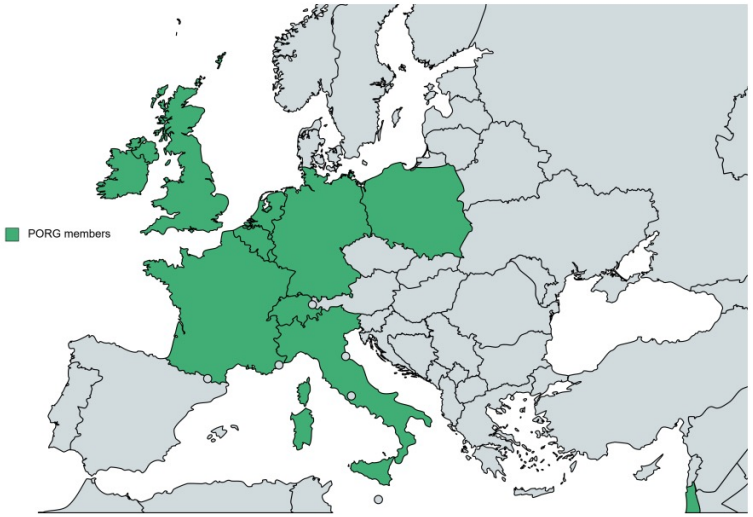
Lo stato della Ricerca per le mutazioni nonsense o rare: aggiornamenti dal Congresso Europeo FC

Giuseppe F. Parisi
Pediatra
UOC Broncopneumologia Pediatrica e Fibrosi Cistica
AOU Policlinico – San Marco – Catania
Direttore: Prof. S. Leonardi

Patient Organisations Research Group (PORG)



- L'obiettivo del PORG è quello di migliorare le partnership tra le organizzazioni europee associate, al fine di espandere la rete europea di ricerca sulla FC e accelerare l'accesso a nuovi farmaci per le persone con FC attraverso la ricerca.
- Il PORG conta attualmente 11 membri, tra cui Belgio, Francia, Germania, Irlanda, Israele, Italia, Lussemburgo, Paesi Bassi, Polonia, Svizzera e Regno Unito.

Patient Organisations Research Group (PORG)

- Priorità di ricerca secondo i pazienti
- Collaborazione con ECFS Patient Registry
- Collaborazione con ECFS Clinical Trials Network
- Organizzazione dell'European CF Young Investigators Meeting (EYIM)
- Organizzazione dell'incontro pre-conferenza prima della ECFS Basic
- Science Conference
- Supporto finanziario (insieme a ECFS) di ricercatori postdoc

LIFC
Lega Italiana
Fibrosi Cistica

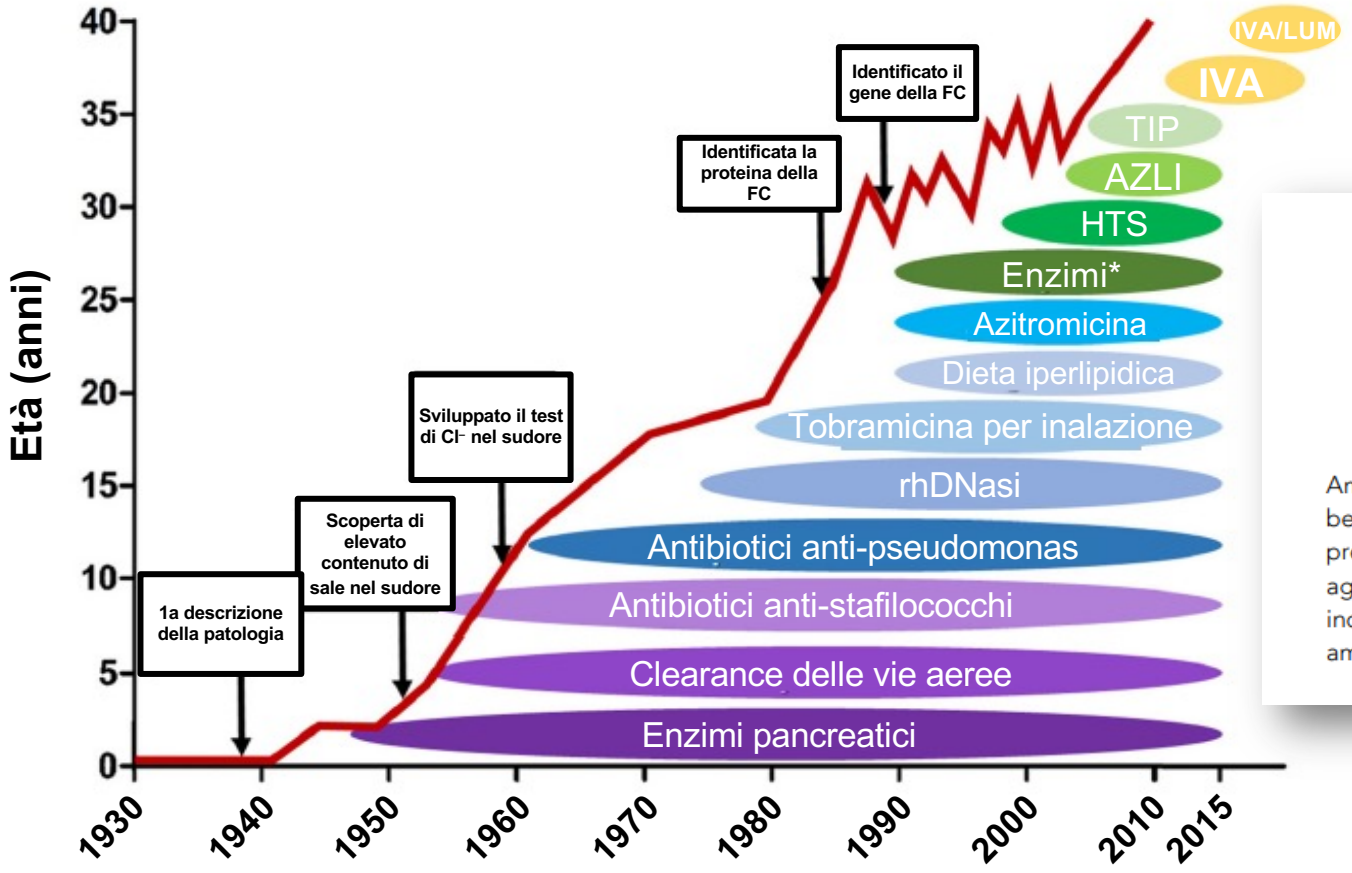
forum 2023

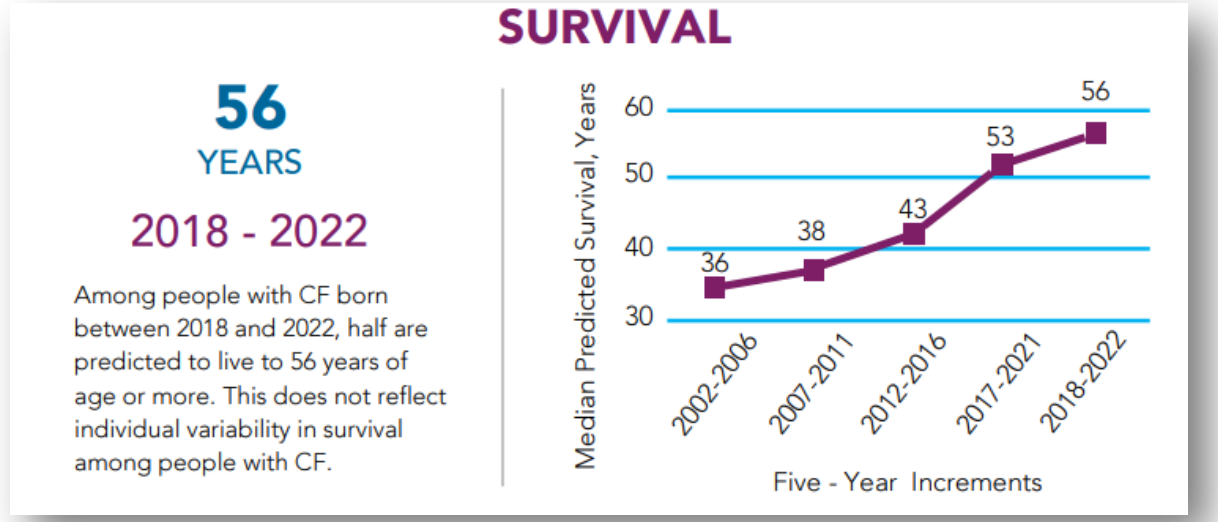
ecfs

7 – 10 JUNE 2023
VIENNA, AUSTRIA

Progressione della FC

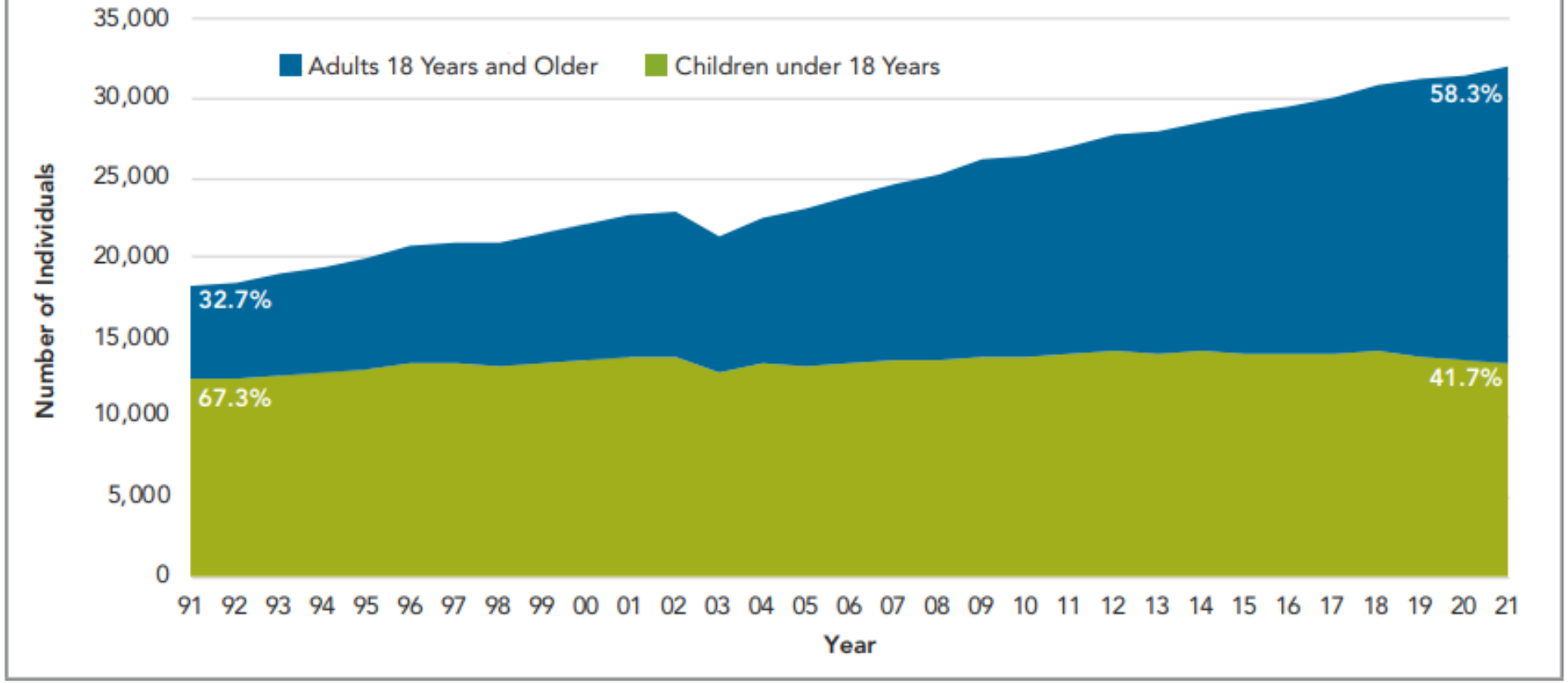
Effetto delle terapie sull'aspettativa di vita dei pazienti con FC





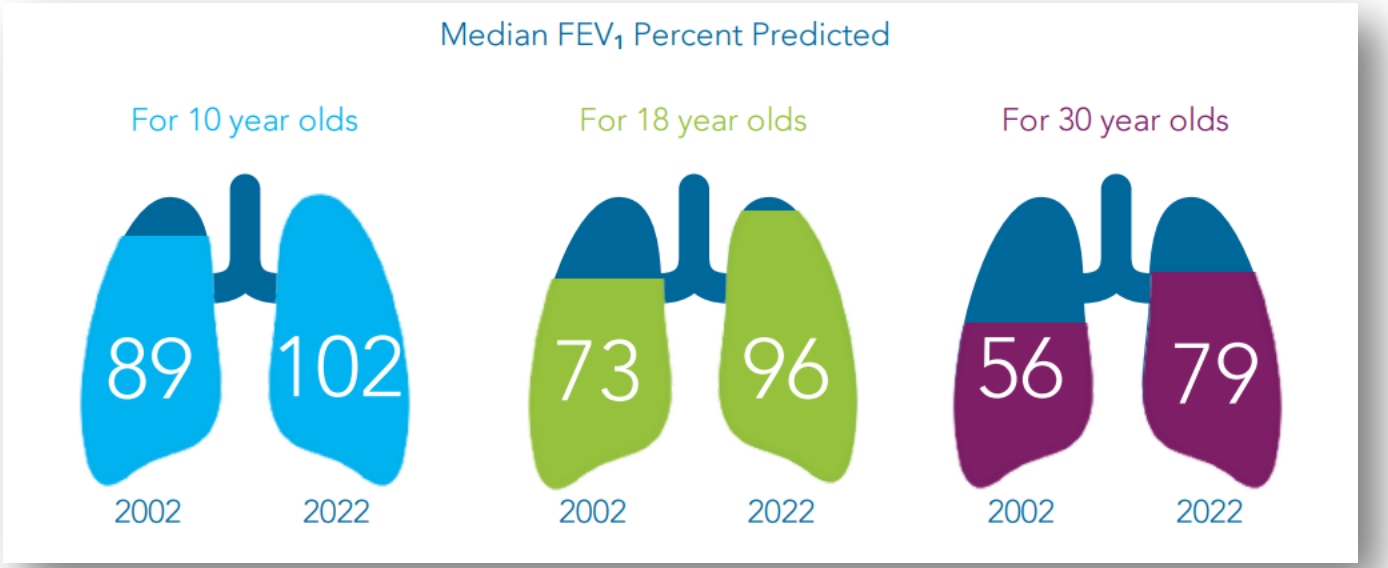
AZLI, aztreonam; HTS, screening ad alta capacità; IVA, ivacaftor; LUM, lumacaftor; rhDNAsi, desossiribonucleasi umana ricombinante; TIP, tobramicina. Riprodotto e adattato col permesso di European Respiratory Society©: *The European Lung White Book Respiratory Health and Disease in Europe*, 2nd Ed. © 2013 European Respiratory Society, Sheffield, UK. Lopes-Pacheco M. *Front Pharmacol.* 2016;7:275.

Number of Children and Adults with CF, 1991–2021



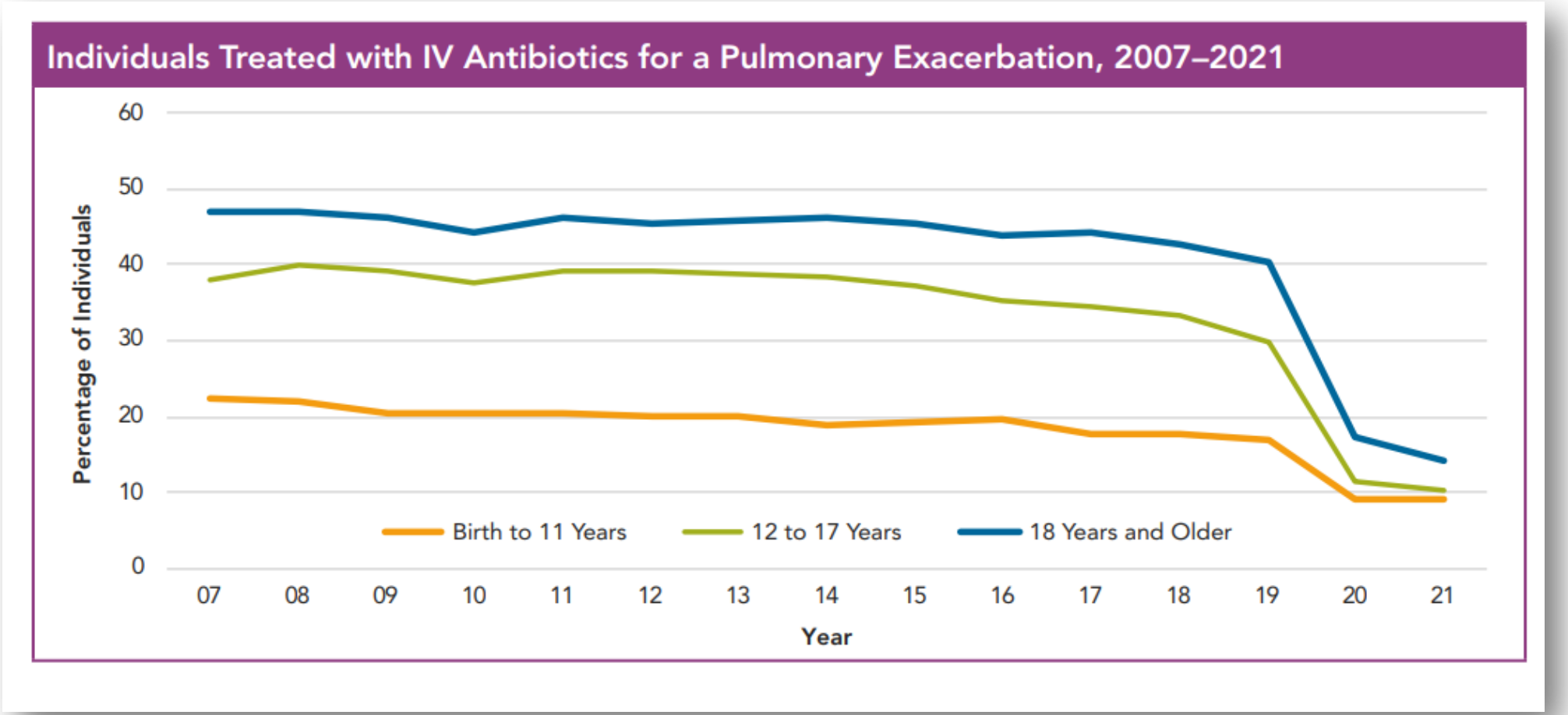
The decrease in the number of individuals reported in 2003 is due to a delay in obtaining informed consent forms before the close of the calendar year at some CF care centers.

Patient Registry. Cystic Fibrosis Foundation 2022



Bacteria	2018 Percent With Infection	2022 Percent With Infection
Pseudomonas aeruginosa	44%	26%
Stenotrophomonas maltophilia	12%	5%
Methicilin-resistant Staphylococcus aureus	25%	16%
Achromobacter xylosoxidans	6%	2%
Burkholderia cepacia complex	3%	1%
Nontuberculous mycobacteria	14%	10%

Patient Registry. Cystic Fibrosis Foundation 2022



Patient Registry. Cystic Fibrosis Foundation 2022

NUTRITION

Proper nutrition is associated with better lung function. CFTR modulator use is associated with weight gain. This has resulted in a healthy weight for most people, but 13% are now considered obese as defined by a BMI greater than 30.

ADULTS MEETING BMI GOALS

65%

Over age 20, the BMI (Body Mass Index) goal is 23 for men and 22 for women.

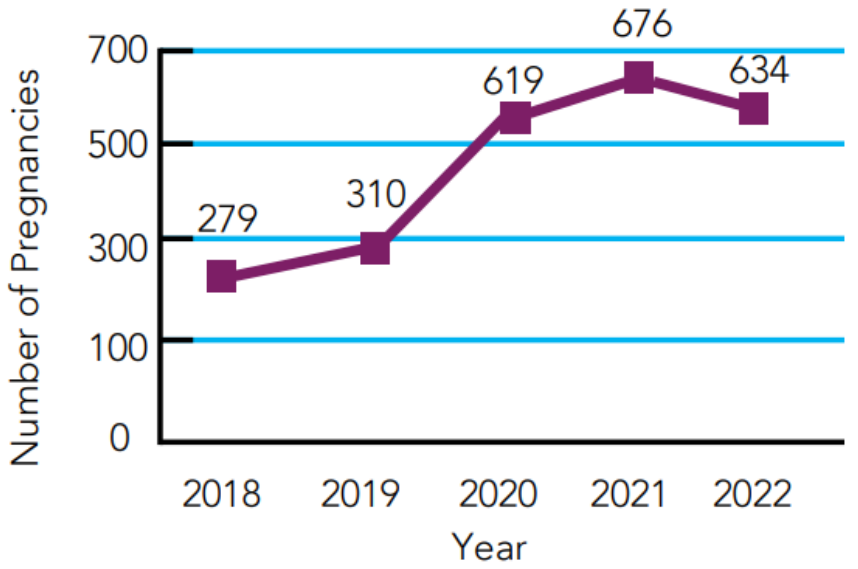
MEDIAN BMI PERCENTILE FOR 2-19 YEAR OLDS

61

The BMI percentile goal is 50 or greater for children and adolescents.

PREGNANCIES

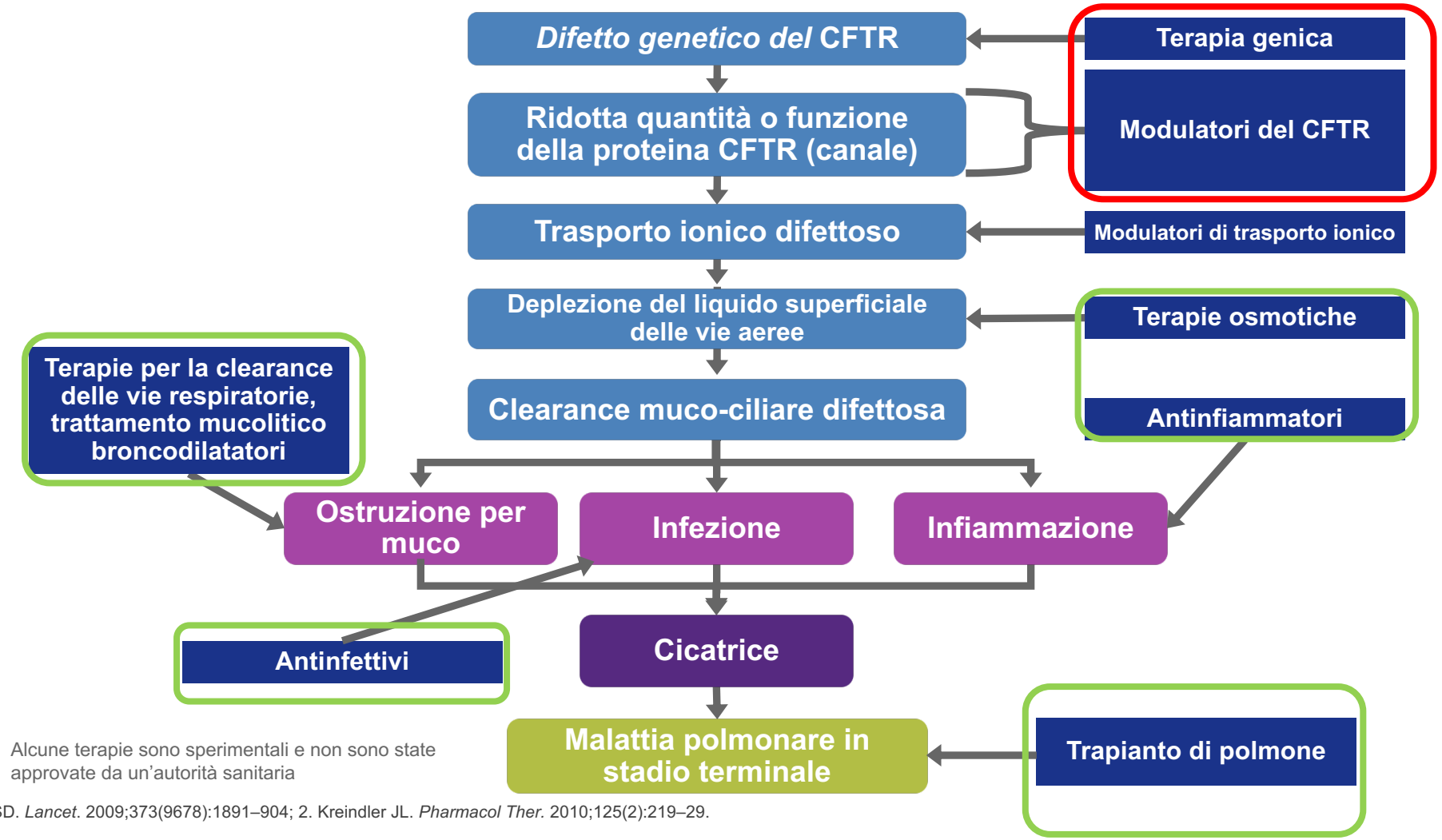
The number of pregnancies remained relatively stable in 2022 as compared to 2020 and 2021. The total number of pregnancies reported among women with CF remained relatively constant between 2000 - 2019, with a marked increase starting in 2020.



Patient Registry. Cystic Fibrosis Foundation 2022

Le terapie che mirano ai difetti sottostanti sono potenzialmente in grado di ritardare o prevenire i sintomi[1,2]

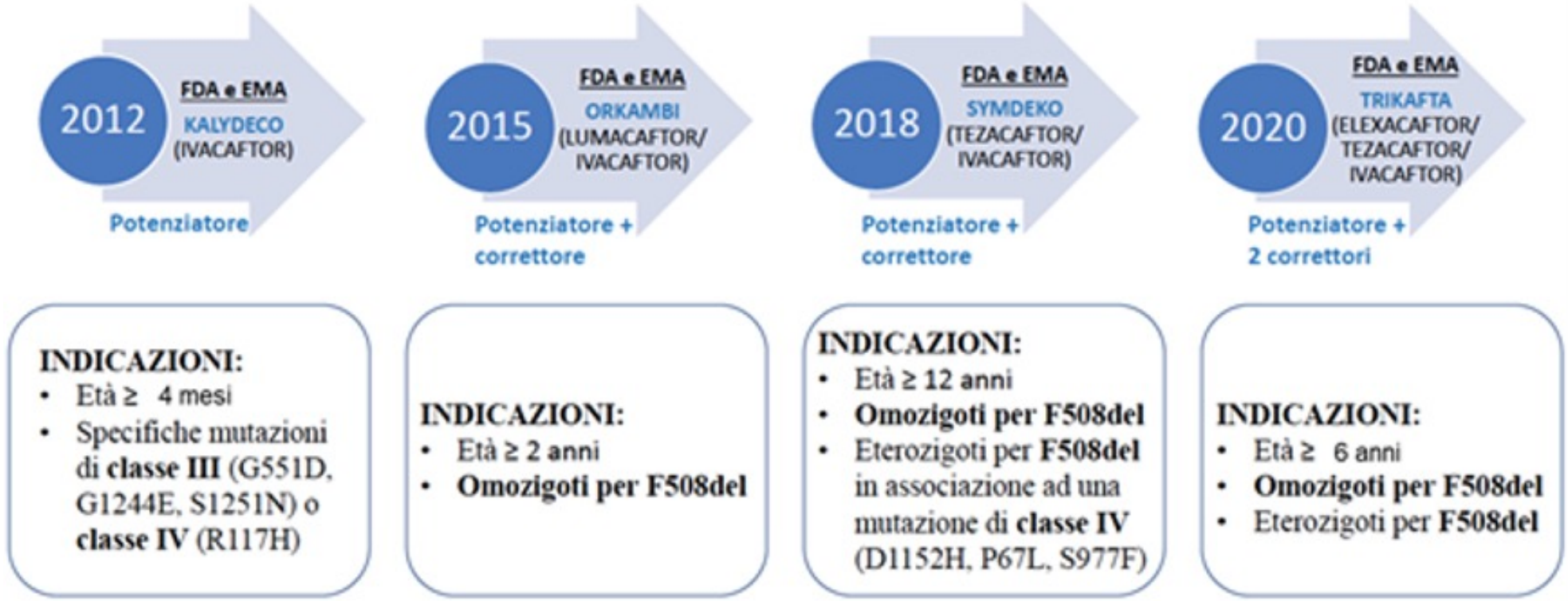
Cascata patofisiologica della malattia polmonare nella FC[1,2]



Alcune terapie sono sperimentali e non sono state approvate da un'autorità sanitaria

1. O'Sullivan BP & Freedman SD. *Lancet*. 2009;373(9678):1891–904; 2. Kreindler JL. *Pharmacol Ther.* 2010;125(2):219–29.

NUOVE TERAPIE VOLTE A MODULARE LA FUNZIONE/QUANTITÀ DELLA PROTEINA CFTR ALTERATA

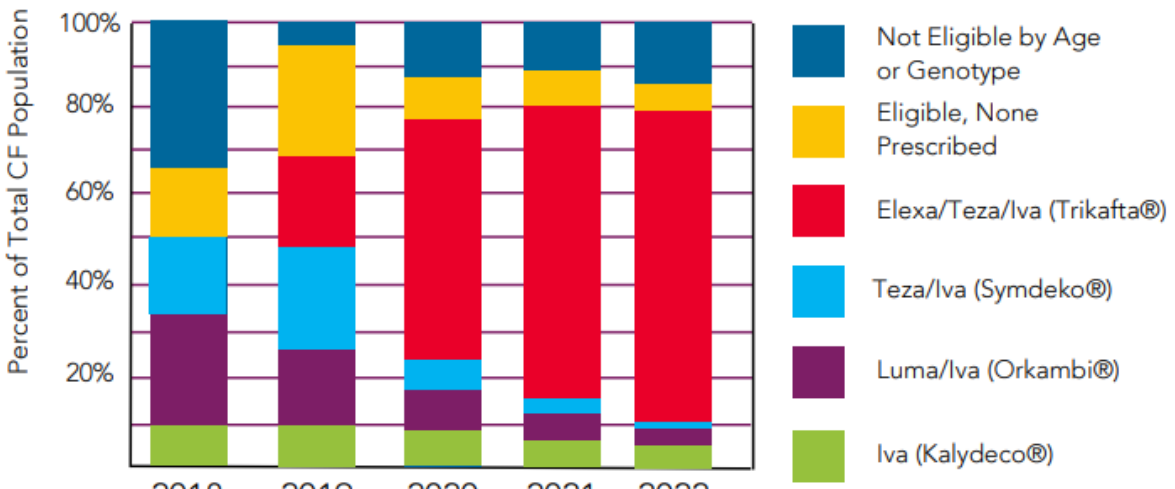


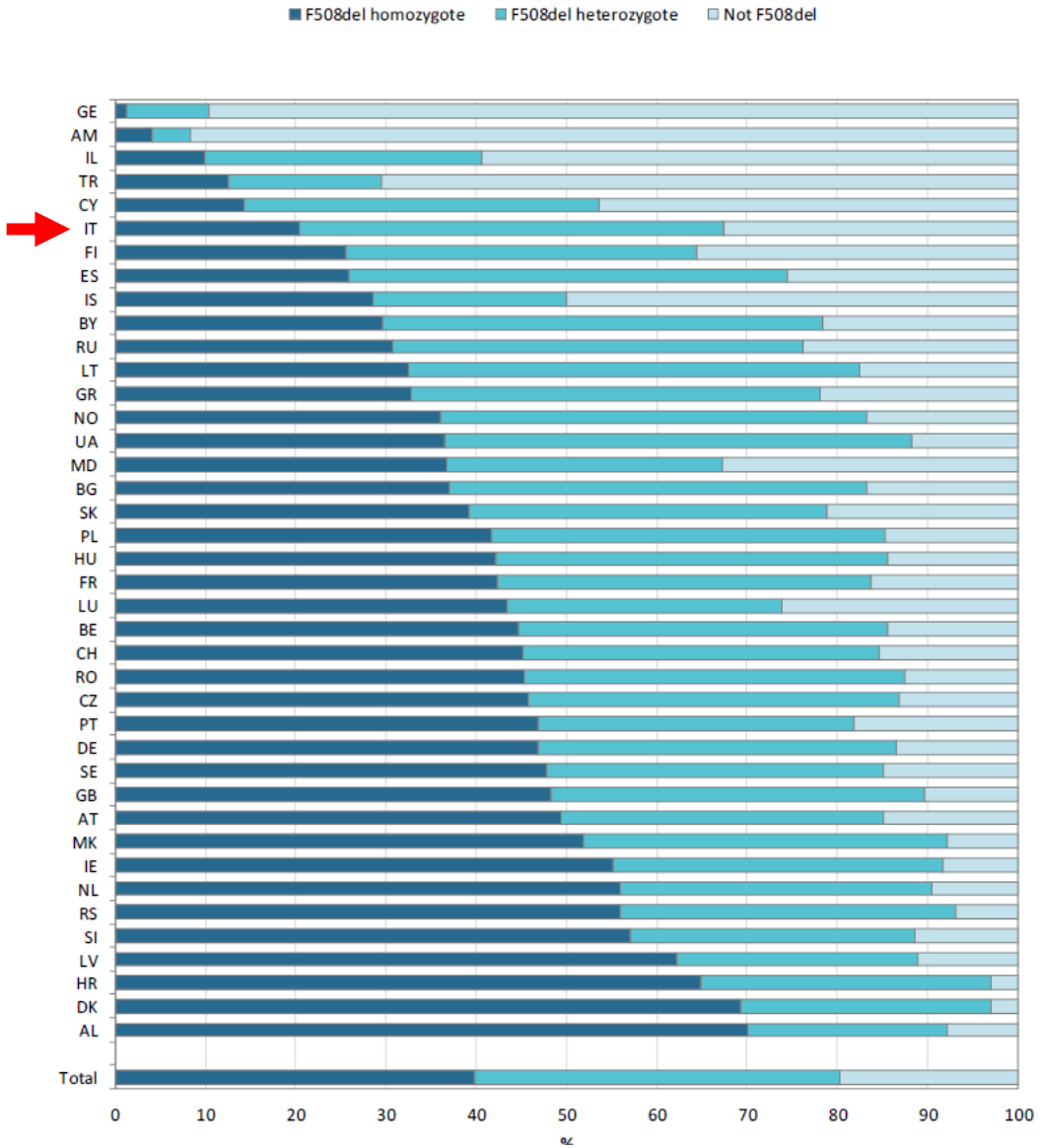
Sepe, Tosco e Raia. Pneumologia Pediatrica 2023

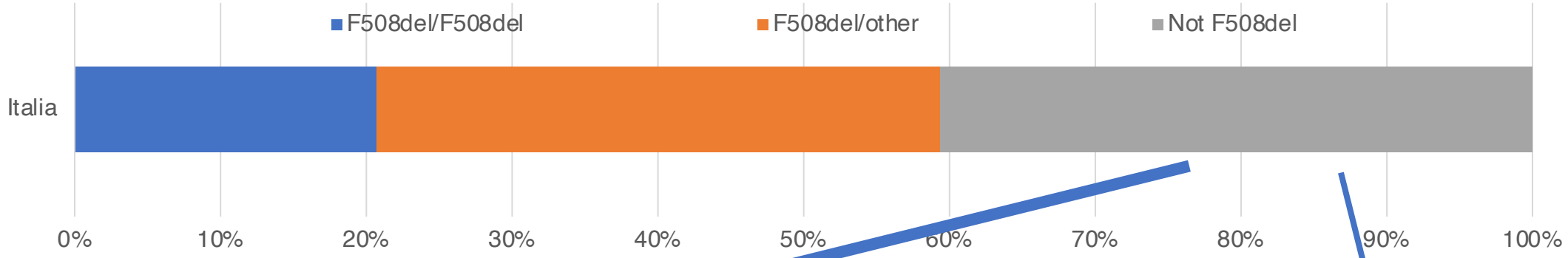
2022 CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY HIGHLIGHTS

CYSTIC FIBROSIS FOUNDATION®

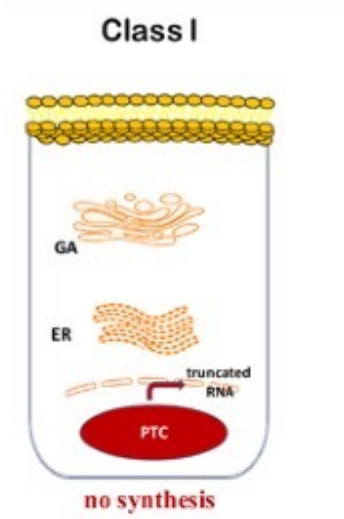
CFTR MODULATOR BY YEAR







Mutazioni non-sense (stop, classe I):
Arresto prematuro della produzione di CFTR



MUTAZIONE TIPO "STOP"	2020	
	n.	%
G542X	518	8,9
W1282X	212	3,7
R553X	130	2,2
R1162X	125	2,2
E585X	53	0,9
R1158X	52	0,9
E831X	23	0,4
S1455X	21	0,4
Q1476X	12	0,2
L732X	10	0,2
R709X	9	0,2
Y849X	9	0,2
R785X	9	0,2
Q220X	8	0,1

NOTA: Omozigosi (mutazione stop/mutazione stop): 62

Tabella 9. Numero di pazienti portatori di almeno una delle mutazioni "non senso" (*stop codon*) (n. 1.191; 20,6%) con frequenza allelica ≥0,1% (n. 5.799). Anno 2020.
Table 9. Number of patients with at least one "non-sense" mutation (stop codon) (No. 1,191; 20.6%) with allelic frequency ≥0.1% (No. 5,799). Year 2020.

Delezioni, duplicazioni, frameshift, missense, splicing, unknown

GENOTIPO	2020	
	n.	%
F508del / Altro*	2.247	38,7
Altri genotipi	351	6,1
F508del / F508del	1.202	20,7
F508del / Funzione residua	491	8,5
Funzione residua/Altro*	456	7,9
Funzione residua/Funzione residua	48	0,8
F508del / Funzione Minima	1.546	26,7
Funzione Minima/ Funzione Minima	696	12,0
Funzione Minima / Altro**	2.415	41,6
Funzione Residua / Altro**	947	16,3
F508del / Gating	105	1,8
Gating / Altro**	191	3,3
F508del / Unknown	59	1,0

*Include tutte le mutazioni non F508del e non funzione residua
**Incluse tutte le altre mutazioni non F508del, non funzione residua, non funzione minima

Tabella 8. Prevalenza dei pazienti con mutazione F508del e funzione residua in omozigosi ed eterozigosi composta (n. 5.489). Anno 2020.
Table 8. Prevalence of homozygous and compound heterozygous patients F508del carriers and residual function carriers (No. 5,489). Year 2020.

Registro Italiano 2019-2020

THERATYPING

Sperimentazione, a livello cellulare, di farmaci già in uso clinico per la FC, su genotipi non precedentemente valutati e per i quali non erano progettati.

ORIGINAL ARTICLE
CYSTIC FIBROSIS AND BASIC SCIENCE

Correction of CFTR function in intestinal organoids to guide treatment of cystic fibrosis

Anabela S. Ramalho[1], Eva Fürstová[2], Annelotte M. Vonk[3,4], Marc Ferrante[5,6], Catherine Verfaillie[7], Lieven Dupont[8,9], Mieke Boon[1,10], Marijke Proesmans[1,10], Jeffrey M. Beekman[3,4], Ifat Sarouk[11], Carlos Vazquez Cordero[12], Francois Vermeulen[1,10] and Kris De Boeck[1,10] on behalf of the Belgian Organoid Project[13]

children

MDPI

Review

Organoid Technology and Its Role for Theratyping Applications in Cystic Fibrosis

Jessica Conti [1], Claudio Sorio [1,*] and Paola Melotti [2,*]

[1] Department of Medicine, Division of General Pathology, University of Verona, 37134 Verona, Italy
[2] Cystic Fibrosis Centre, Azienda Ospedaliera Universitaria Integrata Verona, 37126 Verona, Italy
* Correspondence: claudio.sorio@univr.it (C.S.); paola.melotti@aovr.veneto.it (P.M.)

J Physiol. 2022 Mar;600(6):1285-1286. doi: 10.1113/JP282586. Epub 2022 Jan 31.

Nasal epithelial cells as a gold-standard predictive model for personalized medicine in cystic fibrosis

Nicoletta Pedemonte [1]

Affiliations + expand

PMID: 35038767 DOI: 10.1113/JP282586

Free article

FDA Approves Expansion of Modulators for People With Certain Rare Mutations

The U.S. Food and Drug Administration (FDA) today expanded its approval of three CFTR modulators to include additional people with CF who have certain rare mutations. The approval enables more than 600 individuals with CF who were not previously eligible for modulators to access drugs that treat the underlying cause of their disease for the first time.

Dec. 21, 2020 | 3 min read

Table 6: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO

546insCTA	*E92K*	*G576A*	*L346P*	*R117G*	*S589N*
711+3A→G *	*E116K*	*G576A;R668C*†	*L967S*	*R117H*	*S737F*
2789+5G→A *	*E193K*	*G622D*	*L997F*	*R117L*	*S912L*
3272-26A→G *	*E403D*	*G970D*	*L1324P*	*R117P*	*S945L* *
3849+10kbC→T *	*E588V*	*G1069R*	*L1335P*	*R170H*	*S977F* *
A120T	*E822K*	*G1244E*	*L1480P*	*R258G*	*S1159F*
A234D	*E831X*	*G1249R*	*M152V*	*R334L*	*S1159P*
A349V	*F191V*	*G1349D*	*M265R*	*R334Q*	*S1251N*
A455E *	*F311del*	*H939R*	*M952I*	*R347H* *	*S1255P*
A554E	*F311L*	*H1054D*	*M952T*	*R347L*	*T338I*
A1006E	*F508C*	*H1375P*	*P5L*	*R347P*	*T1036N*
A1067T	*F508C;S1251N*†	*I148T*	*P67L* *	*R352Q* *	*T1053I*
D110E	*F508del* ^	*I175V*	*P205S*	*R352W*	*V201M*
D110H *	*F575Y*	*I336K*	*Q98R*	*R553Q*	*V232D*
D192G	*F1016S*	*I601F*	*Q237E*	*R668C*	*V562I*
D443Y	*F1052V*	*I618T*	*Q237H*	*R751L*	*V754M*
D443Y;G576A;R668C †	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153E*
D579G *	*F1099L*	*I980K*	*Q1291R*	*R933G*	*V1240G*
D614G	*G126D*	*I1027T*	*R31L*	*R1066H*	*V1293G*
D836Y	*G178E*	*I1139V*	*R74Q*	*R1070Q*	*W1282R*
D924N	*G178R*	*I1269N*	*R74W*	*R1070W* *	*Y109N*
D979V	*G194R*	*I1366N*	*R74W;D1270N*†	*R1162L*	*Y161S*
D1152H *	*G194V*	*K1060T*	*R74W;V201M*†	*R1283M*	*Y1014C*
D1270N	*G314E*	*L15P*	*R74W;V201M;D1270N*†	*R1283S*	*Y1032C*
E56K	*G551D*	*L206W* *	*R75Q*	*S549N*	
E60K	*G551S*	*L320V*	*R117C* *	*S549R*	

* Clinical data for these mutations in Clinical Studies *[see Clinical Studies (14.1 and 14.2)]*.
^ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 6 to be indicated.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Table 5: List of *CFTR* Gene Mutations that are Responsive to TRIKAFTA

3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N*†	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del* *	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C†	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N*†	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M*†	*S364P*	*Y161S*
E116K	*G576A;R668C*†	*L165S*	*R74W;V201M;D1270N*†	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data *[see Clinical Studies (14)]*.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

The FDA decision expands the labels for **Trikafta®** (elexacaftor/tezacaftor/ivacaftor), Symdeko® (tezacaftor/ivacaftor), and Kalydeco® (ivacaftor) to include additional rare mutations that were previously not approved for CFTR modulators. Trikafta is now approved for individuals who are 12 years and older with at least one of 177 newly-approved mutations; Symdeko is now approved for individuals who are 6 years and older with one of 127 additional mutations; and Kalydeco is now approved for individuals who are 4 months and older with one of 59 additional mutations.

The French Compassionate Program of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del *CFTR* variant

Pierre-Régis Burgel, Isabelle Sermet-Gaudelus, Isabelle Durieu, Reem Kanaan, Julie Macey, Dominique Grenet, Michele Porzio, Nathalie Coolen-Allou, Raphael Chiron, Christophe Marguet, Benoit Douvry, Nadine Dufeu, Isabelle Danner-Boucher, Pierre Foucaud, Lydie Lemonnier, Emmanuelle Girodon, Jennifer Da Silva, Clémence Martin, on Behalf of the French CF Reference Network study group

Results:

- Tra gli 84 pazienti con FC arruolati, ETI era efficace in 45 di essi.
- Tra i responders, 22/45 (49%) erano portatori di mutazioni non approvate dalla FDA.

Metodi:

- Studio osservazionale sugli effetti di ETI su una popolazione di pazienti FC con patologia polmonare avanzata (FEV1<40%), non eleggibili a ETI.
- Efficacia valutata da una commissione a 4-6 settimane in termini di manifestazioni cliniche, cloro sudorale, FEV1%.

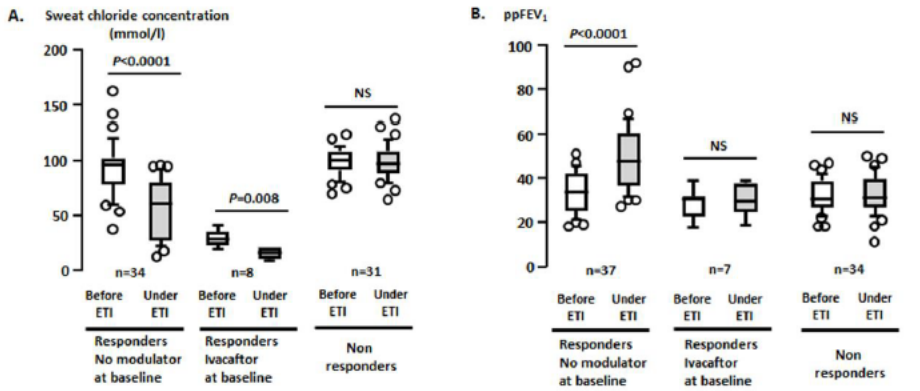


Figure 1. Comparison of sweat chloride concentration and ppFEV1 before ETI and under ETI according to responder status and ivacaftor at baseline. A. Sweat chloride concentration B. ppFEV1. Box plots: median [IQR] (error bars, 10-90 percentile) with outliers. Data were analyzed using the nonparametric Wilcoxon's test.

Eur Respir J 2023

PUBLIÉ LE 19/05/2022 - MIS À JOUR LE 01/06/2023

Mucoviscidose : de nouveaux patients vont pouvoir bénéficier de l'association des comprimés pelliculés Kaftrio et Kalydeco

A+ A-

Actualisation du 1er juin 2023

Depuis le 1er juin 2023, le cadre de prescription compassionnelle (CPC) associant les médicaments Kaftrio et Kalydeco s'étend aux patients atteints de mucoviscidose non porteurs d'une mutation F508del, dès l'âge de 6 ans et quel que soit le degré de sévérité de la maladie. Le traitement n'est pas indiqué chez les patients qui présentent 2 gènes mutés prédictifs de l'absence de synthèse de la protéine CFTR.
L'élargissement du CPC prend en compte l'évolution des connaissances scientifiques.

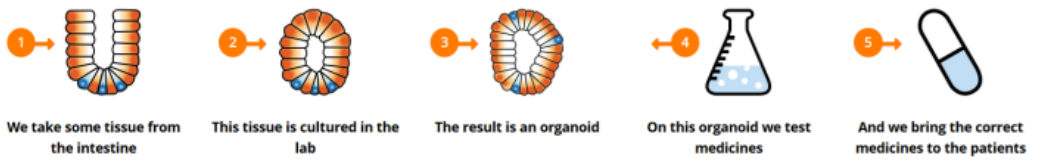
Il est toujours recommandé que la prescription du traitement soit soumise à l'avis du centre coordinateur du centre de référence maladie rare (CRMR) mucoviscidose et affections liées à une anomalie de CFTR, selon la pratique clinique actuelle, et que les patients traités dans le cadre de ce CPC soient inscrits dans le registre français de la mucoviscidose.

Accédez au protocole d'utilisation thérapeutique et de suivi des patients (PUT-SP), qui détaille les modalités d'emploi de Kaftrio 75 mg/50 mg/100 mg comprimé pelliculé, Kaftrio 37,5 mg/25 mg/50 mg comprimé pelliculé, associés respectivement à Kalydeco 150 mg comprimé pelliculé et Kalydeco 75 mg comprimé pelliculé dans les conditions de ce CPC.

Newsletter HIT-CF Europe

September 2018

HIT-CF Europe aims to evaluate the efficacy and safety of three drug candidates in patients with CF and rare mutations, pre-selected by their mini-intestines in the laboratory.



We take some tissue from the intestine | This tissue is cultured in the lab | The result is an organoid | On this organoid we test medicines | And we bring the correct medicines to the patients

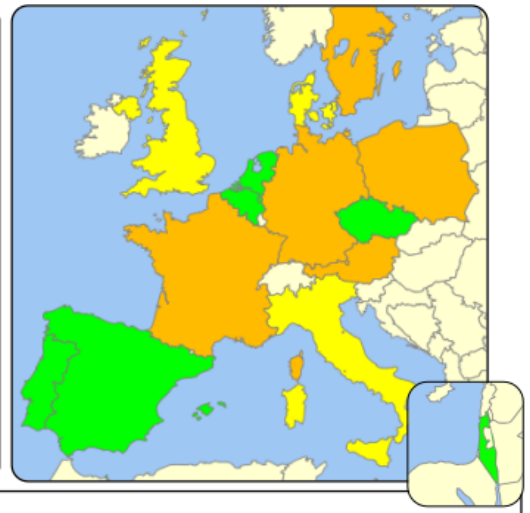
Organoid screening study

The first part of the HIT-CF project aims at enrolling 500 people with CF with two rare CFTR-mutations from across Europe. A biopsy from these people will be taken and organoids will be generated.
In each European participating country separately, approval has to be obtained from the local Ethical Committee before the biopsy can be taken.

This month, recruiting will start in several countries!

- We have received approval for the study in: Czech Republic, Portugal, Spain, Belgium, Israel and the Netherlands!
- In the following countries we hope to get approval very soon: Poland, Sweden, Germany, France and Austria
- The other countries that are initializing the study are the following: United Kingdom, Italy and Denmark

More detailed information on the countries and hospitals that are participating can be found on www.hitcf.org



Testing organoids in different laboratories

All biopsies will be sent to HUB located in Utrecht, the Netherlands. HUB will generate organoids from biopsies and send the organoids to the organoid screening laboratories of University Medical Centre Utrecht, KU Leuven and Lisbon University.

Utrecht, Leuven, Lisbon and HUB have been working hard on preparing for the organoid screening phase, and we are confident we can start screening the first organoids in the months to come.

Do you want to participate, or do you want more info about the HIT-CF project?
Visit the website of HIT-CF or send an e-mail to HITCF@umcutrecht.nl

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 755021

Newsletter HIT-CF Europe

August 2023

The HIT-CF Europe project aims to provide new treatment options to people with cystic fibrosis (CF) and ultra-rare genetic profiles. The project will evaluate the efficacy and safety of drug candidates provided by collaborating pharmaceutical companies in patients selected through preliminary tests in the laboratory on their mini-intestines – also called organoids.

Ultra-rare mutations | Rectal biopsy | Intestinal organoids | Drug testing/ selecting responders | Clinical trial

Long time no hear

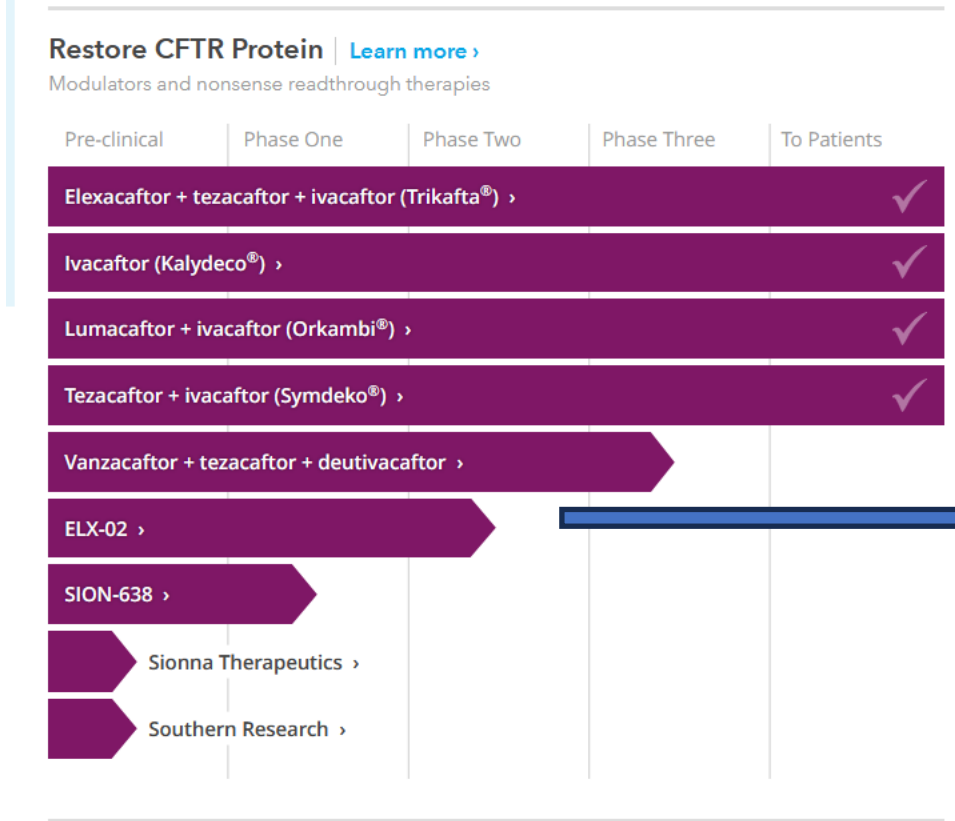
A long time has passed since the last HIT-CF newsletter. We were not able to communicate earlier as there have been a lot of uncertainties. A lot has happened behind the scenes though. Some crucial issues have been cleared out now and we want to share these perspectives with all of you.

Many delays

In our previous newsletter, we informed you about the many delays the project faced. Due to the Covid-19 pandemic, many developments were temporary delayed or stopped. Some of the collaborating pharmaceutical partners in the project had to put their drug pipeline on hold or even completely stop due to lack of investors. The promising CFTR modulating compounds developed by Proteostasis Therapeutics were in danger of being lost, and a new company (Fair Therapeutics) had to be built to secure them. This new company also had to attract proper investments. Moreover, in November last year, the planned CHOICES trial was rejected by **CTIS** (Clinical Trials Information System – a procedure that is mandatory to get permission to run a trial in the European Union) because the necessary documentation on the compounds was not ready yet.

Better days ahead

But fortunately, the partners in the HIT-CF project kept searching for solutions in all possible directions. CF Europe, the European Cystic Fibrosis Society, the participating CF centres from all over Europe, and many of you, never lost faith. Indeed, we are very pleased to say that several generous investors were willing to support Fair Therapeutics, now guaranteeing that the CHOICES trial can be successfully performed. Currently we are still negotiating with the European Commission, the initial funder of the HIT-CF project. In fact, HIT-CF was supposed to officially end in December. We are very glad to see that the European Commission acknowledges the incredible value of the project. HIT-CF is a truly historic achievement as it creates new avenues of drug development for patients with ultra-rare diseases. The close collaboration of the patient community, caregivers, academia and regulators to develop drugs in an affordable way is unprecedented. We cordially hope that the Commission will soon grant an extension.
The HIT-CF team is now preparing everything to resubmit CHOICES into CTIS, and, if everything goes well, **CHOICES should start in early 2024**. This means that by the beginning of next year, the first of 52 selected HIT-CF participants



Eloxx Pharmaceuticals, Inc. annuncia la valutazione dei dati finali dello studio clinico di Fase 2 di combinazione di ELX-02 nei pazienti di Fibrosi Cistica (FC) di Classe 1

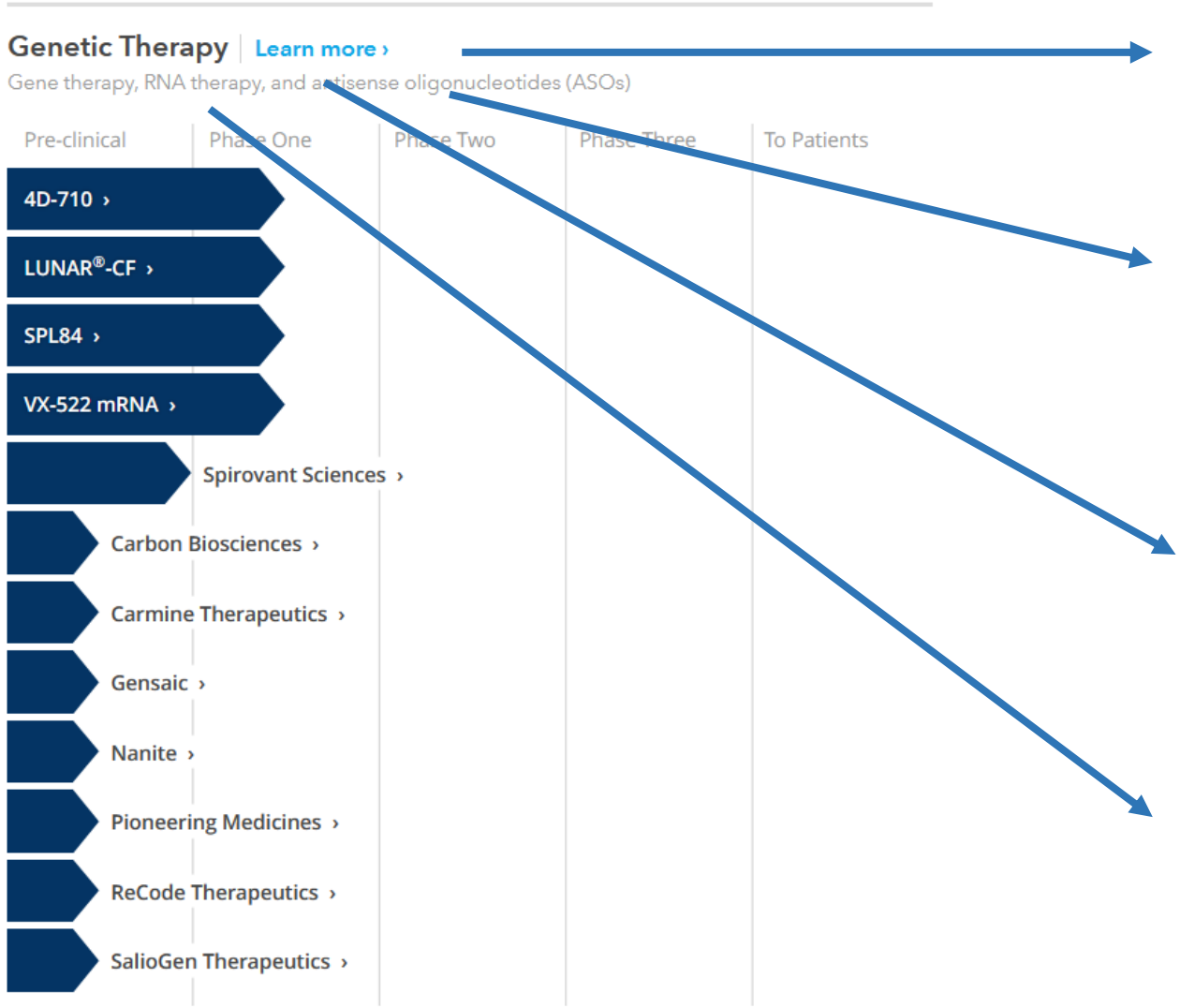
14 giugno 2023 alle 22:53

Condividi

Eloxx Pharmaceuticals, Inc. ha annunciato la valutazione finale dei dati dello studio clinico di Fase 2 di ELX-02 in combinazione con ivacaftor in pazienti FC di Classe 1 con almeno una mutazione nonsense. Nella valutazione finale, ELX-02 ha dimostrato un miglioramento clinicamente rilevante del ppFEV1. La valutazione finale dei dati include una rianalisi che utilizza la variazione di ppFEV1 dal Giorno 1 anziché dal basale, poiché diversi pazienti hanno avuto una progressione della malattia tra lo screening e il trattamento.

I risultati iniziali di questo studio sono stati comunicati nel settembre 2022.
Valutazione finale dello studio di combinazione di fase 2 di ELX-02 in pazienti con FC di classe 1: Lo studio clinico di combinazione di Fase 2 di ELX-02 è stato progettato per valutare la sicurezza e l'attività biologica in pazienti con FC di Classe 1 con mutazione nonsenso G542X, come monoterapia e in combinazione con ivacaftor dopo 5 settimane di trattamento. I risultati dell'analisi finale di 13 pazienti valutabili, rispetto agli 11 al momento della valutazione iniziale, sono riassunti di seguito: 6 dei 13 pazienti sono entrati nello studio dal braccio di monoterapia (dopo una media di 463 giorni) e hanno avuto una diminuzione della funzione polmonare (riduzione annualizzata del -4,26% del ppFEV1) a causa della progressione della malattia.

Il trattamento con ELX-02 ha stabilizzato la malattia nel complesso e ha determinato un aumento clinicamente rilevante del ppFEV1 in sei dei tredici pazienti, in base alla variazione del ppFEV1 alla fine del trattamento, al Giorno 35, rispetto all'inizio del trattamento, al Giorno 1. I dati topline precedenti hanno confermato l'attività biologica.



Terapia genica

fornisce all'organismo una copia corretta di un gene difettoso o un altro gene che possa compensarne il malfunzionamento

mRNA

fornisce alla cellula le informazioni corrette per sintetizzare la proteina CFTR normale

Editing genomico

manipolazione genetica in cui si procede alla delezione, all'inserimento, alla sostituzione o alla modifica del DNA genomico di un organismo vivente

Oligonucleotidi antisenso

piccoli pezzi di DNA o RNA che si legano alla molecola di RNA e correggono queste istruzioni in modo da poter produrre una proteina CFTR a lunghezza intera

CFF, Ottobre 2023

← Back to the Drug Development Pipeline

VX-522 mRNA

Email | Print

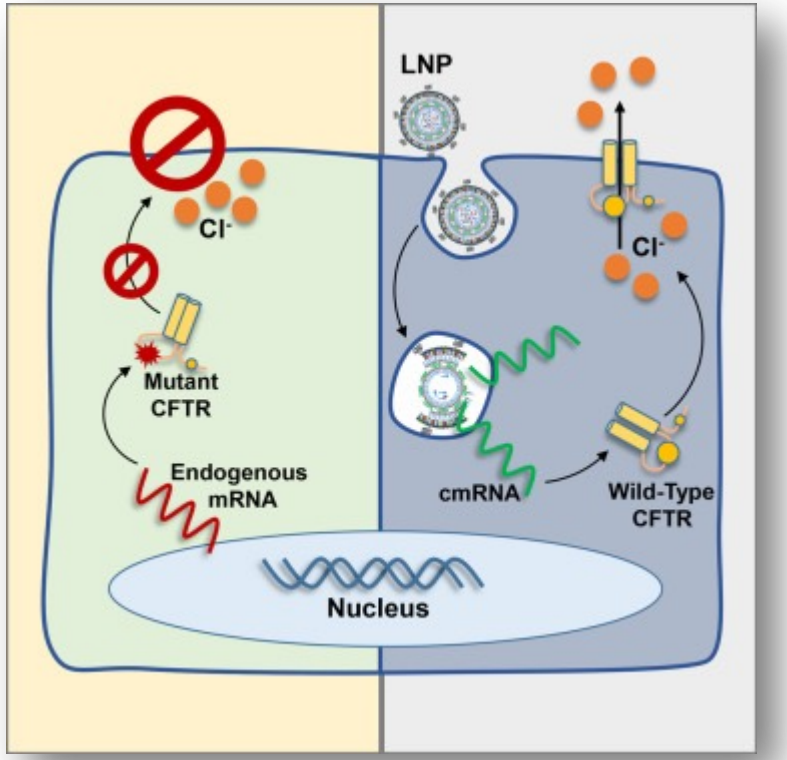
STATUS
Phase One

THERAPEUTIC APPROACH
Genetic Therapy

VX-522 is an inhaled messenger RNA (mRNA) therapy. It aims to deliver a full-length copy of CFTR mRNA to lung cells using a lipid nanoparticle. Lung cells would then use the instructions in the mRNA to create functional CFTR protein. This type of therapy could work for any person with CF, regardless of their CFTR mutations.

Status

A phase 1 study to test the safety and tolerability of VX-522 is underway. The study is for adults with CF who have CFTR mutations that are not responsive to CFTR modulator therapy.



- L'obiettivo è fornire una copia a lunghezza intera del CFTR mRNA alle cellule polmonari utilizzando come vettore una nanoparticella lipidica.
- Le cellule polmonari userebbero quindi le istruzioni contenute nel mRNA per creare la proteina CFTR funzionale.
- Questa terapia potrebbe funzionare per qualsiasi persona con FC, indipendentemente dalle sue mutazioni CFTR.

← Back to the Drug Development Pipeline

LUNAR®-CF

Email | Print

STATUS
Phase One

THERAPEUTIC APPROACH
Genetic Therapy

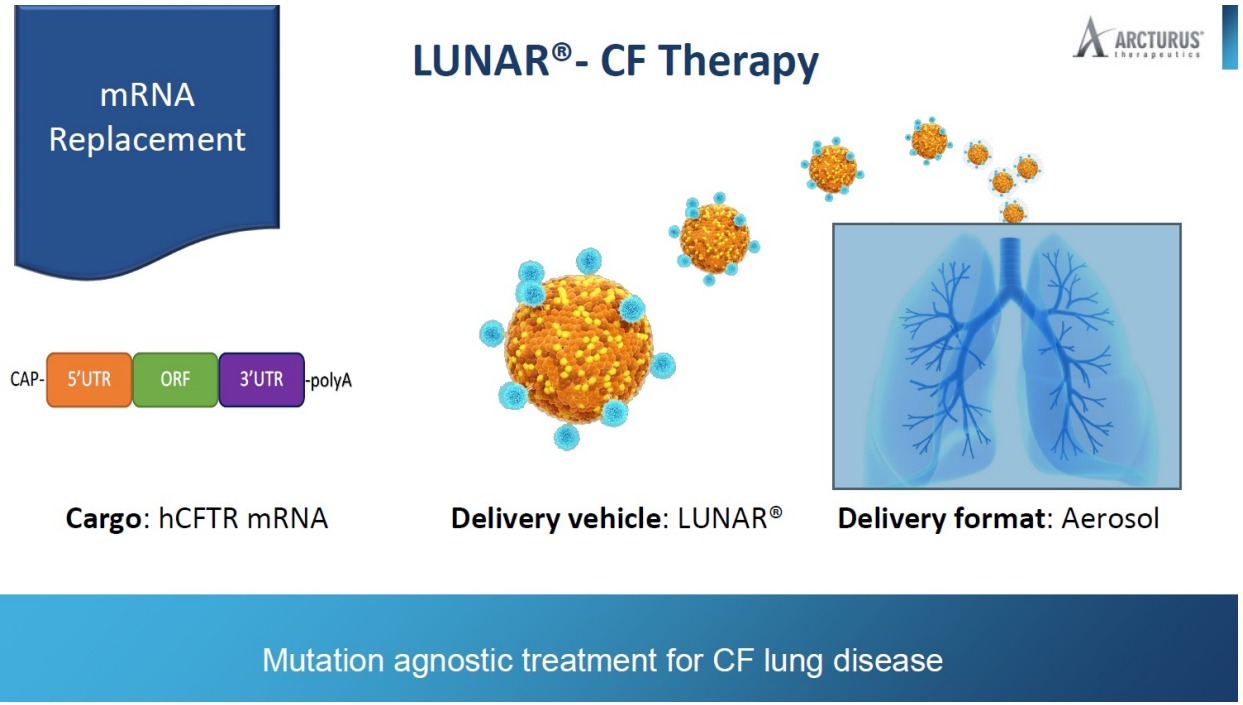
This program is developing a potential inhaled therapy to deliver normal CFTR messenger RNA (mRNA) to the lungs. Lung cells would then use the instructions in the mRNA to create functional CFTR protein. This type of therapy could work for any person with CF, regardless of their CFTR mutations.

Status

A Phase 1 study to test the safety and tolerability of this potential therapy is currently underway in New Zealand. The study initially enrolled healthy volunteers and is planned to expand to adults with CF later this year.

Sponsor

This program is sponsored by Arcturus Therapeutics and is partially funded by the Cystic Fibrosis Foundation.



- LUNAR®-CF è una terapia sostitutiva dell'mRNA, per aerosol per il trattamento della malattia polmonare nella fibrosi cistica ed è indipendente dal genotipo.
- un mRNA CFTR umano incapsulato in LUNAR®, una nanoparticella lipidica, è stato sviluppato per fornire l'mRNA nell'epitelio delle vie aeree. Le proprietà fisicochimiche
- di LUNAR® erano stabili dopo l'aerosol.

← Back to the Drug Development Pipeline

4D-710

Email | Print

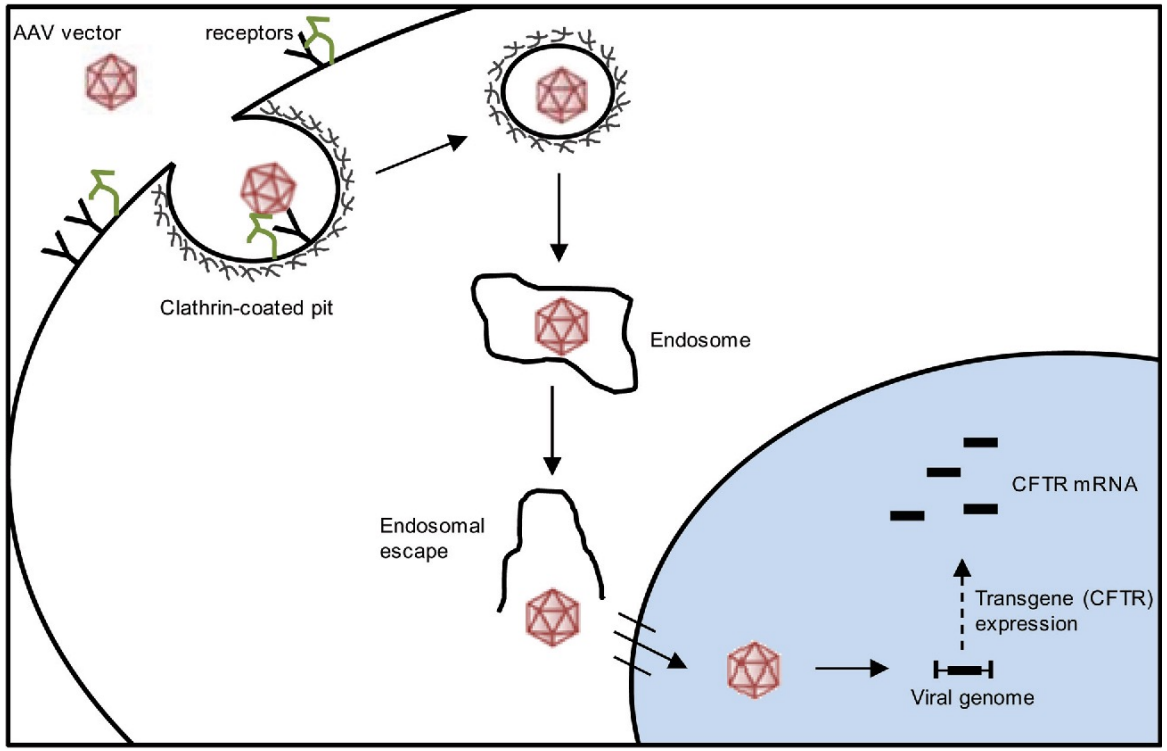
STATUS
Phase One

THERAPEUTIC APPROACH
Genetic Therapy

This program is working to advance a gene delivery vehicle that targets cells in the lung. 4D-710 is a customized adeno-associated virus (AAV) vector designed to deliver a healthy CFTR gene specifically to cells in the lungs of people with CF. This would allow the lung cells to create normally functioning CFTR protein, regardless of an individual's specific CFTR gene mutation.

Status

A Phase 1 study to test the safety of 4D-710 in adults with CF is underway.



- Terapia genica con vettore adenovirus associato
- Ridotta immunogenicità rispetto ai vettori adenovirali «classici»

← Back to the Drug Development Pipeline

SPL84

Email | Print

STATUS
Phase One

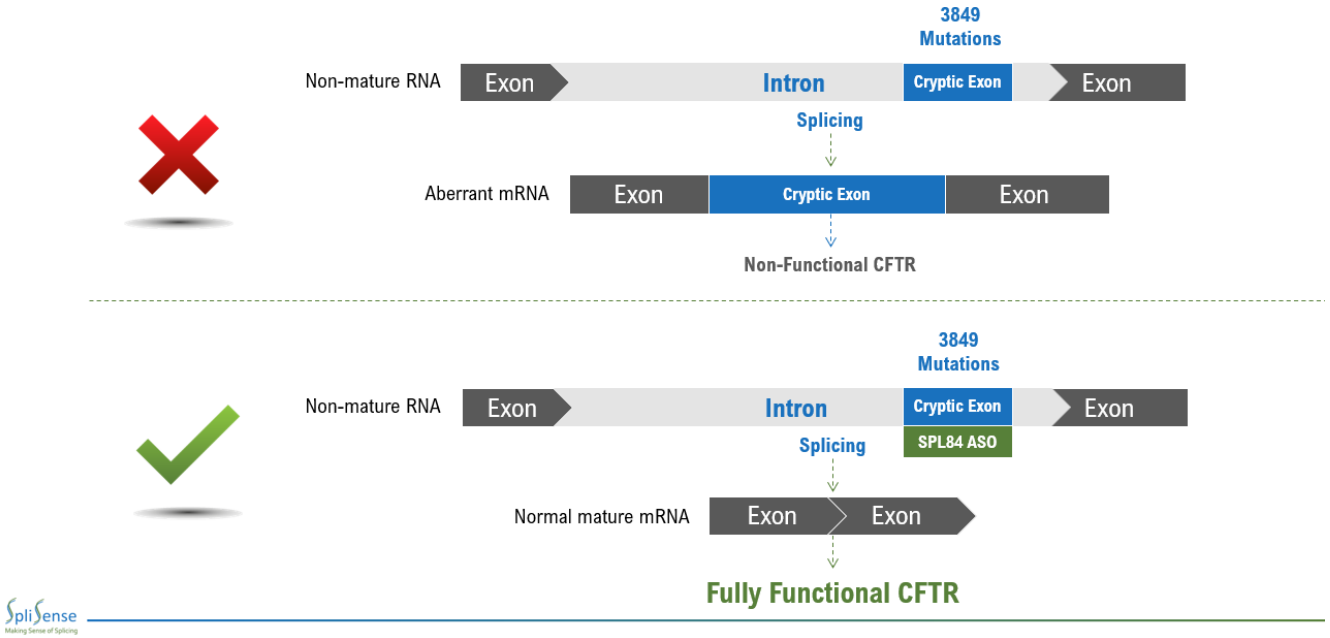
THERAPEUTIC APPROACH
Genetic Therapy

This program is working to develop a potential therapy for people with CF who have splicing mutations. Splicing is an essential process in which RNA is cut into pieces and then stitched back together in a specific way. Splicing mutations in the CFTR gene cause the RNA to be cut or stitched incorrectly, leading to a mutated CFTR protein. SPL84 is a short nucleotide, or a small piece of genetic material, that is designed to bind to RNA and change its properties in specific ways. In the case of a splicing mutation, the short nucleotide is designed to ensure that the RNA is cut and stitched correctly, allowing functional CFTR protein to be made.

Status

A Phase 1 study to test the safety and tolerability of SPL84 is currently underway. Part 1 of the study will enroll healthy volunteers. Part 2 of the study will enroll adults with CF who have at least one copy of the 3849 +10 Kb C->T mutation.

SPL84 Produces Mature and Functioning WT CFTR

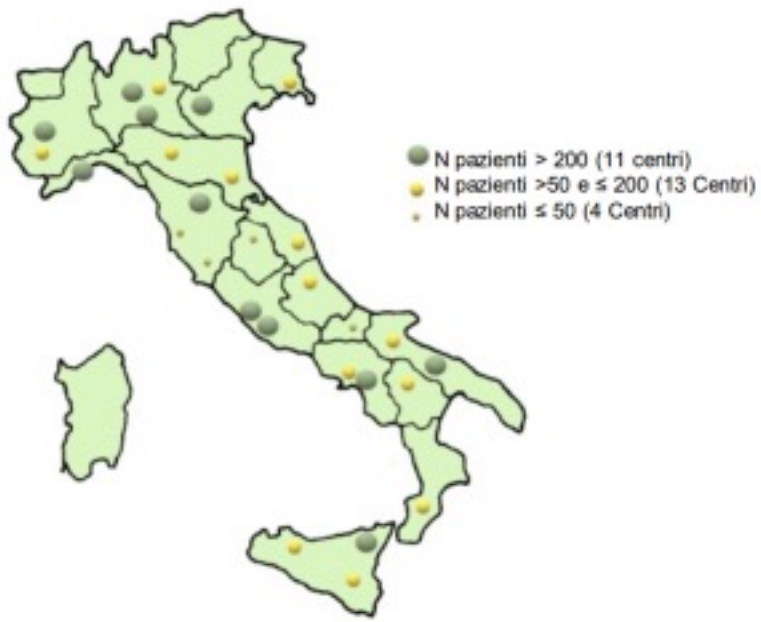


- Oligonucleotide per mutazioni splicing

LIFC
Lega Italiana
Fibrosi Cistica

forum 2023

31 CF centers in Italy



ECSF CLINICAL TRIAL NETWORK

Italy	Florence
	Genoa
6	Milan
	Rome
	Turino
	Verona

National Clinical Trial Network

- Molti Paesi europei (Germania, Francia, UK, Paesi Bassi) hanno creato delle piattaforme nazionali per il coordinamento, il finanziamento e la gestione degli studi clinici che vengono condotti all'interno della nazione e gestiti dalle associazioni di pazienti con il supporto delle società scientifiche.

- Ciò garantisce uguale accesso ai trial clinici, anche per coloro i quali sono seguiti nei centri più piccoli.


Grazie per l'attenzione!