Fondazione per la Ricerca sulla Fibrosi Cistica - ETS

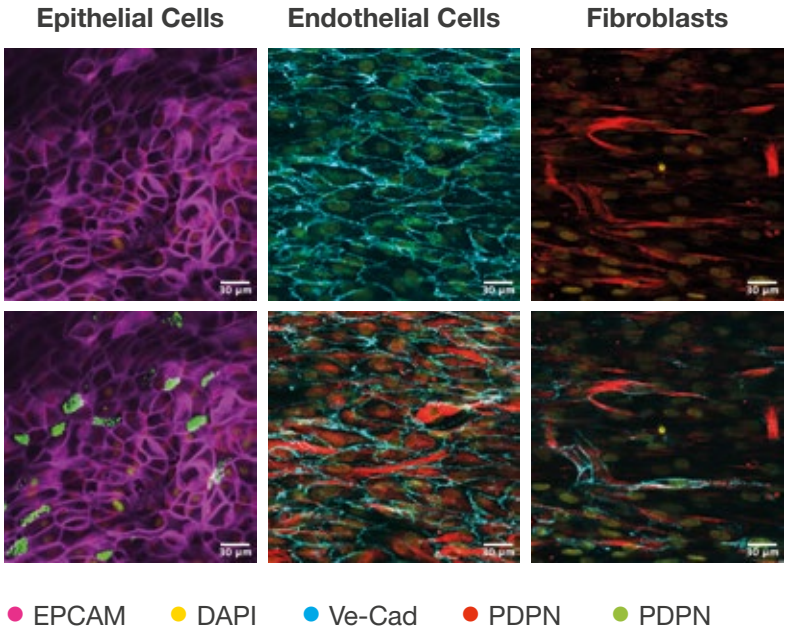
italian cystic fibrosis research foundation

13-15
November
2025
Verona

23RD CONVENTION OF INVESTIGATORS IN CYSTIC FIBROSIS

CENTRO CONGRESSI
CAMERA DI COMMERCIO
VERONA

On the cover: Confocal microscopy characterization of the cystic fibrosis airway-on-a-chip 2.0



Upper images
The constituent cell types of the cystic fibrosis airway-on-a-chip 2.0 - epithelial cells, endothelial cells, and fibroblasts - were immunostained with cell-specific markers: anti-EpCAM (magenta, left) for epithelial cells, anti-VE-cadherin (cyan, center) for endothelial cells, and anti–podoplanin (red, right) for fibroblasts. Nuclei were counterstained with 4′,6-diamidino-2-phenylindole (DAPI, yellow).

Lower images
Merged images highlight the selective expression of EpCAM in epithelial cells (left) and VE-cadherin in endothelial cells (center). Anti-podoplanin staining primarily labels fibroblasts (right) but also detects endothelial and ciliated epithelial cells (pseudocolored in green). The central image, depicting the endothelium adjacent to fibroblasts, demonstrates successful integration of endothelial cells within the culture and suggests close endothelium–stroma interactions.

With the support of

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Fondazione per la Ricerca sulla Fibrosi Cistica - ETS
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23rd Convention of FFC Ricerca investigators in cystic fibrosis

Verona
13 - 15 November 2025
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Appendices

Program at a glance

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Abstracts of oral presentations

SESSION 1

The multifaceted Kaftrio

Efficacy and safety of Kaftrio in real life: an observational multicenter Italian clinical study

Maria Cristina Lucanto

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Maria Cristina Lucanto[1], Cesare Braggion[2], Cristina Cigana[3], Nicoletta Pedemonte[4]

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(Kaftrio in the real life, ongoing)

Background and rationale

The Italian Cystic Fibrosis Research Foundation funded two post-marketing observational studies to evaluate the real-world effectiveness and safety of elexacaftor/tezacaftor/ivacaftor (ETI) in people with cystic fibrosis (pwCF), aged ≥12 years, heterozygous for F508del and a minimal function mutation (F/MFM). The ongoing study investigates pwCF with normal or mild-to-moderate lung disease over 2 years, and those with advanced disease from the previous study (*Kaftrio in advanced disease*) over 4 years of follow-up.

Hypothesis and objectives

The project aims to assess the long-term clinical effects of ETI in a real-world setting across different levels of lung disease severity. Additional aims include evaluating individual responsiveness, identifying reasons for lack of clinical improvement, and comparing clinical benefits and adverse events according to disease severity.

Essential methods

Eighteen Italian CF Centers are participating. PwCF are categorized into two groups: Group A (ppFEV1 <40%, advanced disease) and Group B (ppFEV1 ≥40%, normal/mild-to-moderate disease). Demographic and clinical data were collected retrospectively for 2 years before and prospectively for 2–4 years after ETI initiation. Primary outcomes include changes in ppFEV1, sweat chloride concentration, antibiotic use, BMI, and quality of life. Secondary outcomes include adverse events and treatment discontinuation. Two sub-studies will explore: i) the correlation between CFTR activity and rescue with ETI in nasal epithelial cells and clinical response; ii) phenotypic and genotypic changes in *Pseudomonas aeruginosa* after prolonged ETI treatment in responders and non-responders.

Preliminary results

The study is ongoing and will conclude in 2026. Due to delays in approvals from each hospital, patient enrollment began in August 2025. As of that date, 58 pwCF have been enrolled in Group B from 7 centers, and 103 in Group A.

Conclusions

Real-world evidence on ETI remains limited. However, data from other studies confirm its safety and sustained clinical benefits over two years. The present study will provide valuable long-term data on the effectiveness and safety of ETI, supporting informed clinical decision-making in people with CF.

Investigating the safety of elexacaftor/tezacaftor/ivacaftor (ETI) exposure during pregnancy and early development

In the first pic, left to right: Mattia Camera, Caterina Montani, Lucilla Nobbio, Giovanna Capodivento, Irene Di Patrizi
In the second pic, left to right: Sine Mandrup Bertozzi, Andrea Armirotti, Gaia Boschetti, Rosalia Bertorelli, Angelica Squarzoni

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Lucilla Nobbio[1], Andrea Armirotti[2], Giovanna Capodivento[1], Caterina Montani[1], Rosalia Bertorelli[2], Fabio Benfenati[2], Davide Visigalli[3], Mattia Camera[3], Angelica Squarzoni[2], Gaia Boschetti[2], Sine Mandrup Bertozzi[2], Maria Summa[2], Angelo Serani[2], Tiziano Bandiera[2], Nicoletta Pedemonte[4], Giuliana Cangemi[4], Elisa Milandri[5], Michele Protti[5], Laura Mercolini[5], Roberto Mandrioli[6]

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(FFC#2/2024, ongoing)

Background and rationale

We previously demonstrated that tezacaftor inhibits the enzyme (DEGS) that converts dihydroceramides (dHCer) into ceramides, thus producing an accumulation of dHCer in various cells and tissues. DEGS dysfunction and the resulting accumulation of dHCer are known to cause developmental disorders of the peripheral nervous system (PNS) and central nervous system (CNS), mainly due to an imbalance in myelin formation and maintenance. We here conducted an *in vivo* safety study to investigate the effects of ETI administration during pregnancy and breastfeeding.

Hypothesis and objectives

We have evidence of an inhibitory effect of the triple combination drug Kaftrio (elexacaftor, tezacaftor and ivacaftor, ETI) on DEGS. Therefore, we hypothesise that the use of ETI during pregnancy and in the early phases of human development might be potentially at risk of causing alterations in the physiological neurodevelopment and myelination process.

Essential methods

To rule out our concerns, we conducted an *in vivo* safety study by administering ETI to CD-1 mice during pregnancy and breastfeeding. ETI was incorporated into mouse food (in a high-fat diet regimen). Pups' behaviour was measured with SHIRPA tests. ETI and dHCer levels in plasma and tissues, as well as changes in the global lipidome, were measured by tandem mass spectrometry coupled to liquid chromatography.

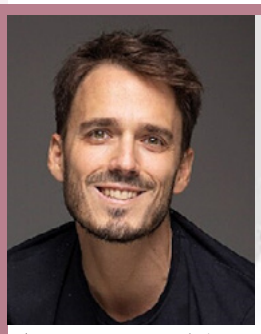
Preliminary results

We already demonstrated that the molecule responsible for the inhibitory effect on DEGS is tezacaftor and that a slight dHCer accumulation occurs in the brain of mice administered with ETI for 5 days. Here, at 10 days after birth, we observed a significant accumulation of dHCer in the brains of pups born from ETI-fed dams compared to controls. No accumulation was observed in the sciatic nerve of these animals, likely due to much lower levels of ETI compared to the brain. We also conducted an untargeted lipidomics survey, which revealed other alterations in lipid metabolism associated with exposure to ETI during pregnancy. During breastfeeding, given the negligible exposure to the drug, these alterations revert and virtually disappear at 28 days after birth, together with other differences in the phenotype and behaviour of the pups observed earlier during development.

Conclusions

We here demonstrate that exposure to ETI during pregnancy is associated with observable molecular changes in the brain lipidome, which are not likely limited to the inhibition of DEGS. These changes are reverted when exposure to ETI ceases.

Understanding the contribution of Kaftrio to antimicrobial therapies against nontuberculous mycobacteria in cystic fibrosis



Santiago Ramón-García and Daniela Maria Cirillo

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Lara Muñoz Muñoz[1], Nicola Ivan Loré[2], Fabio Saliu[2], Daniela Cirillo[2], Vadim Makarov[3], Maria Rosalia Pasca[4] , Santiago Ramón-García[1,5]

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(FFC#9/2024, ongoing)

Background and rationale

VOMG is a new molecule with bactericidal activity against *Mycobacterium abscessus* (Mab) and other cystic fibrosis (CF) pathogens due to a novel mechanism of action targeting cell division. Standard Mab treatments typically involve several drugs. VOMG demonstrated suitability for combination therapy, since no antagonism was verified with any of the antimicrobials currently used in Mab therapy; however, neither any synergistic effect was detected. Interestingly, synergism between VOMG and Kaftrio, used for gene corrector therapies in CF, was detected against Mab.

Hypothesis and objectives

Were Kaftrio to enhance the activity of VOMG, it could be also playing additional synergistic activities with other antimicrobials used in CF therapy. The aim of this study is i) to investigate the interaction profile of Kaftrio with other antibiotics currently used to treat Mab infections in CF and ii) to further characterize the combination of VOMG plus Kaftrio in animal models.

Essential methods

We used classical *in vitro* methods such as Minimum Inhibitory Concentration assays and Time Kill Assays, and more advanced methodologies such as High Throughput Synergy Screens and the Hollow Fiber System to characterize the activity of the compounds and combinations against Mab. We also used novel mouse models to characterize the efficacy of the combinations *in vivo*.

Preliminary results

CFTR modulators compounds, ivacaftor, tezacaftor and elexacaftor, did not show activity alone, in pair-wise or triple combination (Kaftrio) against Mab. However, a positive interaction was observed when VOMG was combined with each gene modulator. The quadruple interaction VOMG plus Kaftrio strongly enhanced the activity. To better study the drug interactions of CFTR modulators with currently used antimicrobials, a synergy screen was performed using compounds commonly employed against Mab. Five were selected (amikacin, bedaquiline clarithromycin, imipenem and tigecycline) for secondary validation combinatorial time-kill kinetics using a broad panel of clinical isolates.

Conclusions

Kaftrio could have a dual effect in CF therapy, as a CFTR corrector and by improving the antimicrobial activity of currently used antimicrobials and VOMG.

Survey on mental health in children with cystic fibrosis

Left to right: Sonia Graziano, Vito Terlizzi, Rita Pescini, Angela Sepe, Cristiana Risso, Alexandra Quittner

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Sonia Graziano[1], Vito Terlizzi[2], Rita Pescini[3], Angela Sepe[4], Cristiana Risso[5], Alexandra Quittner[6]

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(MindKids-CF, new)

Background and rationale

Integration of mental health (MH) screening and treatment into cystic fibrosis (CF) care represents over 10 years of research and clinical progress, driven by elevated rates of depression and anxiety in the first TIDES study (The International Depression and Anxiety Epidemiological Study), development of international MH guidelines, and implementation of MH screening for adolescents and adults. However, TIDES did not include children under 12 years. Depression and anxiety have increased dramatically in young children, with new screening guidelines in primary care. Given the pediatric MH crisis and widespread adoption of new CFTR modulators, with negative side effects, there is an urgent need to collect MH data on children under 12 years.

Hypothesis and objectives

This study aims to: i) evaluate Italian longitudinal prevalence of depression, anxiety and behaviour problems in children aged 2-11; ii) compare the performance of two widely used measures, Pediatric Symptom Checklist (PSC) and PROMIS Modules, in ascertaining these symptoms to identify the optimal screener; and iii) characterize the neuropsychological side-effects of modulator therapy.
Comparisons of MH symptoms and side effects will be made in Italy and the US.

Essential methods

This is a longitudinal, observational epidemiological study. We will enrol 500 children with CF under 12 years consecutively at 11 Italian CF Centers, generating national prevalence estimates for preschool and school-age children. Parents and children will complete a comprehensive assessment of MH problems twice during routine visits, separated by 6-9 months: PSC, PROMIS (sleep, cognition, emotional functioning), SDQ for convergent validity, CFQ-R (QOL), modulator side-effects and for parents, PHQ-9, GAD-7, and CF-PAS (procedural anxiety). Surveys will be administered via iPad using REDCap, a secure, private web-based tool.

Preliminary results

A higher prevalence of MH problems will be found in children with CF compared to published norms, and both PSC and PROMIS will demonstrate adequate reliability ($\alpha > 0.70$), sensitivity and specificity (> 0.80). Prevalence estimates will be generated, and the best brief screener will be identified to update the international MH guidelines for children under 12 years in the EU.

Conclusions

Use of these screening measures will facilitate the development of prevention and intervention efforts for young children and their parents to improve daily functioning and quality of life. MindKids-CF will contribute to provide critical evidence to extend MH screening and care to younger children with CF in the EU and US.

Long-term clinical outcomes of insulin secretory defects and effects of CFTR modulators

Left to right: Alberto Battezzati, Federico Alghisi, Stefano Costa

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Alberto Battezzati[1], Federico Alghisi[2], Stefano Costa[3]

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(FFC#14/2024, ongoing)

Background and rationale

CFTR modulators improve lung function in cystic fibrosis (CF), but extrapulmonary complications like cystic fibrosis-related diabetes (CFRD) persist. We studied insulin secretion defects and glucose tolerance in 600 people with CF (2013-2023), mainly before modulator availability, to assess their long-term impact.

Hypothesis and objectives

This study investigated whether pre-existing insulin secretory defects predicted dysglycemia, respiratory function decline, malnutrition, cardiometabolic risks, and mortality in CF. We also assessed whether modulators mitigated these effects.

Essential methods

This retrospective study is analyzing data from our 2013-2023 cohort. We are extracting clinical outcome data and CFTR modulator therapy information from patient records and correlating these with previously collected glucose tolerance and insulin secretion data.

Preliminary results

Data acquisition from patient records is actively underway. Our foundational analyses on the baseline cohort data have provided critical insights. We identified a dynamic pattern of insulin secretion around puberty and a progressive decline in β-cell glucose sensitivity with age, which correlated with poorer lung function and nutritional status. Furthermore, we have now characterized the phenomenon of reactive hypoglycemia as another manifestation of early glucose intolerance. Our data show this is caused by a large amount of insulin being secreted late in the OGTT, causing hypoglycemia. These findings were presented at the 48th European Cystic Fibrosis Conference. This body of work underscores the clinical relevance of early metabolic monitoring and provides a strong rationale for the current comprehensive outcome analysis.

Conclusions

This study is poised to deliver a definitive understanding of the long-term consequences of early insulin secretory defects in CF. We expect to quantify the impact of these defects and provide an assessment of the effectiveness of CFTR modulators in mitigating glycemic progression and its comorbidities. The final results will be instrumental for refining clinical guidelines for CFRD screening, leading to more personalized, risk-stratified treatment strategies.

SESSION 2

Modulators and genetic therapies

Development of new potentiators active on (ultra)rare mutants of CFTR

Giovanni Marzaro (second row, central pic) and his collaborators

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Giovanni Marzaro[1,2], Gergely Lukacs[3], Tamas Hegedus[4], Adriana Chilin[2], Stefano Negri[2], Guido Veit[3]

[1]Department of Diagnostic and Public Health, University of Verona, Italy - [2]Department of Pharmaceutical Sciences, University of Padua, Italy - [3]Department of Physiology, McGill University, Montréal, Canada - [4]Biophysical Virology Research Group, Hungarian Research Network, Hungary

(FFC#1/2024, ongoing)

Background and rationale

Cystic fibrosis (CF) is caused by mutations that impair the CFTR ion channel function. 40 rare mutations display limited response to Kaftrio exposure, and novel therapeutic interventions are required. No experimentally determined CFTR structure exists in an open-channel state. Molecular dynamics (MD) simulations provide a powerful tool to complement experimental approaches, allowing the characterization of conformational landscapes, allosteric communication, and drug-protein interactions.

Hypothesis and objectives

The additive effect of preclinical class-II potentiators in combination with VX-445 (class-III) and VX-770 (class-I) potentiators shows that gating defective CFTR variants can be further activated by additional drugs. Poor pharmacophore properties of available class-II potentiators need significant improvement. We aim at developing poly-specific class-II potentiators that activate the gating of several CFTR mutants in combination with known drugs and to characterize their mechanism of action at the molecular level. We also hypothesize that MD simulations can reveal how lipid composition, mutations, and therapeutic compounds reshape CFTR's conformational dynamics and allosteric communication.

Essential methods

Chemical optimization to further improve the rescue potency and efficacy of our best class-II potentiator hits was conducted. Functional studies on several poorly responsive CFTR variants were conducted in immortalized and primary human airway cells. The potentiation mechanism and toxicity profile of the best compounds were established. We performed multi-microsecond MD simulations using open and closed CFTR conformations, in either pure POPC or mixed lipid bilayers.

Preliminary results

We have demonstrated that at least 3 binding sites for potentiator exist in CFTR. Starting from our new correctors that synergize with approved drugs, we have developed new class-II potentiators that improved the G551D-, and N1303K-CFTR function in concert with the class-I and -III potentiators and correctors of Kaftrio. We have identified the structural determinant for switching from correctors to potentiators and proposed a potential binding site. Preliminary MD results highlight distinct allosteric pathways between the nucleotide-binding domains and transmembrane helices.

Conclusions

New potentiators for CFTR mutations with poor responsiveness to approved drugs are ongoing. Compounds will be further developed considering the outcomes from *in silico* studies. MD simulations provide critical insights beyond static structures, offering a framework to investigate how drugs and mutations modulate CFTR function. Our project aims at the development of more effective and tailored therapies for people with CF and to provide a computational platform to optimize therapies.

Promoting correct folding to enhance F508del-CFTR rescue induced by correctors

Mauro Salvi (first from the left) and his collaborators

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Christian Borgo[1], Marika Pia Nunzia Coviello[1], Valentina Bosello Travain[2], Luca Cesaro[1], Mauro Salvi[1]

[1]Department of Biomedical Sciences, University of Padua, Italy - [2]Department of Molecular Medicine, University of Padua, Italy

(FFC#3/2024, ongoing)

Background and rationale

Kaftrio represents the current standard pharmacological treatment for people with cystic fibrosis (CF) carrying at least one copy of the F508del mutation in the CFTR gene. Its use has been extended by EMA in 2025 to patients who have at least one non-Class I mutation. Despite the remarkable results achieved, optimization of Kaftrio therapy remains both necessary and feasible. This is particularly important in view of its application to a wide range of mutants, for whom therapeutic efficacy may be limited.

Hypothesis and objectives

We aimed to screen a panel of molecules that share the ability to activate heat shock proteins (HSPs). We hypothesized that activating the HSPs would improve the ability of correctors to rescue F508del-CFTR.

Essential methods

CFBE41o- cells expressing F508del-CFTR were treated with HSP activators in the presence or absence of VX-445/VX-661. Functional rescue of the channel was assessed by western blotting and the YFP assay. Channel stability was evaluated using the cycloheximide assay, while CFTR expression was measured by qPCR. The most effective compounds were then tested in 16HBE gene-edited cells carrying the endogenous F508del mutation. Finally, compounds that proved effective in both models were evaluated in primary patient-derived cells homozygous for F508del-CFTR using Ussing chamber assays. Experiments on primary cells were performed in collaboration with the CFaCore facility and Primary Cultures Service by FFC Ricerca.

Preliminary results

We tested a subset of HSP-activating molecules. Two of these showed efficacy in both CFBE cells and gene-edited cells in potentiating the effects of correctors on the rescue of F508del-CFTR. One of the two compounds was also effective in patient-derived cells, although apparently through a mechanism different from that initially expected. Evaluation of the second compound in patient cells is currently ongoing.

Conclusions

Although we have not yet been able to determine the precise role of HSPs in the functional rescue of F508del-CFTR, the selection of a group of compounds capable of activating HSPs allowed the identification of one compound, already approved as a drug for another pathology, with efficacy in patient-derived cells in potentiating the effect of correctors. A second, very promising compound is currently under evaluation to determine its efficacy in patient cells.

Exploring the cellular pathways to promote rescue of mutant CFTR protein in cystic fibrosis

In the first pic, Carlos M. Farinha (in the middle) and his collaborators
In the second pic, Valeria Tomati (in the middle) and her collaborators

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Carlos M. Farinha[1], Valeria Tomati[2]

[1]BioISI - Biosystems and Integrative Sciences Institute, University of Lisbon, Portugal - [2]UOC Genetica Medica, IRCCS G. Gaslini Institute, Genoa, Italy

(FFC#2/2023, ongoing)

Background and rationale

Regulation of CFTR trafficking requires integrity of correct cytoskeletal organization, because the cytoskeleton is responsible for the scaffolding that stabilizes CFTR at the plasma membrane (PM) and brings several interacting proteins to CFTR's proximity, among which cAMP sensors, such as protein kinase A and EPAC1, have a prominent role

Hypothesis and objectives

As we aim at characterizing the crosstalk between the cytoskeleton and cAMP signalling in the regulation of CFTR traffic, we focused here on the role of the cAMP sensor EPAC1, the capping protein CAPZA2 and the inverted formin INF2, and on their possible role in the regulation of CFTR trafficking.

Essential methods

We used primary cultures of nasal epithelial cells isolated from individuals with CF, CF bronchial epithelial cells expressing wild-type or mutant CFTR, and analyzed them using Western blot, co-immunoprecipitation and cell surface biotinylation. We also performed live cell imaging to assess cAMP pools and proximity labelling to isolate INF2 interactors.

Preliminary results

Results show that:
i) Knockdown (KD) of INF2 and CAPZA2 affects cytosolic and membrane-associated cAMP pools in CFBE wt and F508del cells.
ii) EPAC1 activation in CFBE mCherry-FLAG-CFTR increases the association of wt-CFTR with NHERF1, with the opposite occurring for F508del-CFTR.
iii) INF2 is detected in nasal epithelial cells as the full-length protein and as a lower molecular weight isoform, whose expression is not detected in established cell lines.
iv) The fusion between ER- INF2 and biotin ligase TurboID can be transfected into CFBE cells and increases the amount of recovered biotinylated proteins, prompting the identification of the INF2 interactome in these cells.
v) A bioinformatic analysis performed to derive an MS/MS-based method for ranking of proteins relevant to CFTR PM stabilization allowed the identification of proteins relevant for PM stability for wt- or F508del-CFTR.

Conclusions

The findings of the second year confirm that regulation of CFTR by EPAC1, INF2 and CAPZA2 is complex, highlighting the relevance of exploring their role in the crosstalk between cAMP signalling pathways and the cytoskeleton to affect CFTR modulation, and possibly CF handling.

Optimization and *in vivo* testing of two new classes of modulators and pharmacokinetic studies

Left to right: Luis J. V. Galietta, Paola Barraja, Arianna Venturini and Anna Borrelli

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Stefano Giuffrida[1], Marilia Barreca[1], Fabiana Lo Mascolo[1], Alessandra Li Pani[1], Virginia Spanò[1], Maria Valeria Raimondi[1], Alessandra Montalbano[1], Paola Barraja[1], Mario Renda[2], Anna Borrelli[2], Arianna Venturini[2], Daniela Guidone[2], Luis J. V. Galietta[2]

[1]Department of Sciences and Chemical Biology and Pharmaceutical Technology (STEBICEF), University of Palermo, Italy - [2]Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (NA), Italy

(Molecules 3.0 for CF, ongoing)

Background and rationale

A significant progress has been obtained in the pharmacological treatment of cystic fibrosis (CF) with the development of correctors (VX-809, VX-661, VX-445) and potentiators (VX-770) that, in combination, can restore the function of mutant CFTR. However, the identification of new CFTR modulators may offer further possibilities for maximal CFTR rescue. The project Molecules 3.0 aims at the development of novel CFTR correctors endowed with maximal potency and efficacy.

Hypothesis and objectives

Our previous efforts, led to the identification of a new class of small molecules (called PP compounds) that have a tricyclic core and act as correctors with high efficacy in the rescue of F508del-CFTR on native epithelial cells of CF patients, particularly in combination with class 1 correctors.
PP compounds appear to work with a class 3 corrector mechanism, through the interaction with the second membrane spanning domain (MSD2) of the CFTR protein. Our objective is to improve this interaction through a wide campaign of chemical synthesis, aiming at a multiparametric optimization of PP compounds. Within this campaign, a scaffold hopping strategy led to the identification of SH compounds, derived from the parent tricyclic core structure. These compounds bear a higher conformational flexibility and offer multiple regions for structural diversification with high optimization opportunities.

Essential methods

We explored three different regions of PP and SH families on the basis of their predicted interaction with CFTR (lasso domain and transmembrane helices 10-11). Iterative cycles of chemical synthesis and functional evaluation on CFBE41o- cells expressing F508del-CFTR allowed the identification of the most promising compounds that were then validated on primary bronchial epithelial cells from people with CF.

Preliminary results

In vitro and *in silico* studies oriented the synthesis towards a structure elongation, to increase the number of chemical interactions with the CFTR protein, and the insertion of a fluorine in a specific position. Interestingly, two promising subgroups of PP compounds, named FLM and AL, were also found. In general, nearly 550 compounds have been obtained so far, belonging to the two families, PP and SH, from which several effective candidates have been identified. These compounds are effective in improving CFTR function in short-circuit current recordings on epithelia from people with CF. A selected number of compounds was also tested in FRAP experiments, showing the ability to decrease apical fluid viscosity in CF epithelia. *In vivo* pharmacokinetic studies on mice done for PP028 and SH157A at the Italian Institute of Technology (IIT) indicated moderate oral bioavailability, which needs to be improved.

Conclusions

So far, we have devoted many efforts to exploring the chemical space around the PP and SH scaffolds to maximize the possibility of obtaining compounds endowed with the characteristics needed to reach preclinical and clinical studies. This search has revealed a panel of small molecules with promising characteristics.

Development of CRISPR-Cas delivery system for genome editing applications in cystic fibrosis

Left to right: Elena Guerrieri, Alessandro Umbach, Marta Stancampiano, Francesca Zerbini, Giulia Maule, Anna Cereseto

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Giulia Maule
Department for Cellular, Computational and Integrative Biology (CIBIO), University of Trento, Italy
(GMSG#1/2022, concluded)

Background and rationale

Genome editing holds great promise for correcting CFTR mutations in cystic fibrosis (CF). While efficient CFTR correction has been shown in experimental models, delivery methods remain a major challenge, especially for the lungs, the primary site of disease. Engineered vesicles represent a promising system to deliver genome editing tools, offering transient expression to reduce off-target effects and tunable tissue tropism.

Hypothesis and objectives

This study aims to develop GE-vesicles, a new system to deliver genome editing complexes as ribonucleoproteins to airway epithelial cells. This approach ensures transient expression of the cargo, enabling correction of the CFTR gene while minimizing undesired genomic alterations.

Essential methods

GE-vesicles were engineered to carry different CRISPR tools, including ABE8e-SpCas9, SpCas9, and AsCas12a. Production protocols were optimized to maximize editor and sgRNA incorporation. Particles were characterized for size, concentration, and cargo content.

Results

We demonstrated successful incorporation of base editors (ABE8e-SpCas9) and nucleases (SpCas9, AsCas12a) into GE-vesicles. Editing efficiency reached up to 60% with ABE and 80% with Cas9 in HEK293T and CFBE41o- cells. We evaluated the efficiency of ABE-GE-vesicles in correcting the R553X nonsense mutation, achieving up to 25% correction in 16HBE-R553X cells, and of Cas9-GE-vesicles in targeting the 3849+10kb C>T mutation, reaching up to 50% deletion in HEK293T cells. We aim to modify the tropism of GE-vesicles by incorporating envelopes derived from different viruses to ensure efficient delivery of the genome editing complex to airway cells. The most effective envelope *in vitro* was selected for further testing in CF patient-derived airway cells and in mice.

Conclusions

GE-vesicles represent a promising delivery strategy for genome editing in CF. Their tunability and efficiency support their use not only for CF but also for other lung and genetic diseases, addressing a major bottleneck in the clinical translation of genome editing for the lung.

Tackling gene delivery in lungs for the treatment of cystic fibrosis

Anna Cereseto (second from the right, central row) and her collaborators

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Anna Cereseto[1], Giulia Maule[1], Marta Stancampiano[1], Elena Guerrieri[1], Francesca Zerbini[1], Sheref S. Mansy[1], Arup Dalal[1], Luis J. V. Galietta[2], Anna Borrelli[2], Daniela Guidone[2], Serena Zacchigna[3], Sharad Saxena[3], Andrea Colliva[3], Sven Even Borgos[4], Sjoerd Hak[4]

[1]Department for Cellular, Computational and Integrative Biology (CIBIO), University of Trento, Italy - [2]Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (NA), Italy - [3]ICGEB, Trieste, Italy - [4]SINTEF Trondheim, Norway

(GenDel-CF, ongoing)

Background and rationale

Cystic fibrosis (CF) is caused by mutations in the CFTR gene, leading to defective chloride channel function. While modulators such as Kaftrio have improved prognosis, many patients remain without effective therapy. Gene replacement or correction strategies hold therapeutic potential, but progress is delayed by the lack of efficient and safe delivery systems to the lung.

Hypothesis and objectives

The GenDel-CF project aims to overcome current barriers in pulmonary gene therapy by developing innovative delivery systems for CFTR mRNA and CRISPR-based editing tools. We aim to prove that advanced lipid nanoparticles (LNPs) and engineered genome-editing vesicles (GE-vesicles) can achieve stable, tissue-specific, and safe delivery to airway epithelia. Objectives include: i) design and optimization of lipid and vesicular carriers, ii) validation of functional correction in patient-derived airway epithelia, and iii) preclinical evaluation in mouse models.

Essential methods

We combined lipid chemistry, RNA formulation, and synthetic biology to generate LNPs and GE-vesicles with tailored lung tropism. LNP stability and mRNA encapsulation efficiency were assessed by dynamic light scattering, field-flow fractionation, and RiboGreen assays. Functional testing was performed in CFBE41o- cells and differentiated primary bronchial epithelia grown at air-liquid interface (ALI). *In vivo* efficacy was tested in reporter and CF mouse models after intra-tracheal and/or intravenous administration.

Preliminary results

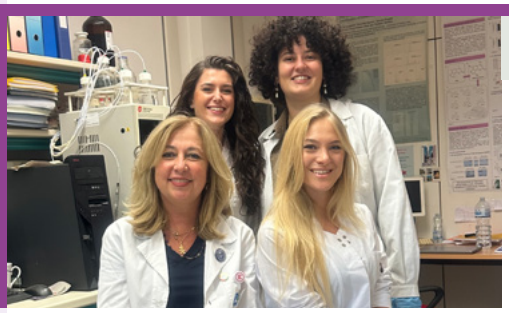
The GenDelCF consortium produced LNP formulations for the delivery of mRNA. The LNP were demonstrated to be stable and with high encapsulation capacity. The delivery efficacy was tested in cell lines, in ALI culture and in an *in vivo* model by using specific reporter systems, which allowed to screen and identify the best-performing LNP. We have obtained LNP formulations that allow efficient delivery of mRNA both *in vivo* and in primary cells. In parallel, we developed GE-vesicles to deliver protein-RNA complexes, which showed a high level of genome editing using diverse types of genome editing tools (base editors and nucleases). We have identified novel targeting molecules for the bronchial epithelium that should enable efficient delivery via GE-vesicles, with promising potential for translation to LNP platforms.

Conclusions

Together, these preliminary results demonstrate the feasibility of diverse platforms for pulmonary gene therapy. The consortium has generated stable LNPs and GE-vesicles with promising tropism and editing activity. Expected final results include the identification of optimal carriers for *in vivo* CFTR correction and proof-of-concept for functional rescue. These advances are an important step toward curing CF and could also lead to new RNA and gene editing treatments for other lung diseases.

Hot inflammation topics

GY971 as anti-inflammatory agent 2.0



Ilria Lampronti (first from the left, second row) and her collaborators

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Ilaria Lampronti[1], Adriana Chillin[2]

[1]Department of Life Sciences and Biotechnology, University of Ferrara, Italy - [2]Department of Pharmaceutical Sciences, University of Padua, Italy

(FFC#11/2024, ongoing)

Background and rationale

Although highly effective CFTR modulator therapy (HEMT) is providing major benefits to people with cystic fibrosis (pwCF), the inflammatory processes progressively damaging pulmonary tissues are not halted. Thus, there is an urgent need for new anti-inflammatory agents complementary to HEMT to be given by the pulmonary route to pwCF.

Hypothesis and objectives

We developed GY971, showing anti-inflammatory action based on the regulation of the abnormal neutrophil chemotaxis in CF bronchial epithelial cells *in vitro* and murine lungs *in vivo*. We hypothesize that GY971 could be developed to obtain an innovative anti-inflammatory drug tailored to the needs of pwCF. To this goal, we wish to consolidate and extend the evidence of its anti-inflammatory efficacy and collect preliminary safety data.

Essential methods

GY971 was tested in human primary bronchial and nasal epithelial cells obtained *ex vivo* from different pwCF carrying the F508del mutation and infected with *Pseudomonas aeruginosa* (PAO-1). Moreover, GY971 was *in vivo* administered in a new zebrafish model infected with PAO-1. In addition, whole human blood was used to study possible COX-1 and COX-2 inhibition.

Preliminary results

GY971 was confirmed to be able to reduce neutrophil chemotaxis mediators both in CF bronchial epithelial cell lines and in CF primary bronchial and nasal epithelial cells. The expression of key inflammatory proteins involved in CF lung disease, mainly IL-8, was significantly reduced using nanomolar concentrations. Importantly, GY971 did not interfere with the ETI-mediated rescue of CFTR protein, did not show cytotoxic effects and, at these concentrations, was unable to inhibit platelet COX-1 and LPS-induced COX-2 activity. *In vitro* analyses designed for early detection of potential clinical adverse drug reactions (ADRs) were completed, and NGS analyses are being finalized to conclude the safety data screening. Moreover, *in vivo* testing with a zebrafish model confirmed its effectiveness.

Conclusions

GY971 appears to be a highly promising derivative for the future development of anti-inflammatory CF treatments. It effectively mitigates inflammation and restores ETI-mediated CFTR function in the presence of bacterial exoproducts. The investigation into the efficacy of GY971 will be extended to *in vivo* murine models of chronic inflammation, with daily administration via aerosol delivery.

Targeting immune system to restrain cystic fibrosis airway inflammation

Domenico Mattoscio (second from the left) and his collaborators

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Domenico Mattoscio

Department of Medical, Oral, and Biotechnology Science, University G. D'Annunzio Chieti-Pescara, Chieti, Italy

(FFC#12/2024, ongoing)

Background and rationale

Accumulating evidence suggests that people with cystic fibrosis (pwCF) generate insufficient T-cell responses, which contribute to excessive inflammation. Among other factors, platelets (PLTs) play a key role in CF inflammation as they can alter the response of various immune cells, including CD8 T lymphocytes.

Hypothesis and objectives

The central hypothesis of the proposed research is therefore that PLTs dampen CD8 actions to fuel CF inflammation. Targeting PLT-CD8 crosstalk could therefore be beneficial. The study addresses the following objectives: i) determine how PLTs affect CD8s; ii) evaluate the impact of PLT-CD8 crosstalk on airway inflammation; iii) test strategies to promote CD8 reactivation and the resolution of inflammation.

Essential methods

We used purified blood cells from pwCF and healthy donors (HD); reconstituted lung-on-chip models; *in vivo* models of lung bacterial infection; proteomics and phosphoproteomics assays.

Preliminary results

Our ongoing work highlights global proteomic and phosphoproteomic changes in PLTs that affect their interaction with adaptive immune cells. We have also demonstrated an increase in circulating PLT/CD8 aggregates i) in pwCF compared to HD due to PLT hyperactivity, ii) *in vivo* in the airways of CF mice and iii) in a reconstituted lung-on-chip model with human cells. CD8+ T cells in PLT/CD8 aggregates in pwCF express high levels of exhaustion markers and have lower cytotoxic ability. Thus, PLTs stimulate the differentiation of CD8 T cells towards dysfunction. Reinvigorating CD8 T cell function with the immune checkpoint inhibitor anti-PD-1 alleviated bacterial infection and inflammation *in vivo* in CF mice.

Conclusions

During the first year, we established that PLTs interact with CD8 T cells and that these aggregates may play a pathological role in CF airway disease. These studies are highly relevant to the FFC Ricerca's mission to promote innovative treatment and care for CF, as they investigate innovative strategies to limit inflammation-based pathology by targeting a previously unexplored pathological mechanism. This proposal will also shed more light on the functions of adaptive cells in CF and pave the way for new research aimed at dissecting the role of CF lymphocytes.

Unravelling proresolving effects of CFTR modulators on lung inflammation and infection

In the first pic, Antonio Recchiuti (first from the left) with his collaborators
In the second pic, Pietro Ripani (first from the right) with his collaborators

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Antonio Recchiuti
Department of Medical, Oral, and Biotechnology Science, University G. D'Annunzio Chieti-Pescara, Chieti, Italy
(FFC#13/2024, ongoing)

Background and rationale

CFTR modulators like elexacaftor/tezacaftor/ivacaftor (ETI, or Kaftrio) have fundamentally transformed cystic fibrosis (CF) treatment. Nevertheless, significant knowledge gaps persist regarding the variability of patient response to lung inflammation and the precise mechanism by which ETI influences the complex host immune defense system. This indicates that our understanding of the deep functionality of these drugs is still incomplete.

Hypothesis and objectives

The main goal of this project is to study the effects, mechanisms and interactions of the drug ETI on the body's ability to resolve inflammation and infections in the lungs of people with CF. The persistent, damaging lung inflammation in CF is exacerbated by a deficiency in SPM consequent to the underlying CFTR defect.
This study posits that CFTR modulators, like ETI, exhibit a dual action: restoring CFTR protein function and upregulating SPM. This is proposed to re-educate inflammation in people with CF, shifting this response from a destructive to a protective mechanism.

Essential methods

This is a cross-sectional study with volunteers with CF receiving ETI (n = 40) and an untreated cohort (n = 20). Peripheral blood and nasal swabs will be collected to quantify ETI and SPM concentrations in the systemic circulation (to track overall distribution throughout the body) and airways (to determine the levels reached in the main site of the disease).
scRNAseq will be used to characterize changes in transcriptomic signatures of leukocytes and airway cells. Biostatistical analyses will subsequently determine if ETI elevates SPM in people with CF, how it modifies immune and epithelial cell phenotypes, and whether these changes correlate with local and systemic drug exposure.

Preliminary results

In the first year, the recruitment of study participants and sample collection were completed. We developed a state-of-the-art, clinically validated method to precisely measure the concentration of the ETI drug: both in the blood and in the nasal wash fluids. Moreover, scRNA-Seq was initiated. The second year will focus on the in-depth analysis of the collected samples, including scRNAseq and SPM quantification.

Conclusions

These results will reveal whether the inflammatory improvement seen in patients is directly due to increased SPM production and linked to the amount of ETI reaching the lungs, providing the foundation for more targeted and effective CF treatment strategies in the future.

Melanocortins to control cystic fibrosis airway inflammation

In the first pic, Shameer Pillarisetti, Mario Romano and Roberto Plebani
In the second pic, Lucy Norling
In the third pic, Mauro Perretti

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Roberto Plebani[1], Lucy Norling[2], Shameer Pillarisetti[1], Mauro Perretti[2], Mario Romano[1]

[1]Department of Medical, Oral, and Biotechnology Science, University G. D'Annunzio Chieti-Pescara, Chieti, Italy - [2]The William Harvey Research Institute, Queen Mary University of London, United Kingdom

(FFC#15/2023, ongoing)

Background and rationale

A sustained inflammatory response represents a significant pathogenic factor of cystic fibrosis (CF) lung disease, even in the era of CFTR modulators. Pro-resolving pharmacology appears to be a valid alternative to the scarcely effective conventional anti-inflammatory treatments. Pro-resolving molecules include melanocortins, peptide hormones that activate specific receptors (MC1-5). Synthetic melanocortins are now in advanced clinical trials in various pathologies.

Hypothesis and objectives

We hypothesize that melanocortins may have efficacy in controlling CF inflammation. The main objectives of the program are to: i) develop a 3D model of CF airways to verify the pro-resolving properties of synthetic melanocortins; ii) integrate evidence provided by 2D and 3D models as preclinical testing procedures in CF.

Essential methods

We used 2D (transwell) and 3D (airway-on-a-chip) models, constructed with primary cells (respiratory epithelial or vascular endothelial) from people with CF, in the presence or not of bacterial infection (*Pseudomonas aeruginosa*), and of CF neutrophil leukocytes (PMNs). We examined the modulatory properties of BMS-470539 (BMS), a synthetic MCR1-selective agonist, and of α-MSH (pan MCR agonist). We assessed PMN recruitment and activation status, mucus production, transepithelial electrical resistance (TEER), cell monolayer integrity, cytokine and chemokine release, and the transcriptome of endothelial and epithelial cells.

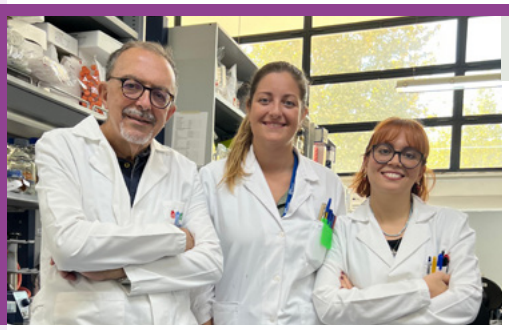
Preliminary results

Treatment with BMS (0.1-5 μM) resulted in increased TEER, associated with changes in mucus production and reduced PMN recruitment. However, these effects were donor-dependent. Less pronounced effects were observed with α-MSH. BMS also improved some dysfunctional parameters of CF endothelial cells.

Conclusions

These results suggest that melanocortins may exert beneficial effects on specific components of the CF lung inflammatory response. However, the donor-dependent variability of these effects requires further study. Relevant insights may be provided by ongoing evaluations of cytokine and chemokine release and the transcriptomic profiles of the epithelium and endothelium.

Airway surface as a battleground against bacteria



Daniela Guidone (in the middle), between Luis J. V. Galietta and Martina De Santis

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Daniela Guidone[1], Martina De Santis[1], Maria Stabile[2], Eliana De Gregorio[2], Luis J. V. Galietta[1,3]

[1]Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (NA), Italy - [2]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy - [3]Department of Translational Medical Sciences (DISMET), University of Naples Federico II, Naples, Italy

(GMRF#1/2024, ongoing)

Background and rationale

The airway epithelium deploys innate defense mechanisms that are further modulated during inflammation to boost its ability to fight pathogens and recruit immune cells. In cystic fibrosis (CF), the absence of chloride secretion through CFTR leads to dehydration of the airway surface, bacterial colonization, inflammation and lung damage. We found that bronchial epithelia (BE) exposed to IL-17A+TNF-α have upregulation of genes for antimicrobial peptides, chemotactic molecules for leukocyte recruitment, MUC5B mucin and ion channels/transporters (ENaC, CFTR, SLC26A4).

IL-17A+TNF-α causes a hyperviscosity of the airway surface, which is reversed in non-CF epithelia by beta-adrenergic stimulation of CFTR. Moreover, BE releases extracellular vesicles (EVs), particularly upon cytokine stimulation.

Hypothesis and objectives

We hypothesize that these properties of the airway surface may be involved in the innate defense response. We aim to i) identify potential bactericidal mechanisms coordinated by the airway epithelium and ii) define the properties and role of extracellular vesicles (EVs) released by BE.

Essential methods

We used BE from non-CF and CF patients and performed Ussing chamber, FRAP and RNAseq experiments to evaluate changes in gene expression and ion transport elicited by cytokines. We dealt with PAO1 and RP73 bacteria to measure their diffusion on the airway surface. Regarding EVs, we performed serial centrifugation and capillary-automated immunoblot analysis, FACS and electron microscopy.

Preliminary results

We have compared the effects of IL-17A and IL-17F. From RNAseq, short-circuit current recordings and FRAP, we found that IL-17F increased CFTR and TMEM16A activity and had a fluid surface, resembling a Th2 response. These results also suggest that the hyperviscous state induced by IL-17A is probably caused by ENaC and/or SLC26A4. Our data in BE with genetic ablation of SLC26A4 supports this finding. We found that the viscosity of the airway surface has an impact on bacterial diffusion. We further characterized the EVs in their molecular content and tested their ability to deliver cargo.

Conclusions

Our results are relevant to better understanding the physiology of the airway surface in the context of inflammation and reveal new targets for therapeutic interventions (e.g. IL-17RA, SLC26A4) in people with CF who cannot benefit from CFTR modulators.

A personalized repurposing approach based on antinflammatory/ antioxidant treatment to increase the efficacy of CFTR modulators

In the first pic, Onofrio Laselva and Caterina Allegretta
In the second pic, Valeria Capurro
In the third pic, Enza Montemitro

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Onofrio Laselva[1], Valeria Capurro[2], Enza Montemitro[3]

[1]Department of Clinical and Experimental Medicine, University of Foggia, Italy - [2]UOC Genetica Medica, IRCCS G. Gaslini Institute, Genoa, Italy - [3]Pediatric Hospital Bambino Gesù, Rome, Italy

(FFC#4/2024, ongoing)

Background and rationale

People with CF (pwCF) are prone to contracting bacterial lung infections by *P. aeruginosa*, known to be the major pathogen in the CF lung, leading to increased inflammatory response, significantly contributing to morbidity and mortality.

Hypothesis and objectives

The patient-to-patient variation in Kaftrio response might be attributed to several mechanisms, including the different inflammatory responses and the related oxidative stress across patients. Therefore, *in vitro* studies of patient-specific response to anti-inflammatory/ antioxidant compounds under infection could help elucidate the role of chronic inflammation and oxidative stress in drug resistance in order to develop personalized combination therapies.

Essential methods

We performed a dose-response evaluation of 10 anti-inflammatory compounds in pre-clinical and clinical stages using CFBE cells. We analyzed the inflammatory and oxidative status by detecting specific markers. We investigated the gene expression and protein release of pro-inflammatory cytokines (using RT-qPCR and ELISA assays) and the antioxidant activity of these drugs by measuring intracellular ROS levels (using a ROS-sensitive fluorescent probe) in F508del-CFTR CFBE cells under inflammatory conditions.

Preliminary results

Interestingly, we found that a few anti-inflammatory compounds, at specific doses, significantly reduced IL-6 and IL-8 cytokine levels (both mRNA and protein) in F508del-CFTR CFBE cells treated with IL-17A+TNFα. Other compounds, however, did not exhibit anti-inflammatory activity in the CFBE cell line. To further investigate the antioxidant activity of these compounds, we developed a high-throughput fluorometric assay to measure ROS levels using a ROS-sensitive fluorescent probe. We performed a dose-response drug screening to investigate their antioxidant activity. These compounds interestingly exhibited antioxidant activity, in a dose-dependent manner, in F508del-CFTR CFBE cells treated with H_2O_2.

Conclusions

During the first year, we identified a few good compounds acting as anti-inflammatories and antioxidants in the F508del-CFTR CFBE cell line.

Assessing the safety and clinical potential of GY971, an anti-inflammatory compound for cystic fibrosis

In the first pic, left to right, Giulio Cabrini, Ilaria Lampronti, Marco Prosdocimi and Adriana Chilin
In the second pic, Alessandra Bragonzi
In the third pic, Nicoletta Pedemonte
In the fourth pic, Sjoerd Hak

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Giulio Cabrini[1,2], Marco Prosdocimi[3,2], Sjoerd Hak[4], Ilaria Lampronti[1,2], Adriana Chilin[5,2], Alessandra Bragonzi[6], Nicoletta Pedemonte[7]

[1]Department of Life Sciences and Biotechnology, University of Ferrara, Italy - [2]Center on Innovative Therapies for Cystic Fibrosis, Department of Life Sciences and Biotechnology, University of Ferrara, Italy - [3]Foundation's Research Valorization Initiative team, FFC Ricerca, Verona, Italy - [4]Department of Biotechnology and Nanomedicine, SINTEF Trondheim, Norway - [5]Department of Biomedical Sciences, University of Padua, Padua, Italy - [6]Infection and Cystic Fibrosis Unit San Raffaele Scientific Institute, Milan, Italy - [7]UOC Genetica Medica, IRCCS G. Gaslini Institute, Genoa, Italy

(De-risking GY, new)

Background and rationale

Highly Effective CFTR Modulator Treatment (HEMT) has represented a breakthrough advancement in the treatment of people with cystic fibrosis (CF). However, clinical trials with Kaftrio showed that pulmonary inflammation is reduced but not halted, which implies the progression of lung damage. The anti-inflammatory drugs ibuprofen and azithromycin revealed adverse effects limiting their use. Novel effective and safe anti-inflammatory drug to be associated with HEMT is an unmet need in the cure of CF.

Hypothesis and objectives

Excessive recruitment of neutrophils in the lumen of CF bronchi is considered the main cause of lung damage, since neutrophils release enzymes that degrade protein structures (proteases), oxidizing reactive species and long DNA filaments, worsening the viscous CF surface liquid. Innovative anti-inflammatory strategies in trials are presently targeting one of these damaging mechanisms (neutrophil proteases). Our alternative strategy aims to downmodulate the excessive recruitment of neutrophils, thus the three harmful effectors, leaving active the anti-infective defences. The molecular target we devised is the excessive release of molecules that recruit neutrophils in the airways of CF. The anti-inflammatory molecule GY971, which we identified and propose for pulmonary delivery, European Medicines Agency designated Orphan Drug for CF, now needs to proceed to safety validation and development of formulations for pulmonary delivery.

Essential methods

Pre-clinical safety experiments will be developed in different steps (*in vitro* toxicity testing on different cell lines, *in vivo* pharmacokinetics and toxicology in rats, *in vivo* organ distribution in mice) with GY971 in new delivery formulations. The preservation of its anti-inflammatory efficacy will be tested in CF primary bronchial epithelial cells *in vitro* and in mice with pulmonary infection.

Preliminary results

The project is already based on a series of positive preliminary safety verifications of GY971 *in vitro*, already obtained at the Universities of Padua and Ferrara, results that are encouraging the extensive and thorough experiments to be performed by SINTEF.

Conclusions

The large series of positive pre-clinical results already obtained on the efficacy of GY971 as an anti-inflammatory molecule, which will be extended and accomplished in this project, will aim to provide solid bases for the clinical development of a novel anti-inflammatory drug for CF.

SESSION 4

The NTM challenge

Evaluation of the efficacy of the VOMG new antibiotic against *Mycobacterium abscessus*

In the first pic, Maria Rosalia Pasca (3rd from the left) with her collaborators
In the second pic, Riccardo Manganelli (at the top, 3rd from the right) with his collaborators
In the third pic, Fabio Saliu (3rd from the right) with his collaborators

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Maria Rosalia Pasca[1], Riccardo Manganelli[2], Fabio Saliu[3], Vadim Makarov[4]

[1]Department of Biology and Biotechnology Lazzaro Spallanzani, University of Pavia, Italy - [2]Department of Molecular Medicine, University of Padua, Italy - [3]Infection and Cystic Fibrosis Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy - [4]Bakh Institute of Biochemistry, Russian Academy of Science, Moscow, Russia

(FFC#9/2023, concluded; FFC#11/2025, new)

Background and rationale

Mycobacterium abscessus (Mab) is an emerging non-tuberculous mycobacterium (NTM) of clinical concern, particularly in individuals with cystic fibrosis (CF). Its treatment is complicated by intrinsic drug resistance, biofilm formation, and poor intracellular antibiotic efficacy. There is a critical need for novel, effective therapeutics. Through four projects funded by the Italian Cystic Fibrosis Research Foundation (FFC Ricerca), we identified VOMG, a promising new drug candidate, active *in vitro* against several NTM and other pathogens. It is water-soluble with high bactericidal activity against Mab growth, also *in vivo*. VOMG target is FtsZ cell division protein. Because of its physicochemical properties, it is suitable for novel drug delivery formulations, including aerosol inhalation.

Hypothesis and objectives

This study aimed to further study the mechanism of action of VOMG, to evaluate its intracellular and *in vivo* efficacy in combination with amikacin, and to develop relevant infection models.

Essential methods

We used microbiological and biochemical methods to reach the aims of the project.

Results

We optimized the CRISPR interference (CRISPRi) system for Mab and generated conditional mutants in genes involved in cell division (ftsZ, envC, steA, ftsQ, and sepF). The characterization of the FtsZ mutants confirmed its essentiality and it as VOMG target. We optimized both the Granuloma-like structure (GLS) assay and the macrophage monolayer models in Mab to evaluate drug activity. Among the tested antibiotics, clarithromycin and bedaquiline exhibited the highest efficacy. Although VOMG showed limited intracellular activity, its combination with amikacin enhanced antibacterial effects, consistent with the results achieved in two murine models of Mab infection.

Conclusions

These findings validate FtsZ as the VOMG target and support its further development as a therapeutic candidate.

Appendix (FFC#11/2025)

Future efforts will focus on enhancing intracellular delivery: in order to improve the bioavailability of VOMG, particularly in Mab-infected lungs, VOMG will be encapsulated in liposomes. The new VOMG formulation will be tested both in *ex vivo* assays and in Mab-infected murine models.

Fostering pathogen host-mediated clearance to neutralize *Mycobacterium abscessus* infection

Right to left: Edoardo Scarpa, Marta Zaccaria, Diego Rondelli e Anna Griego

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Anna Griego[1,2], Stefano Muzzioli[1,2], Marta Zaccaria[1,2], Diego Rondelli[1,2], Alessandra Altomare[3], Giancarlo Aldini[3], Nicola I. Loré[4], Loris Rizzello[1,2], Daniela Cirillo[4], Edoardo Scarpa[1,2]

[1]Department of Pharmaceutical Science, University of Milan, Italy - [2]National Institute of Molecular Genetics (INGM), Milan, Italy - [3]Phan Lan, Department of Pharmaceutical Science, University of Milan, Italy - [4]Emerging Bacterial Pathogens Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

(FFC#12/2023, concluded)

Background and rationale

Innate immune responses in macrophages are rapidly tuned by stimulus-dependent histone post-translational modifications (PTMs), yet how these chromatin changes interface with lipid metabolism and antigen presentation during nontuberculous mycobacterial infection remains unclear. We focused on histone H3 lysine 14 acetylation (H3K14ac), a modification associated with open chromatin and transcriptional activation, in alveolar-like macrophages (mAMs), the primary niche for *Mycobacterium abscessus* (Mab). Mab is a major cause of difficult-to-treat pulmonary disease in people with cystic fibrosis (pwCF), where chronic infection accelerates lung-function decline and complicates transplant eligibility, underscoring the need for host-directed strategies.

Hypothesis and objectives

This project focuses on understanding how H3K14ac remodulation could enhance AMs' capacity to hinder Mab infection by shifting their polarization from a permissive to an eradicating phenotype.

Essential methods

Using single-cell high-resolution confocal microscopy with multiparametric quantification, we mapped H3K14ac and MHC-II abundance in steady state, after pharmacologic histone Histone Deacetylase (HDAC) inhibition, and during early Mab infection. We complemented imaging with targeted transcriptomics and unbiased quantitative proteomics to define pathway-level shifts.

Results

At baseline, mAMs displayed intrinsic heterogeneity in both H3K14ac and MHC-II, consistent with phenotypic plasticity. Mab infection selectively reduced H3K14ac and MHC-II -most prominently in macrophages harboring intracellular bacilli- suggesting pathogen-driven repression of antigen-presenting capacity. To test whether increasing acetylation could counter this program, we applied Panobinostat, a broad HDAC inhibitor, at subclinical, non-cytotoxic concentrations (<100 nM). Panobinostat induced time-dependent gains in H3K14ac and shifted mAMs toward a pro-inflammatory-like state while increasing MHC-II abundance. Proteome-wide analysis revealed coordinated metabolic remodeling: contraction of lipid-storage programs with concordant expansion of catabolic/processing pathways, including lysosome, peroxisome, and fatty-acid oxidation. Consistently, lipid-droplet burden measured by confocal microscopy decreased following treatment. Crucially, in Mab-infected mAMs, Panobinostat reversed infection-induced H3K14ac loss and restored MHC-II, particularly within cells carrying intracellular bacteria. This epigenetic rescue was accompanied by diminished lipid accumulation and a measurable restriction of intracellular bacterial growth by colony-forming-unit enumeration, despite Panobinostat lacking direct antimycobacterial activity. These data delineate a tunable epigenetic–metabolic circuit in alveolar macrophages in which HDAC activity couples chromatin state to lipid handling and antigen presentation.

Conclusions

Given the lipid-rich, inflamed, and infection-prone airway milieu characteristic of CF, our findings suggest that targeted chromatin modulation could complement antibiotics to rebalance macrophage metabolism and enhance antigen presentation in pwCF with Mab disease. More broadly, they highlight H3K14ac dynamics as a mechanistic lever for host-directed intervention against bacterial strategies that suppress immune function without directly targeting the pathogen.

Phenotypic medicinal chemistry approaches to identify new anti-*Mycobacterium abscessus* agents

Left to right: Serena Massari, Giuseppe Manfroni, Stefano Sabatini, Violetta Cecchetti, Maria Letizia Barreca

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Stefano Sabatini[1], Laura Rindi[2]

[1]Department of Pharmaceutical Sciences, University of Perugia, Italy - [2]Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, Italy

(FFC#10/2024, ongoing)

Background and rationale

Mycobacterium abscessus (Mab) is a rapidly growing nontuberculous mycobacterium associated with several diseases in humans, of which lung disease is the most common as in people with CF. The treatment of this pathogen represents a challenge due to the multi-drug-resistant nature of this species.

Hypothesis and objectives

The project aims to contrast Mab spread by a two-pronged strategy involving phenotypic medicinal chemistry approaches. In the first strategy we would exploit our in-house library of antimicrobial compounds in search of Hits endowed of anti-Mab activity. The second one will take advantage from High Throughput Screenings (HTSs) already reported in literature, selecting Hit compounds not yet developed by other medicinal chemistry groups. The identified Hit compounds hopefully will be optimized in potent and safe anti-Mab Lead compounds and then preclinical candidates.

Essential methods

Once anti-Mab Hit compounds will be emerged from the screening against Mab ATCC19977, an iterative cycle of chemical modification/biological evaluation will start with the aim of improve anti-Mab activity, cytotoxicity and ADME-Tox profile to obtain validated Hit compounds ready for studies on clinical isolates (MIC, antibiofilm activity and intracellular activity on THP-1 infected cells).

Preliminary results

In the first year of research a total of 117 compounds have been tested for anti-Mab activity (MIC) against Mab ATCC19977 strain (11 quinolone drugs, 44 quinolone/quinolone-like compounds, 16 drugs/compounds reported as endowed of anti-Mab activity, 20 drug/drug-like compounds for repurposing approach, 2 newly synthesized M20 analogues, 4 synthesized ID-1 derivatives/intermediates, and 20 niclosamide analogues). 27 compounds have been synthesized (3 quinolone, 4 indenone, and 20 niclosamide analogues) with 3 different synthetic strategies. 8 Hit compounds were identified/confirmed (3 quinolone/quinolone-like compounds, 4 drugs/compounds already reported as endowed of anti-Mab activity, 1 by the repurposing approach). Currently, 4 hit compounds are under evaluation for anti-Mab activity (MIC) against clinical isolates.

Conclusions

The antibiofilm and intracellular activity we would obtain with the anti-Mab Lead compounds can improve the killing efficacy and reduce the time of treatment with future benefits for Mab infected people with CF.

SESSION 5

Flash Presentation: FFC Ricerca Facilities and New Projects

FFC Ricerca Research facilities: the Cystic Fibrosis Animal Core Facility (CFaCore)

Left to right: Martina Rossano, Davide Gugliandolo, Ida Defino and Alessandra Bragonzi

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Ida De Fino, Davide Gugliandolo, Martina Rossano, Alessandra Bragonzi

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Background and rationale

Treating bacterial infections and inflammation remains a top priority for the cystic fibrosis (CF) community, as these are key challenges in people with CF, regardless of the availability of CFTR modulator treatments. Within this area, FFC Ricerca supports studies focused on identifying and validating new antibacterial and anti-inflammatory therapies, which require testing in pre-clinical animal models to advance translational research.

Objectives

The Cystic Fibrosis animal Core Facility (CFaCore) was established to support research by offering dedicated scientific and regulatory expertise. It provides models within a preclinical platform designed to study pathological processes and evaluate candidate therapeutic molecules aimed at reducing infection or inflammation, thus facilitating the development of new drugs.

Resources and services

Consolidated experience in research, state-of-the-art infrastructures and innovation capacity are our core values. Our team has developed mouse models for both acute and long-term chronic infections and continues to enhance the CFaCore with new models to meet evolving research needs. We have defined protocols and endpoints to ensure the predictive value and preclinical relevance of drug testing. Specifically, we offer: i) access to pre-clinical models of acute and chronic respiratory infections, utilizing reference and clinical bacterial strains, as well as transgenic cystic fibrosis mice; ii) customized experimental protocols, including systemic or aerosol pharmacological delivery, tailored to each project's needs; iii) comprehensive read-outs and data analysis, covering both the pathogen and host response, including lung function measurements. Clear milestones are set for each project to ensure efficient progress toward the overall goal. Our vision is to foster a truly collaborative effort to achieve tangible impacts for the benefit of patients.

FFC Ricerca Research facilities: the Cystic Fibrosis Database (CFDB)

From the left Valeria Raia, Donatello Salvatore, Natalia Cirilli, Roberto Buzzetti, Alessio Daniele

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Roberto Buzzetti[1], Natalia Cirilli[2], Valeria Raia[3], Donatello Salvatore[4], Alessio Daniele[5]

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Background and rationale

The Cystic Fibrosis Database (CFDB), active for about fifteen years, is a free web tool that allows healthcare professionals, researchers, and students to evaluate the current scientific evidence on the clinical effectiveness of interventions in cystic fibrosis. The CFDB includes over 1,400 articles: more than 100 Cochrane reviews; approximately 90 other reviews (systematic reviews, HTA reports, and economic analyses); over 1,100 primary studies, including 950 randomized studies; and 80 ongoing studies from major clinical trials registries. CFDB can be very useful for clinicians who wish to understand the effectiveness of interventions (e. g. the best antibiotic regimens, effective anti-inflammatory drugs, CFTR modulators, as well as numerous diagnostic, dietary, physiotherapy, and other interventions). Researchers can quickly consult the state of the art for different areas of cystic fibrosis research ("Topics"), obtaining a powerful and up-to-date synthesis. Patients and their families may also find it of interest although the language used in the scientific literature is not always easily understandable.
The database is freely accessible on the website www.cfdb.eu to the entire international scientific community.

Resources and services

What can we do with CFDB?
1 - Create a query by selecting terms from the search menus (using free text or keywords, by year, or by author).
2 - Select one or more citations and read a structured abstract for each article, including the type of study, participants, interventions, outcomes, results, and conclusions.
3 - Consult fifty up-to-date state-of-the-art summaries on the most relevant topics in cystic fibrosis. Each summary critically presents i) what is known: the current state of evidence, and ii) the unanswered questions: what remains to be clarified by future research.
For this reason, CFDB can be considered a concise compendium of evidence-based medicine in cystic fibrosis.

FFC Ricerca Research facilities: the Primary Cell Cultures Service (SCP)

Valeria Capurro

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Valeria Capurro[1], Luis J. V. Galietta[2]

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Background and rationale

The Primary Cell Culture Facility has been active since 2012, established through a collaboration between the Italian Cystic Fibrosis Research Foundation (FFC Ricerca) and the Medical Genetics Laboratory of the Giannina Gaslini Institute. The facility provides researchers with a collection of primary human bronchial epithelial cells (HBECs), obtained from both cystic fibrosis (CF) and non-cystic fibrosis (non-CF) bronchial tissues.

Objectives

The main goal of the Facility is to offer researchers within the FFC Ricerca network, as well as those supported by CF-related grants, the most relevant biological model of the airway epithelium for studies focusing on: i) the physiology of the airway epithelium and the defects arising from CFTR dysfunction; ii) the evaluation of pharmacological and genetic therapies designed to correct the underlying CF defect; iii) the interactions between bacteria and epithelial cells, as well as the mechanisms driving the inflammatory response.

Resources and services

The Facility isolates HBECs from explanted bronchi, expands them in culture, and produces large stocks of cryopreserved cell aliquots. Over time, it has built an extensive collection that includes a wide range of CF genotypes and samples from numerous non-CF donors. Frozen aliquots of these cells are available upon request and are supplied together with the specific culture medium required for experimental use. To obtain access, researchers must submit a request form including a brief description of the intended experiments, which allows assessment of their technical feasibility. The Facility also provides its users with: i) a detailed protocol for the correct culture and handling of the supplied cells; ii) the possibility for interested researchers to carry out a period of training at the Facility laboratories; iii) the technical and scientific expertise of Facility staff. Additionally, an Advanced Service is available upon request, offering fully differentiated, ready-to-use epithelial tissues, shipped under refrigerated conditions and embedded in a solid support medium to preserve their integrity.

Damage and repair mechanisms in epithelial tissues in cystic fibrosis

Margarida Amaral (front row, fourth from the right), Ines Pankonien (back row, third from the left), Cláudia Rodrigues (back row, first from the left), with their collaborators

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Margarida D. Amaral[1], Ines Pankonien[1], Cláudia S. Rodrigues[1], Emanuela Pesce[2], Emanuel Gonçalves[3]

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(FFC#1/2025, new)

Background and rationale

The approval of CFTR modulators (CFTRm) has significantly increased life expectancy for people with cystic fibrosis (pwCF). However, as this population ages, new challenges emerge, including a higher prevalence of gastrointestinal complications. Besides its function as anion channel, CFTR has emerged as a regulator of other key cellular processes, e.g., epithelial differentiation/polarization, regeneration, and epithelial-mesenchymal

transition (EMT). We revealed that CFTR loss of function (LoF) in CF epithelia drives active EMT, namely disrupted cell junctions, elevated mesenchymal markers and EMT-transcription factors (TF), impaired wound healing, and lower resilience to pro-inflammatory stimuli. We found that these changes are mediated by EMT-TF TWIST1 and identified TF YAP1, a master regulator of EMT, as aberrantly active in F508del-CFTR expressing cells. Current CFTRm do not fully revert these defects. Such findings suggest that functional CFTR helps maintain epithelial integrity and, in its absence in CF, regeneration is impaired. However, the molecular mechanism remains unclear.

Hypothesis and objectives

Our hypothesis is that functional CFTR prevents EMT and that in CF this protective role is lost. The main objective of the project is to advance our mechanistic understanding of how dysfunctional CFTR leads to EMT and impaired regeneration in CF.

Essential methods

We will analyse primary human airway cells and patient-derived intestinal organoids (PDIOs) by transcriptomics/proteomics to deeply explore cellular and molecular changes. Multi-omics data integration by bioinformatics will identify key pathways, cell trajectories and fate, transcriptional switches, and also novel therapeutic targets.

Preliminary results

Our preliminary data show that CFBE cells expressing defective, but plasma membrane (PM) located p.Gly551Asp-CFTR have improved junction organization and polarization vs F508del-CFTR cells, in which CFTR does not reach the PM. Hence, EMT progression seems to depend not only on CFTR function but also on its cell surface presence.

Conclusions

This project will advance the mechanism of how CFTR LoF leads to EMT and deterioration of epithelial integrity. The expected results have the potential to unravel novel strategies for predicting and preventing epithelial dysfunction-related complications in pwCF, like cancer.

An antisense oligonucleotide-based strategy for the rescue of CFTR stop and splicing mutations

Debora Baroni

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Debora Baroni[1], Mirko Pinotti[2]

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(FFC#2/2025, new)

Background and rationale

Cystic fibrosis (CF) arises from CFTR gene mutations; more than 2,000 variants are known. Nonsense (~8%) and splicing (~10%) mutations yield absent or minimal CFTR protein and remain largely unresponsive to current modulators. Antisense oligonucleotides (ASOs) can modulate RNA splicing, stabilize transcripts and restore the reading frame, enabling the production of functional CFTR isoforms.

Hypothesis and objectives

We hypothesize that ASOs, alone or combined with CFTR modulators such as Kaftrio (elexacaftor/tezacaftor/ivacaftor), can rescue mutant CFTR mRNA and increase functional protein in genotypes with nonsense or splicing defects. Our objectives are to: i) design mutation-directed ASOs; ii) quantify effects on mRNA, protein maturation, and epithelial function; iii) validate lead ASOs in patient-derived airway epithelial preparations *in vitro*.

Essential methods

We will design ASOs targeting CFTR pre-mRNA and assess their ability to rescue mutant transcripts and increase CFTR protein expression and function in human airway epithelial cell lines. Candidate ASOs will be tested for specificity to ensure they do not interfere with native CFTR expression. To confirm therapeutic potential, patient-derived human bronchial (HBE) and nasal (HNE) epithelial cells carrying homozygous or heterozygous nonsense or splicing mutations will be used to evaluate the effects of lead ASOs on CFTR-mediated transepithelial ion and fluid transport, as well as key airway surface liquid (ASL) properties, including pH, protein concentration, osmolarity, and viscosity.

Preliminary results

We designed and tested two ASO pairs targeting exons 19 and 23 of CFTR pre-mRNA, where the R1162X and W1282X nonsense mutations are located. In 16HBEge bronchial epithelial cells harboring these mutations, ASOs drove mutation-specific exon skipping. The resulting transcripts were in-frame and NMD-resistant, yielding mature Δex19 and Δex23 CFTR. Combination with elexacaftor/tezacaftor/ivacaftor further increased mature protein abundance. In differentiated R1162X and W1282X 16HBEge epithelia, ASOs improved CFTR-dependent ion and fluid transport and reduced ASL viscosity.

Conclusions

ASO-mediated exon skipping emerges as a precision strategy for CF genotypes poorly served by CFTR modulators. This project aims to further develop ASO-based strategies, potentially paving the way for novel therapeutic approaches for CF.

Optimizing gene therapy and delivery systems for CF untreatable mutations

Left to right: Marianne Carlon, Anna Cereseto, Laurens Ceulemans, Federico Mingozzi

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Laudonia Lidia Dipalo[1,2], Alessandro Umbach[3], Giulia Maule[3], Pheline Kortleven[1,2], Mattijs Bulcaen[1,2], Kasper Gryspeert[1], Jan Van Slambrouck[1,4], Annalisa Barbarossa[1,4], Sam Thierie[1], Maxime Smits[2], Anabela S. Ramalho[5], François Vermeulen[5,6], Rik Gijsbers[2], Marjolein M. Ensinck[1], Federico Mingozzi[7], Laurens J. Ceulemans[1,4], Anna Cereseto[3], Marianne S. Carlon[1]

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(FFC#3/2025, new)

Background and rationale

Recent advances in genome editing (GE) and delivery methods renew hope for gene therapy in cystic fibrosis (CF), especially for modulator-ineligible (MI) CFTR mutations. Key challenges remain, notably the large size of GE tools limiting delivery efficiency.

Hypothesis and objectives

We hypothesize that compact GE tools will i) improve packaging into delivery vehicles like lipid nanoparticles (LNPs), and ii) reduce particle size, enhancing delivery to airway epithelial cells (AECs). We aim to develop small base editors for MI CFTR mutations and test novel LNPs for lung delivery. We will compare compact nuclease-derived base editors to standard ones and assess LNP toxicity. This 3-year project has two goals: i) develop GE strategies for undruggable CF mutations (R553X, 1717-1G>T), and ii) study LNP targeting of AECs using advanced lung models.

Essential methods

We will engineer base editors using small RNA-guided nucleases with broad PAM recognition to improve LNP loading and CFTR targeting. LNP-184, developed by Nava Tx, will be tested for packaging and delivery. We will compare its performance to larger SpCas-ABE editors. Editing efficacy will be evaluated in CF cell lines (HEK293T, 16HBEge-R553X) and primary AECs. To profile LNP-184 targeting, we will use advanced models: i) differentiated CF/non-CF human nasal epithelial (HNE) mono-/co-cultures with lung endothelial cells, and ii) a rat *ex vivo* lung perfusion (EVLP) model. These models allow mechanistic study of delivery barriers, especially via systemic administration. Inflammation will be monitored post-LNP-184 delivery using pulmonary compliance and scRNAseq to assess early tolerability.

Preliminary results

1. Nava Tx developed lung-tropic LNPs via *in vivo* screening in primates.
2. The Cereseto group identified novel GE tools from microbiome metagenomes.
3. Cereseto & Carlon groups achieved efficient base editing of R553X and 1717-1G>A in patient-derived cells.
4. Carlon lab developed translational lung models: HNE mono-/co-cultures and rat EVLP with real-time inflammation monitoring (Ceulemans group).

Conclusions

We aim to develop compact base editors delivered via lung-tropic LNPs for functional CFTR correction. Specifically, we target GE strategies for undruggable CF mutations and efficient LNP delivery to CF AECs via IV administration.

Pharmacological approaches to target nonsense mutations in cystic fibrosis

Left to right: Luis J. V. Galietta, Daniela Guidone, Martina De Santis, Anna Borrelli, Arianna Venturini, Michele Genovese

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Luis J. V. Galietta

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(FFC#4/2025, new)

Background and rationale

People with cystic fibrosis (CF) with nonsense mutations, also known as premature termination codons (PTCs), are insensitive to drugs (correctors, potentiators) that correct the defect of other CF mutations. There are already several small molecules with the ability to target PTC-associated biological processes, such as the nonsense-mediated RNA decay (NMD) and the translational machinery. It is important to test these agents on different PTCs to find the most effective treatment. We also found evidence that pro-inflammatory stimuli *in vitro* improve the rescue of CFTR with PTCs.

Hypothesis and objectives

We hypothesize that the combined modulation of targets having complementary mechanisms of action may result in additive/synergic effects, leading to a substantial rescue of CFTR function, thus correcting the basic defect. Our overall objective is to find optimal pharmacological treatments for each mutation or group of mutations. In this respect, we previously demonstrated that CF-causing PTCs do not respond equally to treatments but require a tailored approach.

Essential methods

Our project aims at identifying pharmacological treatments to correct the basic defect in people with CF with PTCs. We will use both primary bronchial/nasal epithelia from patients and the 16HBE14o- cell line to test the effect of treatments on CFTR rescue at the functional and protein level. These cell types will also be used to clarify the mechanism of inflammatory cytokines.

Preliminary results

We recently identified by high-throughput screening three novel NMD inhibitors which can be particularly suited for the rescue of W1282X and other PTCs localized at the terminal region of the CFTR coding sequence. We also found that *in vitro* pro-inflammatory stimuli amplify the rescue of CFTR with PTCs obtained with pharmacological agents. The study of the underlying effect of cytokines may reveal novel targets for CFTR rescue.

Conclusions

We anticipate that our results will reveal small molecules, mechanisms, and targets important for the correction of the basic defect in CF patients with PTCs.

Characterization of protein kinase D1 as a novel regulator of CFTR trafficking and stability

Left to right: Emilio Hirsch, Marco Mergiotti and Alessandra Ghigo

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Marco Mergiotti[1], Angela Della Sala[1], Alessandra Ghigo[1,2], Emlio Hirsch[1,2]

[1]Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Italy - [2]Kither Biotech S.r.l.,Turin, Italy

(FFC#5/2025, new)

Background and rationale

Cystic fibrosis (CF) is caused by mutations in the CFTR gene, impairing chloride and water transport. CFTR modulators such as Kaftrio (elexacaftor/tezacaftor/ivacaftor) have improved therapy, but only partly restore CFTR function, leaving patients with symptoms and complications. For this reason, new therapeutic strategies are needed. Our group has identified protein kinase D1 (PKD1), a cAMP effector, as a previously unexplored regulator of CFTR trafficking and stability at the plasma membrane, thus indicating PKD1 targeting as a new therapeutic avenue.

Hypothesis and objectives

We hypothesize that PKD1 is a regulator of CFTR trafficking and stability. The project aims to define how PKD1 controls secretion and membrane stability of mutant CFTR, focusing on F508del and rare class VI mutants, and to validate its functional impact in CF models by testing whether PKD1 activation can boost Kaftrio efficacy in F508del-CFTR and stabilize class VI mutants.

Essential methods

We will use biochemical assays and live-cell imaging to study PKD1 mechanisms. Functional outcomes will be assessed by YFP-quenching and short-circuit current measurements in Ussing chambers. Experiments will be performed in CF cell lines and in primary airway epithelial cells. PKD1 activation will be induced by a PI3Kγ mimetic peptide.

Preliminary results

Preliminary data demonstrate that combining Kaftrio with a PI3Kγ mimetic peptide markedly increases the abundance of F508del-CFTR at the plasma membrane compared to Kaftrio alone. This effect translated into functional improvement, since primary airway epithelial cells from patients treated with Kaftrio plus the peptide showed significantly higher chloride currents than those treated with Kaftrio alone. Crucially, when PKD1 activity was pharmacologically inhibited, the increase in membrane expression elicited by the peptide was completely abolished. These findings establish PKD1 as a central player in the regulation of CFTR trafficking and stability and provide a strong basis for the current project.

Conclusions

This project will clarify the role of PKD1 in CFTR regulation and assess its potential as a therapeutic target. By enhancing Kaftrio efficacy in F508del-CFTR and stabilizing rare class VI mutants, PKD1 activation could broaden the benefits of modulators and lay the basis for future PKD1-targeting therapies.

Exploring the dual function of Esc peptides and their derivatives as CFTR potentiators and antimicrobial agents

In the first pic, Maria Luisa Mangoni (third from the right) and her collaborators
In the second pic, Loretta Ferrera
In the third pic, Mattia Mori

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Maria Luisa Mangoni[1], Loretta Ferrera[2], Mattia Mori[3]

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(FFC#6/2025, new)

Background and rationale

CFTR is an anion channel controlling chloride and bicarbonate transport in epithelial cells. Variants in the CFTR gene cause cystic fibrosis (CF) by impairing channel function through different mechanisms. The most common, F508del, leads to trafficking and gating defects, while mutations such as G551D and G1349D alter channel opening. Impaired ion transport in airways results in thick mucus that traps pathogens, mainly *Pseudomonas aeruginosa* and *Staphylococcus aureus*, promoting chronic infection and lung damage. Although CFTR modulators (correctors and potentiators) like Kaftrio have significantly improved lung function, ~15% of patients lack effective therapies, and persistent infections remain a major challenge. We identified frog-skin-derived antimicrobial Esc peptides, Esc(1-21) and its diastereomer Esc(1-21)-1c, which eradicate *P. aeruginosa* in planktonic and biofilm forms, enhance airway epithelial wound repair, and unexpectedly potentiate the activity of defective CFTR (F508del, G551D), likely via direct channel interaction.

Hypothesis and objectives

Considering Esc peptides and isoforms as promising dual-function candidates to restore CFTR activity and combat lung infections in CF, the project aims to: i) test their potentiator effect on CFTR gating mutants (especially those refractory to current modulators) and investigate synergy with existing modulators, ii) study their interaction with CFTR to uncover the mechanism of action, and iii) evaluate their antibacterial activity in CF-like lung conditions.

Essential methods

A multidisciplinary approach combining electrophysiological, biochemical, cell biology and computational methods, as well as mouse models for *in vivo* studies.

Preliminary results

We showed that Esc peptides and the alpha-aminoisobutyric acid (Aib) analogue significantly enhance F508del and gating-mutant CFTR activity, likely by stabilizing the open state of the channel. Cross-linking experiments confirmed peptide binding at predicted sites in the nucleotide-binding domains of CFTR. The Aib analogue was also found to be active against *S. aureus* without cytotoxicity. Both Esc(1-21)-1c and this analogue outperformed colistin in CF-like mouse lungs.

Conclusions

While therapies like Kaftrio and ivacaftor improve outcomes for many patients, some mutations remain resistant, leaving individuals with no effective options. We expect to identify the best combined therapy based on Esc peptides and CFTR modulators, to restore CFTR function and treat *P. aeruginosa*/*S. aureus* infections, thereby improving outcomes and quality of life of people with CF through airway administration.

Unconventional approaches to combat cystic fibrosis bacteria

Marta Mellini (second from the left) and her collaborators

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Marta Mellini

Department of Science, University of RomaTre, Roma, Italy

(GMSG#1/2025, new)

Background and rationale

The survival rate of people with cystic fibrosis (CF) has increased considerably with the introduction of modulator therapies for a subset of cystic fibrosis transmembrane regulator (CFTR) mutations. However, airway infections remain a major challenge for people with CF. The CF lung hosts complex microbial communities, and lifelong antibiotic treatments drive the emergence of multidrug-resistant (MDR) pathogens, severely limiting current therapeutic options.

Hypothesis and objectives

Conventional antibiotics are derived from microbial products for which resistance mechanisms have already spread in nature. In contrast, xenobiotic agents, as Peptide Nucleic Acids (PNAs), are unlikely to encounter pre-existing resistance mechanisms. PNAs are DNA mimics that stably interact with complementary RNA, thereby preventing their translation. PNAs resist enzymatic degradation and evade existing resistance mechanisms, constituting promising antimicrobial candidates. On this basis, this project aims to develop broad-spectrum PNAs targeting conserved essential genes shared by CF pathogens.

Essential methods

Over three years, this project will pursue the proposed objective by: i) *in silico* identification of "universal" targets through comparative genomic analysis of CF pathogens; ii) design of PNAs based on the results of *in silico* analyses, and screening through *in vitro* transcription/translation assays; iii) conjugation of selected PNAs with Cell Penetrating Peptides (CPP) to enhance uptake into bacterial cells, and validation of CPP-PNAs broad-spectrum antibacterial activity by using standard assays (e.g. MIC, MBC, biofilm formation); iv) evaluation of CPP-PNAs toxicity in pulmonary epithelial cell lines; v) *in vivo* validation of their efficacy in a mouse model of lung infection.

Preliminary results

CPP-conjugated PNAs targeting essential prokaryotic RNAs have already shown potent antibacterial activity against several bacteria, including CF pathogens. The PI has previously contributed to a project aimed at developing broad-spectrum PNAs against multiple MDR pathogens, identifying candidates with promising antibacterial activity.

Conclusions

The project has the potential to deliver CPP-PNAs with antimicrobial activity against multiple CF pathogens, paving the way for candidates suitable for future clinical trials.

Exploiting *P. aeruginosa*'s zinc dependency to potentiate antibiotic activity

In the first pic, Andrea Battistoni and his collaborators
In the second pic, Luigi Scipione and his collaborators

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Andrea Battistoni[1], Luigi Scipione[2]

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(FFC#7/2025, new)

Background and rationale

The ability of *Pseudomonas aeruginosa* to thrive in the lungs of people with cystic fibrosis (CF) is dependent on its noteworthy ability to acquire zinc (Zn) and evade the immune responses that limit accessibility to this metal. This capability depends on the secretion of zincophores of the opine family, which scavenge Zn from the extracellular environment. Such a mechanism of Zn uptake offers possibilities to exploit a "Trojan horse" strategy to enhance antibiotic delivery, overcoming key resistance mechanisms in CF pathogens.

Objectives

This project aims to characterize Aztreopine, an Aztreonam-zincophore conjugate developed in a recent FFC Ricerca pilot study and assess its preclinical efficacy. Additionally, we will apply the same Trojan horse approach to develop new antibiotic-zincophore conjugates against *P. aeruginosa*.

Essential methods

We will validate Aztreopine as an effective antimicrobial for *P. aeruginosa* infections by optimizing its synthesis and testing its efficacy against clinical isolates, including Aztreonam-resistant strains. We will assess ZrmA receptor conservation in CF isolates and evaluate cytotoxicity in human lung epithelial cells. Preclinical efficacy will be validated in mouse lung infection models. Additionally, we will expand this strategy by generating novel Trojan horse antibiotics targeting *P. aeruginosa*, by conjugating additional antibiotics to the same zincophore moiety used for the synthesis of Aztreopine.

Preliminary results

Pilot studies identified Zn uptake as a drug delivery target. We synthesized Aztreopine, a conjugate of Aztreonam with a simplified form of the zincophore pseudopaline. It showed strong activity against *P. aeruginosa* in Zn-limited conditions, outperforming Aztreonam alone. The specificity of the drug was demonstrated by its ineffectiveness against mutants defective in the zincophore receptor. Aztreopine also reduced biofilm formation and exhibited efficacy in *Galleria mellonella*.

Conclusions

Targeting Zn acquisition presents a promising strategy to combat resistance, offering pathogen-specific treatments with reduced toxicity and enhanced efficacy. This project will provide preclinical validation of Aztreopin and yield new Trojan horse antibiotics against resistant *P. aeruginosa*

Targeting *Pseudomonas aeruginosa* virulence factors to counteract infections in cystic fibrosis

Francesco Imperi (third from the left) and his collaborators

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Francesco Imperi[1], Giorgio Giardina[2], Antonio Coluccia[3]

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(FFC#/10/2025, new)

Background and rationale

Pseudomonas aeruginosa lung infection contributes to progressive lung damage in people with cystic fibrosis (CF). Antibiotic resistance and biofilm-associated persistence of *P. aeruginosa* limit the efficacy of antibiotic therapies. Antivirulence strategies offer an alternative treatment option, targeting bacterial virulence rather than growth, reducing selective pressure for resistance, and enhancing host immune clearance. Recent studies have identified the intracellular signaling molecule diadenosine tetraphosphate (Ap4A) as a key regulator of *P. aeruginosa* virulence, with the Ap4A hydrolase ApaH playing a central role in this pathway.

Hypothesis and objectives

The rationale of the project is that pharmacological inhibition of ApaH can significantly reduce *P. aeruginosa* virulence, providing a new strategy to treat lung infections in CF individuals. The main objectives are i) characterization of druggable sites on ApaH, ii) identification of putative ApaH-targeting compounds, and iii) *in vitro* and *in vivo* validation of ApaH inhibitors.

Essential methods

Molecular docking, site-specific mutagenesis, and fragment-based crystal screening will be carried out to identify and characterize ApaH druggable sites. Structure-based virtual screenings will be performed to identify potential inhibitors of ApaH. Biochemical assays and virulence factor analysis in *P. aeruginosa* reference and CF strains will be conducted to validate the putative ApaH inhibitors both *in vitro* and *in vivo*.

Preliminary results

Recently, we demonstrated that ApaH inactivation leads to a drastic reduction in the expression of key virulence traits in both reference and CF strains, significantly impairing *P. aeruginosa*'s ability to cause infection in different experimental models. We also performed a structural characterization of ApaH, providing a foundation for inhibitor design. Additionally, we developed enzymatic and virulence assays for testing potential ApaH inhibitors.

Conclusions

In this one-year project, we aim to identify small molecules that inhibit ApaH and attenuate *P. aeruginosa* virulence. These compounds will constitute the first *in vivo* validated inhibitors of ApaH and will serve as lead molecules for further optimization and/or preclinical evaluation.

Tracking lung infections via gut microbiota

Left to right: Cristina Cigana, Valeria Daccò and Barbara Kahl

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Cristina Cigana[1], Valeria Daccò[2], Barbara Kahl[3]

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(FFC#13/2025, new)

Background and rationale

CFTR modulators, including Kaftrio, have improved survival in people with cystic fibrosis (pwCF) but cannot reverse established lung damage, leaving respiratory infections and inflammation unresolved. Reduced sputum production further limits the timely detection of pathogens. There is a need for innovative, non-invasive strategies to monitor infections. Emerging evidence points to a gut–lung axis in CF, with the gastrointestinal tract potentially serving as a reservoir for bacteria relevant to airway disease.

Hypothesis and objectives

We hypothesize that fecal samples from pwCF may contain bacterial pathogens also present in the lungs, and could serve as a surrogate for airway infection diagnosis. The objective is to test whether fecal analysis provides a simple, reliable, and non-invasive tool for detecting and monitoring lung infections, particularly in pwCF treated with Kaftrio.

Essential methods

Three groups will be enrolled: i) pwCF chronically colonized by *Pseudomonas aeruginosa* and not on modulators, ii) pwCF never colonized by *P. aeruginosa* and not on modulators (negative controls), iii) *P. aeruginosa*–colonized pwCF on Kaftrio. Respiratory (sputum, oropharyngeal swab, induced sputum) and fecal samples will be collected in parallel. Pathogens will be identified by culture and, when negative, by shotgun metagenomic sequencing. Strain relatedness between fecal and respiratory isolates will be assessed. Particular attention will be given to *P. aeruginosa*, the main pathogen guiding pwCF stratification, on which phenotypic traits such as biofilm formation, virulence, and antibiotic susceptibility will be primarily assessed. Other CF-relevant bacteria will also be monitored.

Preliminary results

In CF mouse models, gut barrier dysfunction, enteric bacterial overgrowth, and shared lung–gut microbiota were observed. Pilot data in pwCF showed identical bacterial strains in fecal and sputum samples, supporting the feasibility of gut–lung crosstalk analyses.

Conclusions

This project will establish whether feces can serve as a non-invasive surrogate for monitoring respiratory infections. Expected results include improved early detection of *P. aeruginosa* and other pathogens, providing insights into host–microbe dynamics in CF. In the long term, this approach could enhance infection surveillance, guide personalized therapy, and improve quality of life.

Development of a combined therapy with bioactive liposomes encapsulating antibiotics to treat *M. abscessus* infection

Left to right: Noemi Poerio, Tommaso Olimpieri, Greta Ponzecchi, Marco Maria D'Andrea and Maurizio Fraziano

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Tommaso Olimpieri[1], Noemi Poerio[1], Fabio Saliu[2], Federica Vacca[2], Greta Ponsecchi[1], Fabiana Ciciriello[3], Marco Maria D'Andrea[1], Nicola Ivan Lorè[2], Federico Alghisi[3], Daniela Maria Cirillo[2], Maurizio Fraziano[1]

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(FFC#8/2025, new)

Background and rationale

Mycobacterium abscessus (Mab) is an opportunistic pathogen intrinsically resistant to most antibiotics, frequently linked to chronic pulmonary infections in people with cystic fibrosis (pwCF). We have previously described bioactive liposomes as a novel host-directed therapeutic tool able to enhance macrophages' antimicrobial response, leading to intracellular killing of multidrug-resistant (MDR) bacterial pathogens, while limiting inflammatory response. Recently, bioactive liposomes composed of phosphatidylserine (PS) and phosphatidic acid (PA), effective against *in vitro* Mab infections, have been optimized via microfluidics technique (PSPA-M liposomes) in terms of homogeneity, stability and scaling up properties.

Hypothesis and objectives

To develop PSPA-M liposome formulation, encapsulating Amikacin (PSPA-M/AMK), Clarithromycin (PSPA-M/CLR) or Azithromycin (PSPA-M/AZM), to combine the host-directed action, exerted by liposomes, with the pathogen-directed action, exerted by antibiotics, in a single, more active therapeutic formulation.

Essential methods

PSPA-M formulation was generated by microfluidics technique and characterized in terms of z-potential, size and polydispersity index, immediately after its production by using Zeta-Sizer. Possible PSPA-M cytotoxic effects were tested by cell viability assay on monocytes from healthy donor (HD) induced to differentiate into either type 1 (M1) or type 2 (M2) macrophages, both at 18 hours and 5 days after stimulation. Finally, both M1 and M2 from HD and primary macrophages derived by pwCF were *in vitro* infected with Mab and stimulated with PSPA-M for 18h. Treatment efficacy was assessed in terms of intracellular mycobacterial killing by CFU assay.

Preliminary results

PSPA-M liposomes are homogeneous and stable, do not induce any *in vitro* toxic effects and enhance intracellular bacterial killing in both M1 and M2 macrophages from HD and pwCF *in vitro* infected with Mab.

Conclusions

Development of a combined host- and pathogen-directed therapeutic strategy based on PSPA-M liposome encapsulating antibiotics that may i) specifically target intracellular pathogens in the lung, ii) improve the therapy regimen, and iii) reduce the antibiotic time of therapy with its related toxicity, for a better control of pulmonary MDR (myco)bacterial infections in pwCF.

Identification of novel drug targets in persistent *Mycobacterium abscessus* in cystic fibrosis

In the first pic, Elisabetta Iona, Federico Giannoni, Maria Cristina Gagliardi, Sabrina Mariotti, Angelo Iacobino, Alessio Lanni
In the second pic, Riccardo Manganelli, Roberta Provvedi, Francesca Boldrin, Shaiq Sultan, Davide Sorze, Enrica Campagnaro, Greta Segafreddo, Ilaria Bortoluzzi, Marlon Heggdorne de Araújo, Joao Victor Richa Reis

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Federico Giannoni[1], Riccardo Manganelli[2], Maria Cristina Gagliardi[1], Elisabetta Iona[1], Angelo Iacobino[1], Sabrina Mariotti[1], Alessio Lanni[1], Katia Fecchi[1], Roberta Provvedi[2], Davide Sorze[2], Francesca Boldrin[2]

[1]Istituto Superiore di Sanità, Rome, Italy - [2]Department of Molecular Medicine, University of Padua, Italy

(FFC#9/2025, new)

Background and rationale

Mycobacterium abscessus (Mab) is the most common nontuberculous mycobacterium species isolated in persons with cystic fibrosis (CF). Multidrug therapy for Mab infections is very long and frequently unsuccessful. Dormant and persistent cells are responsible for treatment failures and chronicity of the infection. Dormants arise from thick biofilm layers, whereas drug-resistant persisters are formed stochastically within Mab populations. Both forms are hard to eradicate.

Hypothesis and objectives

To combat Mab infections in CF, we need to address how these subpopulations are formed and survive killing doses of drugs in culture, in biofilm and inside host cells. The objective of this project is to identify specific genes responsible for persister formation, to study these genes in different conditions, and to test which drugs are active on these forms in the different conditions mentioned. Moreover, the generation of knock-out strains of genes up-regulated in persisters will shed light on mechanisms of persistence.

Essential methods

Mab ATCC 19977 strain is used in all experiments. All drugs are used at their maximum drug concentration (Cmax). RNA is extracted using a combination of cell disruption and kit purification and analyzed by qRT-PCR. Mab biofilm will be produced in 96-well MBEC Innovotech MBEC 96-well Assay Plates. Monocyte-derived macrophages and A549 human alveolar epithelial cells will be grown and used for Mab infection studies.

Preliminary results

We have performed RNAseq on Mab incubated with bedaquilin+amikacin (Bq+Ak), a combination that kills replicating bacteria, and compared gene expression to the untreated control. Overall, up to 250 genes were highly differentially expressed. Among these, we observed transcription factors, toxins/antitoxins, and anti-oxidative stress response genes. Some genes were strongly upregulated with Bq+Ak and activated in persisters generated with different drug combinations. We also tested some drug associations on Mab persisters with some promising results. RNA extracted from biofilm Mab cultures showed the activation of dormancy-related genes when compared to replicating Mab.

Conclusions

Finding new targets for drug development and new strategies in the therapy of Mab infections in CF is the main purpose of the project. Shortening the therapy, introducing the ability to kill dormant and persister cells will definitely improve the quality of life of people with CF.

Studying the immune system's response to nontuberculous mycobacterial infections

Nicola Ivan Lorè and his collaborators

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Francesca Nicola[1], Carla Chernichero[1], Chiara Ferrari[1], Gaia Saldarini[1], Mariagiulia Conte[1], Valeria Capurro[2], Francesco Blasi[3], Daniela Maria Cirillo[1], Camilla Margaroli[5], Stefano de Pretis[4], Andrea Gramegna[2], Nicola Ivan Lorè[1]

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(FFC#12/2025, new)

Background and rationale

People with cystic fibrosis (pwCF) are at high risk of developing serious lung infections, including those caused by NonTuberculous Mycobacteria (NTM). These bacteria can cause chronic lung disease, particularly in individuals with pre-existing lung problems. While new CF treatments have improved health outcomes, some patients still struggle with persistent infections, and others cannot access these treatments. Further, treatments for NTM are often unsuccessful and carry several side effects.

Hypothesis and objectives

This study aims to understand how the immune system of people with CF responds to NTM infections compared to those without CF. Researchers believe that pwCF have a unique immune response that may influence how the disease progresses. The study will focus on two main goals: i) identifying differences in immune system activation between CF and non-CF individuals with NTM infections; ii) examining how CF lung cells react when infected with NTM compared to non-CF lung cells.

Essential methods

This research will use advanced techniques (scRNAseq and *in vitro* models with human primary cells) to analyze immune cells and lung tissues to uncover key differences between CF and non-CF responses to NTM.

Preliminary results

Early findings suggest that people with CF have an overactive immune response to NTM, which might contribute to lung inflammation and damage.

Conclusions

The expected results could help identify markers of infection severity, leading to more personalized treatments. Ultimately, this work supports the mission of the Italian Cystic Fibrosis Research Foundation by improving our understanding of CF-related lung infections thus guiding the development of better treatments for those who do not benefit from existing therapies.

SESSION 6

Phages and fungi

Development of phage therapy for treating *Mycobacterium abscessus* lung infections in people with cystic fibrosis

Upper row, right to left: Luca Magnani, Andrea Bonacorsi, Laura Rindi, Mariagrazia Di Luca, Caterina Ferretti, Noemi Poma, Sjoerd Entius
Lower row, right to left: Elisa Fausti, Claudia Campobasso, Greta Amendola, Alessandro Fusco, Giacomo Tornabene, Sara Bolognini

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Andrea Bonacorsi[1], Alessandro Fusco[1], Davide Manessi[1], Fabio Filippini[2], Giovanni Delogu[3], Ivana Palucci[3], Michele Lai[2], Giulia Freer[2], Silvia Dominici[4], Federico Pratesi[4], Graham Hatfull[5], Arianna Tavanti[1], Andrea Moscatelli[6], Laura Rindi[2], Mariagrazia Di Luca[1]

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(FFC#6/2024, ongoing)

Background and rationale

Mycobacterium abscessus poses a major clinical challenge due to its extensive antibiotic resistance and intracellular persistence, especially in people with cystic fibrosis (CF). Bacteriophages represent a promising solution for treating infections caused by mycobacteria.

Hypothesis and objectives

This study aimed to characterize the *ex vivo* activity of Pisa4, a novel mycobacteriophage isolated using the non-pathogen Mycobacterium smegmatis mc²155 as host, as well as to genetically modify it in order to confer a strictly lytic phenotype, needed for clinical applications.

Essential methods

Ex vivo infection models were established using THP-1 macrophages and primary human neutrophils, and phage activity was analysed by bacterial plating, plaque assay and confocal laser scanning microscopy. Phage engineering was performed via the bacteriophage recombineering method with electroporated DNA.

Preliminary results

Among the mycobacteriophages of our phage library, Pisa4 was selected for its favourable characteristics for potential clinical applications, including the absence of known virulence and antibiotic resistance genes, rapid replication, high burst size, and stability under acidic conditions mimicking the phagosomal environment. Co-incubation of Pisa4 with *M. smegmatis* significantly increased intracellular phage particles in THP-1 cells observed by high-resolution imaging, which confirmed phage entry and co-localization with bacteria. However, post-infection treatment was ineffective, even though phages co-localized with the bacteria, likely due to bacterial metabolic reprogramming affecting phage replication. Notably, Pisa4 did not trigger neutrophil extracellular trap release by primary human neutrophils, indicating a favourable safety profile, particularly in the context of pathological conditions characterized by hyperinflammation, such as in CF. Activity against *M. abscessus* clinical isolates was observed in 8/49 strains, consistent with the narrow host range of mycobacteriophages. Molecular analysis of Pisa4 mutant phage confirmed the deletion of the immunity repressor gene, responsible for the establishment of the lysogenic cycle, conferring a strictly lytic phenotype.

Conclusions

These findings support Pisa4 as a promising candidate against susceptible mycobacteria, with ongoing studies exploring engineered phage efficacy and host immune responses. The strictly lytic Pisa4 phage might be applied in compassionate use to treat people with CF infected with Mab, after magistral preparation and ethics committee approval.

Facing resistance to therapeutic phages observed in *Pseudomonas aeruginosa* isolates from people with cystic fibrosis

Left to right: Francesca Forti, Federica Briani, Jimena Nieto Noblecia, Federica Falchi, Shila Shehu

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Alessandra Bosc[1], Shila Shehu[1], Allegra Laricchia[1], David S. Horner[1], Federica A. Falchi[1], Francesca Forti[1], Anna Pistocchi[2], Marco Cafora[2], Lisa Cariani[3] and Federica Briani[1]

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(FFC#16/2023, ongoing)

Background and rationale

This project is part of ongoing research with the final goal of making phage therapy a practicable option to cure the *Pseudomonas aeruginosa* (Pa) pulmonary infection in people with cystic fibrosis (CF). Since phages are extremely specific for their bacterial hosts, phage therapy requires a personalized approach, tailored to the susceptibility of the infecting bacterial strain to specific phages.

Hypothesis and objectives

The specific aims of this project are: i) to develop a collection of phages able to kill Pa CF isolates, which are frequently multi-phage resistant; ii) to assess whether Pa infections in patients treated with Kaftrio could be cured by the same phages active against isolates from untreated patients or require specific phages; iii) to understand mechanism determining phage resistance in CF isolates.

Essential methods

To reach the above aims, we have i) profiled phage susceptibility of Pa strains isolated before and at different times after the initiation of Kaftrio therapy; ii) characterized natural phages to assess their suitability for phage therapy; iii) modified the host range of natural phages through random approaches like UV mutagenesis and *in vitro* evolution; and iv) characterized new phage cocktails *in vitro* and *in vivo*, in a zebrafish model of Pa infection.

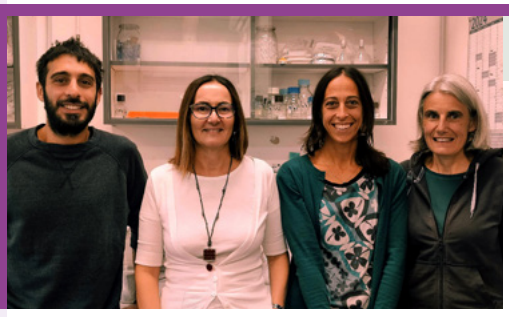
Results

The results obtained in the project are as follows: i) no correlation was found between the months of treatment with Kaftrio and the susceptibility to phages of new isolates from people with CF; ii) five phages potentially suitable for phage therapy have been identified through genomic and phenotypic characterization. Moreover, the mechanism of adsorption of DEV, a component of phage cocktails for phage therapy; has been clarified; iii) both UV mutagenesis of DEV phage and *in vitro* evolution of a two-phage cocktail confirmed to be effective in broadening phage host range towards CF clinical isolates.

Conclusions

With only a few months left before the project ends, we can say that we have achieved the main goal of obtaining phages with a relatively broad host range against clinical Pa strains.

Ex vivo pig lung as a new model to study the efficacy of phage therapy against *Pseudomonas aeruginosa* infection in cystic fibrosis



Marco Cafora (on the left) with Federica Briani, Anna Pistocchi and Francesca Forti

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Marco Cafora[1], Francesca Forti[2], Freya Harrison[3], Federica Briani[2], Anna Pistocchi[1]

[1]Department of Medical Biotechnology and Translational Medicine, University of Milan, Italy - [2]Department of Biosciences, University of Milan, Italy - [3]School of Life Science, University of Warwick (UK)

(GMRF#1/2023, ongoing)

Background and rationale

Colonization by *Pseudomonas aeruginosa* (Pa) drives the establishment of persistent biofilm infections in the lower airways of people with cystic fibrosis (pwCF). Yet, there is still a lack of standardized models capable of reproducing the features of *in vivo* mature biofilm. Most available *in vitro* models rely on abiotic surfaces and therefore provide limited translational relevance.

Hypothesis and objectives

This three-year project is embedded within a broader research effort to advance phage therapy as a therapeutic strategy for antibiotic-refractory Pa chronic lung infections in pwCF. In this perspective, there is a critical need for biofilm models that reliably recapitulate the physicochemical conditions of CF airways and support the development of clinically meaningful biofilm structures.

Essential methods

We established the *ex vivo* pig lung (EVPL) CF model, designed to mimic the environment of human CF airways. Swine bronchial tissue is incubated with artificial sputum medium reproducing the composition of CF airway secretions and subsequently challenged with a panel of Pa strains (both laboratory and clinical), allowing the growth of an extensive and thick *in vivo*-like biofilm. The anti-biofilm potential of phage preparations is then assessed through quantitative biomass measurements and qualitative microscopy analyses.

Preliminary Results

In previous projects, we isolated and characterized phages specific for Pa. In the EVPL model, phage treatment almost completely eradicated biofilms formed by laboratory strains, as demonstrated by a marked reduction in bacterial biomass. Phages also showed synergistic effects with commonly used antibiotics. In particular, combined treatment eradicated biofilms generated by clinical isolates from pwCF, regardless of Kaftrio therapy status. Our findings indicate that the efficacy of mono versus multi-phage formulations can vary depending on the specific Pa strain. Finally, phage treatment disrupted biofilm architecture and strongly inhibited matrix production.

Conclusions

The study underscores the potential of the EVPL CF model as a robust tool for assessing the activity of phages against Pa biofilms. Given the persistence of Pa, the development of effective phage-based strategies holds strong clinical relevance for pwCF. Furthermore, the implementation of this cost-effective, easy-to-use CF biofilm model may help accelerate the introduction of phage therapy towards clinical application.

Study on anti-fungal immunoglobulins, as a potential diagnostic biomarker and therapeutic values for Allergic Bronchopulmonary Aspergillosis in children with cystic fibrosis

Teresa Zelante (in the middle) between her collaborators

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Teresa Zelante

Department of Medicine and Surgery, University of Perugia, Italy

(FFC#15/2022, concluded)

Background and rationale

Despite being a widespread global disease, ABPA still lacks a clear understanding of pathogenesis, which limits the ability to be diagnosed and hinders the development of therapeutic strategies. Current treatments focus on reducing Th2 immunological response using corticosteroids and lowering fungal burden with the use of antifungal agents. Unfortunately, even if treated, many patients still suffer from active disease or frequent exacerbation, which poses a further health burden on patients who are often already compromised. In addition, existing therapies focus only on treating symptoms of ABPA, which forces therapies to always be reactionary, as ABPA lacks clear biological markers to predict the development and progression of the disease.

Hypothesis and objectives

By understanding how the cytokine pattern may affect isotype switch, we are identifying the induction of non-beneficial IgE responses depending on the type of cell immunity and therefore the cytokine microenvironment. Our interest is also focused on anti-fungal IgG with known anti-inflammatory role, also acting as a non-anaphylactic or "blocking immunoglobulin" against non-beneficial IgE responses. Pivotal, the role of IL-17F in shaping the IgE switch is investigated here.
Our objectives are: i) to understand the kinetics and determine the titres of the human antibody repertoires against *Aspergillus* in ABPA; ii) to identify different cytokine patterns, which are known to correlate with Ig enhancement and disease severity and remission; iii) to investigate which cytokine pattern can shape the protective or non-protective antifungal Ig subclasses.

Essential methods

The titres of antigen-specific/total IgG subclasses and IgE are first determined at different stages of ABPA in people with cystic fibrosis (CF) coming from three different centres. In parallel, we are determining the cytokine pattern induced to understand the main cells involved in IgE switching. *In vitro* organoid model and mouse model of ABPA help with results validation.

Results

IL-17F was found to be increased in ABPA patients while barely detectible in cystic fibrosis and sensitized patients, and it is positively correlated to both specific anti-*Aspergillus* IgE and total serum IgE. IL-17F and IL-22 are detected when B and T cells directly interact, and B cells produce IL-23 via Dectin-1 and *Aspergillus* recognition.

Conclusions

This peculiar IL-17F-IL-22-IL-23 cytokine signature characterizes ABPA patients compared to non-ABPA patients. The B-T cell synapse is the key to better understanding the immunological function in determining the lung remodelling and the goblet metaplasia that deteriorate the lung function in CF upon *Aspergillus* sensitization. The same mechanism may be applied to other pathogens able to activate in a direct way, B cells and Dectin-1.

Tackling Pseudomonas aeruginosa

Targeting bacterial small RNA to develop non-traditional therapeutic options against *Pseudomonas aeruginosa*

Left to right: Silvia Paparoni, Giovanni Bertoni, Silvia Ferrara, Tarcisio Brignoli, Saira Arfan, Nadya Shalpoush

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Giovanni Bertoni[1], Silvia Ferrara[2]

[1]Department of Biosciences, University of Milan, Italy - [2]CNR Institute of Biophisics, Milan, Italy

(FFC#5/2024, ongoing)

Background and rationale

The increase in resistance to antibiotics, together with the delay in discovering new antibacterials, is drastically limiting our ability to fight pathogenic bacteria. The development of molecules with anti-virulence effects and/or capable of resensitizing resistant strains to antibiotics is an emerging approach that can produce targeted antibacterial therapies in cystic fibrosis. From this perspective, bacterial small RNAs represent an unexploited category of therapeutic targets. Our focus is on the small RNA ErsA of the pulmonary pathogen *Pseudomonas aeruginosa*, due to its role in regulating functions associated with lung pathogenesis and antibiotic resistance. Specifically, we previously found that the deletion of ErsA i) induces resensitization to ceftazidime, cefepime, and meropenem in the multidrug-resistant clinical strain RP73 and ii) strongly attenuates the laboratory strain PAO1 in a mouse model of infection. Anti-ErsA molecules are expected to be precursors of multi-functional drugs with antivirulence and antibiotic adjuvant activity at the same time.

Hypothesis and objectives

In previous projects funded by FFC Ricerca, we designed and tested a collection of anti-ErsA PNA oligomers that could bind to ErsA and prevent its regulatory function. In particular, we found that four anti-ErsA PNAs in our collection were remarkably effective in re-sensitizing the clinical strain RP73 to meropenem at micromolar concentrations. This project aimed to optimize the efficacy of these anti-ErsA PNAs through *in vitro* studies and to evaluate their potential for use *in vivo* in a preclinical murine infection model.

Essential methods

We used well-established protocols to assess the efficacy of antibiotic activity *in vitro* and a mouse model of acute lung infection to assay anti-ErsA PNAs *in vivo*.

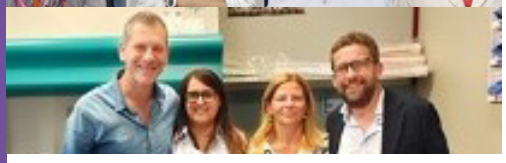
Preliminary results

We have developed a pipeline to optimize the use of anti-ErsA PNAs to increase the effectiveness of meropenem on cultured bacterial cells and also tested the emergence of bacterial variants evading the resensitizing activity of the anti-ErsA PNAs. We are currently conducting studies on the efficacy of anti-ErsA PNAs as adjuvants to meropenem in a mouse model of acute infection, testing micromolar concentrations, which we previously used *in vitro*.

Conclusions

Overall, we expect to provide innovative molecules for further use as anti-*Pseudomonas* drugs in combination with antibiotic therapies currently used in cystic fibrosis.

Targeting quorum sensing to fight *Pseudomonas aeruginosa* infections



First pic, left to right: Sandra Gemma, Gabriele Carullo, Andrea Cappelli, Mirko Pineschi
Second pic, left to right: Giovanni Di Bonaventura, Arianna Pompilio, Annalisa Chiavaroli, Claudio Ferrante

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Sandra Gemma[1], Gabriele Carullo[1], Mirko Pineschi[1], Andrea Cappelli[1], Annalisa Chiavaroli[2], Claudio Ferrante[2], Ersilia D'Alessandro[3], Giovanni Di Bonaventura[3], Arianna Pompilio[3]

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(FFC#7/2024, ongoing)

Background and rationale

Chronic respiratory infections caused by *Pseudomonas aeruginosa* are among the leading contributors to morbidity and mortality in people with cystic fibrosis (CF). The bacterium's ability to form biofilms and produce a wide range of virulence factors enables it to withstand both antibiotics and host immune defenses. A critical regulator of these processes is quorum sensing (QS), which coordinates the development of biofilms and the expression of virulence.

Hypothesis and objectives

This project aims to discover novel quinazoline-based antivirulence compounds that target PqsR, a key regulator in *P. aeruginosa* quorum sensing. PqsR plays a central role in controlling virulence and is the most prevalent QS regulator identified in clinical isolates from people with CF. The goal is to identify clinically relevant compounds with potential efficacy against CF-associated infections.

Essential methods

Methods used for addressing the expected goals can be divided into: i) medicinal chemistry: computer-aided drug design, synthesis of libraries of PqsR modulators, *in silico* prediction of drug-like properties, structure-activity relationship studies; ii) microbiology: assays for determination of biofilm formation and production of virulence factors (pyocyanin, pyoverdine) in *P. aeruginosa* strains (RP73 and BJ3525) under both "classical" and CF-like conditions.

Preliminary results

Virtual libraries were generated through side chain hopping, exploring various modifications of the quinazolinone scaffold. Docking, clustering, and property analyses guided the prioritization of compounds for synthesis. The libraries were then assembled using a convergent synthetic approach. To investigate antivirulence activity, assay conditions were carefully optimized. A set of compounds was identified able to significantly reduce pyocyanin production in a strain-independent manner. Moreover, some compounds significantly affected biofilm formation by *P. aeruginosa* RP73 strain under classic conditions, and by both *P. aeruginosa* strains under CF-like conditions, showing high potential for strain- and settings-independent effectiveness.

Conclusions

The synthesis and characterization of novel antivirulence compounds targeting PqsR has been accomplished, and valuable information has been collected that will drive the subsequent phases of the project.

A combined therapy against *Pseudomonas aeruginosa* - *Staphylococcus aureus* co-infections in cystic fibrosis

Annalisa Guaragna (third from the left) and her collaborators

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Annalisa Guaragna[1], Eliana De Gregorio[2]

[1]Department of Chemical Sciences, University of Naples Federico II, Italy - [2]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Italy

(FFC#8/2024, ongoing)

Background and rationale

Staphylococcus aureus (Sa) and *Pseudomonas aeruginosa* (Pa) are the two highly prevalent pathogens in people with cystic fibrosis (pwCF). Interactions among these organisms seem to profoundly impact their persistence and virulence, resulting in enhanced resistance to antibiotics. Therefore, the identification of novel agents able to control polymicrobial infections represents a compelling need in CF drug discovery.

Hypothesis and objectives

Our previous investigations (FFC#23/2018, #20/2019 and #13/2020) enable us to select two lead compounds, L-IM15 and L-IM16, among the class of iminosugars (glycomimetics). Both compounds exhibited anti-inflammatory and antibacterial activity in mouse models of Pa acute and chronic infections. L-IM16 was also able to inhibit the growth and biofilm formation of Sa and of other CF-relevant pathogens. In-depth studies suggested that they could act as an anti-virulence (L-IM15) and as a classical antimicrobial agent (L-IM16).
Our aim, herein, is to evaluate their efficacy in models of Pa-Sa co-infections that mimic the conditions of pwCF. Exploiting their different mechanisms of action, the effect of the combined administration of L-IM15 and L-IM16, on both mono- and co-infection models will be evaluated in search of an additive or synergistic anti-infective effect.

Essential methods

L-IM15 and L-IM16 have been synthesized with an eco-friendly and scalable procedure. *In vitro* antibacterial and antibiofilm activity were evaluated by broth microdilution and crystal violet biofilm staining methods, respectively. Murine models of acute Pa and Sa monoinfections were used to evaluate the efficacy and the most suitable administration route.

Preliminary results

During this first year of activity, L-IM15 and L-IM16 have been successfully prepared at a multigram scale. Early *in vitro* studies focused on the effect of the combination of L-IM15 and L-IM16, which revealed a reduction in bacterial growth and biofilm formation in Pa and Sa strains. Preliminary *in vivo* tests indicated: i) oral administration as the most suitable route of administration for both compounds, and ii) promising antibacterial and anti-inflammatory activity for both molecules in acute Sa infection models.

Conclusions

In vivo assays are currently ongoing to assess the efficacy of the combined administration of L-IM15 and L-IM16, on both mono- and co-infection models, while proteomic studies and other microbiological assays will be exploited to deeper evaluate the antimicrobial activity and elucidate the mechanism of action of these iminosugars.

Analysis of the evolution of virulence factors and antimicrobial resistance of *Pseudomonas aeruginosa* in people with cystic fibrosis

First pic, left to right: Vanessa Fini, Serena Raimondi, Gianluca Vrenna, Martina Rossitto, Vanessa Tuccio Guarna Assanti, Valeria Fox
Second pic, left to right: Marco Artini, Laura Selan, Irene Paris, Marika Trecca, Rosanna Papa
Third pic: Enza Montemitro

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Martina Rossitto[1], Marco Artini[2]

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(FFC#15/2024, ongoing)

Background and rationale

Pseudomonas aeruginosa (Pa) causes chronic lung infections in people with cystic fibrosis (CF). During its adaptation to the CF lung, Pa undergoes changes allowing antibiotic resistance and immune system evasion. How these modifications relate to the patient's clinical course over time, drug therapies administered, and existing bacterial co-colonization remains unclear. In addition, the impact that modulator therapies have on CF lung microbiology remains to be elucidated.

Hypothesis and objectives

This project aims to study how Pa adapts over the years of lung colonisation and how it responds to modulators, to personalise treatment and predict disease outcomes based on the characteristics of colonising strains.

Essential methods

We began to investigate, by Whole Genome Sequencing, changes over time in the resistome and virulome of 620 isolates collected and stored for up to 20 years from 62 CF patients. We also began to compare genetic and phenotypic data on resistance and virulence by examining antibiotic sensitivity and the capacity of 145 selected Pa strains to form biofilm, move, and produce compounds that cause lung damage.

Preliminary results

Our initial data provide an overview of the circulating clones in the patient cohort, including the dynamics between co-infecting clones and their potential negative impact on prognosis. Several patients have been observed to show the initial ST evolving into clonal complexes in response to challenging events such as transplantation or modulator start, as part of an ongoing evolution. Data also reveal probable cross-infection events between patients that spread the high-risk clone (HRC) ST274 and a new epidemic clone, ST3243. Resistance was a predominant feature among the 620 Pa isolates, mostly supported by chromosomal mutations. Preliminary phenotypic virulence investigation showed the inability of ST3243 to produce biofilm and exhibit swarming motility in any tested condition, even when mimicking the CF lung environment, whereas ST274 displayed high strain-specific variability in biofilm formation. Production of oxidative stress-related molecules was generally low. The effect of different modulators was preliminary seen in 35 patients and ranged from the acquisition of new clones (also HRC) to the adaptation and persistence of colonising ones.

Conclusions

Extending these data will allow the design of personalized therapy, tailored to patients according to the characteristics of the bacterial colonizing strain, and to understand in detail the effect of modulators on bacteria.

Using a Virtual Screening approach to find new drugs against *Pseudomonas aeruginosa* and *Staphylococcus aureus*

Left to right: Sara Costa, Viola Camilla Scoffone, Silvia Buroni, Giulia Barbieri

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Silvia Buroni[1], Antonio Coluccia[2]

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(FFC#6/2023, ongoing)

Background and rationale

Pseudomonas aeruginosa and *Staphylococcus aureus* can cause chronic infections in adults and children with cystic fibrosis (CF), and they are particularly difficult to treat due to their multidrug resistance (MDR). To promote innovative treatments and care for CF, we applied an innovative approach, the Virtual Screening (VS), to identify bactericidal molecules with a mechanism of action different from that in clinical use, i.e. targeting proteins involved in cell division.

Hypothesis and objectives

We applied the VS approach to proteins involved in cell division, which are essential for bacterial survival, i.e. FtsZ, and the complex FtsA-FtsN, to find new molecules able to block *P. aeruginosa* and *S. aureus* growth.

Essential methods

The VS provides a fast and cheap method for the selection of small molecules predicted to be effective in the inhibition of the selected enzymes. After identifying the molecules, we evaluated their activity on the target proteins and their efficacy in inhibiting bacterial growth, as well as the ability of bacteria to form biofilms. The compound showing the best properties will be tested *in vivo* in a mouse model of infection.

Preliminary results

The VS on FtsZ led to the identification of the compound C11 with antimicrobial activity against *S. aureus*, CF clinical isolates, MRSA, a very low toxicity and synergy with other antibiotics. Its efficacy is going to be tested *in vivo* in a mouse model of *S. aureus* infection. The VS approach on the essential cell division proteins of *P. aeruginosa*, FtsA and FtsN, led to the identification of 9 molecules. Six of these are able to impair the FtsA/N interaction *in vitro*, but are not effective in inhibiting *P. aeruginosa* growth, so further chemical optimization will be necessary to improve their activity.

Conclusions

The reported results indicate that the C11 compound is a promising drug candidate with great potential against *S. aureus* infections, including MDR strains, while the compounds targeting FtsA-FtsN need further chemical optimization in order to inhibit *P. aeruginosa* growth. In summary, the VS approach is a valuable method to find new therapeutic solutions for CF airway pathogens, thus promoting the introduction of innovative treatments.

Evaluation of cefiderocol activity against *Pseudomonas aeruginosa* in cystic fibrosis lung infections

Barbara Citterio (top left picture, 2nd from the left) and her collaborators

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Gianmarco Mangiaterra[1], Massimiliano Lucidi[2], Giorgia Piccioni[1], Riccardo Rosa[1], Carla Vignaroli[3], Natalia Cirilli[4], Davide Gugliandolo[5], Ida De Fino[5], Martina Rossano[5], Alessandra Bragonzi[5], Barbara Citterio[1]

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(FFC#7/2023, concluded)

Background and rationale

Biofilm formation and the development of bacterial persisters, even the viable but non-culturable (VBNC) cells, hamper the eradication of the cystic fibrosis (CF) lung infections caused by *Pseudomonas aeruginosa*. The activity of cefiderocol (CFD), exploiting the bacterial iron uptake systems to enter the cell and achieve a high bactericidal effect, against these specialized phenotypes has been investigated only in limited studies, lacking the detection of the VBNC forms.

Hypothesis and objectives

To evaluate the CFD antipersister activity, this project's aims are: i) investigating the *P. aeruginosa* persistence to CFD in both planktonic and sessile cultures; ii) assessing the induction of persistent and VBNC *P. aeruginosa* cells after exposure to sublethal CFD doses; iii) validating the obtained results in a preclinical mouse model of chronic infection.

Essential methods

P. aeruginosa persistence to CFD was tested against *P. aeruginosa* PAO1 biofilms, maintained in conditions of nutrient depletion with/without sublethal CFD concentrations, and in a murine lung infection model. The amounts of culturable survivors and VBNC cells have been determined by plate count and qPCR assays, respectively. The results have been confirmed by confocal microscopy tests. The same approach was used to evaluate the efficiency of the CFD treatment in the murine model of *P. aeruginosa* lung infection. The synergy of CFD with tobramycin (TOB) was tested by checkerboard assays.

Results

We previously demonstrated the lower induction of VBNC *P. aeruginosa* forms in CFD-exposed biofilms, rather than in TOB- and ceftazidime-exposed ones. The biofilm maintenance in the presence of sublethal CFD concentrations also led to a decrease in the amount of VBNC cells (87% of total viable cells) compared to simply starved biofilms (92%). The antibiotic treatment of the murine infection mirrored the *in vitro* data, showing a lower VBNC induction in CFD-treated animals. The combination TOB/CFD showed a synergistic effect (FIC index < 0.5) against both *P. aeruginosa* PAO1 cultures and biofilms.

Conclusions

CFD-treatment showed a lower tendency to induce the VBNC state both in *in vitro P. aeruginosa* biofilms and *in vivo* infection models. This suggests the possibility of combinatory therapies with other drugs as effective eradication strategies. The combination TOB/CFD seems a promising alternative to be further evaluated and characterized in future studies.

Inhalable nanoparticles delivering peptidomimetic/ antibiotic combinations for local treatment of CF lung infections

First pic, left to right: Andrea Bosso, Ilaria Di Nardo, Elio Pizzo, Eugenio Notomista, Valeria Cafaro, Ida Palumbo, Francesca Tortora, Maria Cristiano
Second pic, left to right: Ivana d'Angelo, Pouria Savadi, Andrea Casale, Vincenzo Vendemia.

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Eugenio Notomista[1], Ivana d'Angelo[2]

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(FFC#8/2023, concluded)

Background and rationale

P13#1 is a protease-resistant peptoid mimicking cationic antimicrobial peptides. It shows antibacterial, antibiofilm and anti-inflammatory activities as well as synergy with colistin (Col) and tobramycin (Tb), two antibiotics widely used in cystic fibrosis lung infection. Unfortunately, its polymeric nature hampers direct delivery to the lung, where poor biodistribution and slow diffusion reduce efficacy and exacerbate its toxicity.

Hypothesis and objectives

The main aim of the project was to develop inhalable polymeric nanoparticles (NPs) for lung delivery of P13#1, Col and Tb, alone and in combination.

Essential methods

NPs made of polylactic-co-glycolic acid (PLGA) plus poloxamer P407, loaded with 2% drugs, were prepared using the solvent emulsion/diffusion technique at different PLGA:P407 ratios. Size, polydispersity index, ζ-potential, drug encapsulation efficiency, mucus interactions, drug release kinetics, antimicrobial and antibiofilm activity were determined. Given the low antimicrobial activity of P13#1-loaded PLGA/P407 NPs, we also developed chitosan (CS) NPs containing P13#1. CS-NPs were produced by ionic gelation with tripolyphosphate in the presence of P407, to modulate CS mucoadhesive properties. *In vivo* analysis in the CFaCore mouse model of lung infection of selected formulations is in progress.

Results

PLGA/P407 NPs exhibited properties suitable for pulmonary drug delivery and low interaction with mucin, suggesting that NPs can promote diffusion across lung barriers. Drug release was prolonged and sustained, especially for P13#1 (>20 days). Increasing the percentage of P407 resulted in a faster release rate due to enhanced hydrophilicity and porosity. Tb-loaded NPs showed biological activities slightly lower than those of free Tb, likely due to delayed release. Surprisingly, Col-loaded NPs showed antimicrobial and antibiofilm activity slightly higher than that of free Col. We demonstrated that the "excess" activity is due to the fact that P407 unexpectedly enhances Col efficacy. P13#1-loaded NPs showed essentially no antimicrobial activity due to the very slow release. The newly developed P13#1-loaded CS-NPs showed features suitable for pulmonary delivery: size =~300 nm, low PDI (0.1–0.2), positive ζ-potential. P13#1 was efficiently encapsulated and showed a sustained release for over 15 days.

Conclusions

PLGA/P407 NPs proved to be very well suited to deliver Col and Tb in a highly active form, but not suited for P13#1 due to the very strong binding to PLGA. We are confident that the new CS-based NPs should solve the issue, as CS, differently from PLGA, is a cationic/ hydrophilic polymer.

Building simple molecules containing regions of *Pseudomonas aeruginosa* to stimulate the immune system against this pathogen

In the first pic: Marco Sette
In the second pic: Marco Rinaldo Oggioni and Claudia Trappetti

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(FFC#13/2023, ongoing)

Background and rationale

People with cystic fibrosis are prone to bacterial infections, especially by *Pseudomonas aeruginosa*, a bacterium resistant to many antibiotic therapies. New care tools are therefore needed in these cases.

Hypothesis and objectives

The project aims to build peptides that stimulate the immune system against *P. aeruginosa* infections. We use an immunogenic region of the pilA protein of type IV pilus bound to a peptide scaffold. This region, the disulfide loop, is structured in a loop, and the scaffold is a peptide called TrpZip2, which forms a very stable hairpin. A cocktail of peptides, each with the immunogenic region of a specific strain, can be used as a vaccine.

Molecular dynamics (MD) studies have shown that either by inserting the disulfide loop of the PAK strain in place of the TrpZip2 loop (molecule APT2) or by inserting it in the C-terminal position (molecule APT3), stable structures are obtained. In the first year, APT3 was shown to fold as expected, while APT2 showed a more complex folding.

Essential methods

The molecules are modelled using Alphafold, and MD studies the stability of the folding. The experimental verification of the tertiary structure is studied with Circular Dichroism (CD) and Nuclear Magnetic Resonance (NMR). The first set of molecules was tested on mice.

Preliminary results

In the second year, we addressed *in vitro* the structure of APT2 modified in the APT2KKK and APT4 peptides, which show a similar degree of structuring to APT2 using the NMR technique, i.e., a degree of partial structuring or the presence of multiple conformers in solution. We have returned to using the CD, which shows how APT3 is structured in a similar way to the scaffold, but APT2 is also not very different, thus suggesting using this molecule *in vivo*, too. *In vivo* tests of vaccination of mice with APT3 using two different aluminium-based adjuvants showed protection from *P. aeruginosa* bacteremia with a limited increase in antibody levels.

Conclusions

The promising *in vivo* tests suggest that we continue the project using the same scheme for the disulfide loops of other strains.

SESSION 8

Different challenges, different approaches

Understanding the mechanisms behind the variable efficacy of CFTR modulators on the N1303K mutation on human primary nasal epithelial cells

Renata Bocciardi (second from the right) and her collaborators

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Renata Bocciardi[1,2], Cristina Pastorino[2], Valeria Capurro[2], Mariateresa Lena[1], Ludovica Menta[2]

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(FFC#3/2023, ongoing)

Background and rationale

Cystic fibrosis (CF) is a frequent, multisystemic genetic disease due to bi-allelic loss-of-function variants of the CFTR gene. CFTR modulators, developed to rescue the CFTR defects due to specific variants, represent a significant advancement in CF treatment. The N1303K, the second most common CF-causing variant among Italian people with CF (pwCF), shows both trafficking and gating alterations, with heterogeneous response to modulators approved to rescue such defects.

Hypothesis and objectives

Several factors may be responsible for this variability, and our data suggest that it is likely due to intrinsic properties of these epithelia. We aimed at investigating the molecular basis of the variable response of the N1303K variant to approved modulators by focusing on cis-acting factors that may modulate CFTR expression or function.

Essential methods

We assessed CFTR expression in N1303K-carrying and control human nasal epithelial cells (hNECs) through qPCR and end-point RT-PCR, combined with Sanger sequencing to assess potential unconventional splicing events or additional variants (both in cDNA and in genomic regulatory regions). A bulk RNA sequencing analysis has also been conducted on a selected subgroup of samples.

Preliminary results

Functional analysis of CFTR activity in hNECs from N1303K pwCF samples revealed variable levels of pharmacological rescue, allowing classification into distinct response groups. We found that overall CFTR mRNA levels are similar in controls and N1303K samples, with a higher variability in controls compared to CF samples. RNAseq results revealed greater heterogeneity in terms of differentially expressed genes in controls compared to cases; notably, within the CF cohort, a non-responder was distinctly different from other responders; however, cDNA analysis did not identify additional variants. Moreover, an integration of locus-specific expression data with the results of RNAseq analysis has also been performed with the identification of allele-specific expression imbalances.

Conclusions

CFTR expression levels do not reliably predict response to modulators, suggesting a more intricate regulatory landscape and the need for further study to enable personalized therapies for pwCF without approved treatments.

Developing a new respiratory 3D model as an innovative strategy to study the inflammation pathology in cystic fibrosis

Roberto Plebani (first picture), Anna Stejskalová (second picture) and Giovanni di Bonaventura (third picture)

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Roberto Plebani

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(GMSG#1/2023, ongoing)

Background and rationale

Inflammation plays a central pathogenic role in cystic fibrosis (CF). We previously developed the first human CF airway-on-a-chip for inflammation studies. In year one of the project, we improved this model by assembling the "airway-on-a-chip 2.0" that incorporates CF endothelial cells (ECs) and CF fibroblasts (FBs). In year two, we studied vascularisation and analyzed inflammatory responses under elexacaftor/tezacaftor/ivacaftor (ETI).

Hypothesis and objectives

Since the endothelium is dysfunctional in CF and ECs and FBs in co-culture can form pseudo-vascular structures *in vitro*, we hypothesized that promoting neo-vascularisation within the chip would provide a more physiologically relevant platform for studying inflammation. The objectives were to: i) optimise endothelial–stromal interactions, ii) establish conditions for vascularized airway chips, iii) assess ETI effects on polymorphonuclear leukocyte (PMN) adhesion and migration.

Essential methods

We first optimised EC–FB co-cultures in transwells and then transferred the knowledge to the chip. We tested different seeding strategies, comparing early versus late EC introduction to achieve stromal vascularisation without system obstruction. We run PMN perfusion assays in the presence or absence of ETI and collected media for cytokine/chemokine analysis. We also analyzed CF EC and FB monocultures for PMN adhesion and proteolytic activity.

Preliminary results

Transwell cultures showed EC-derived pseudo-vessels in the stroma. In chips, early high-density FB seeding induced extensive vascularisation but obstructed the flow, plausibly biasing PMN behaviour. Introducing ECs two days before PMN perfusion enabled endothelial–stromal remodeling while preserving system functionality. Preliminary data showed that ETI treatment did not affect PMN recruitment in the chip but decreased PMN adhesion to CF ECs. CF FBs showed reduced MMP-1, MMP-9, and Cathepsin-S, suggesting impaired matrix remodeling and a potential fibrotic phenotype.

Conclusions

We consolidated the airway-on-a-chip 2.0 by defining vascularisation conditions and initiating ETI testing. Results highlight the crucial contribution of CF ECs and FBs to inflammation, with ETI reducing PMN adhesion to CF ECs but not overall recruitment in the chip. Findings provide insights into the role of endothelium and matrix remodeling in CF airway inflammation. The optimised model will be used in year three for ETI treatment and bacterial infection.

Alternative therapeutic target to restore the mucociliary clearance in CF

Michele Genovese (in the middle) between Luis J. V. Galietta and Anna Borrelli

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(GMSG#1/2024, ongoing)

Background and rationale

Loss-of-function of the CFTR chloride channel impairs mucociliary clearance (MCC), causing cystic fibrosis (CF) lung disease. Alternative targets, such as the Ca^{2+}-activated TMEM16A chloride channel, are considered for the treatment of patients carrying undruggable CFTR mutations. However, the best approach to target TMEM16A in CF, whether with potentiators or inhibitors, is a matter of debate. Another alternative target is the TRPV4 calcium channel. TRPV4 is a potential sensor of mechanical and chemical stimuli, involved in the response to pathogens and linked to CFTR activity.

Hypothesis and objectives

We hypothesise that TMEM16A and TRPV4 could be alternative therapeutic targets in CF. Our goal is to clarify their role in the airways to modulate them in the most appropriate way. For TMEM16A, we used the CRISPR/Cas9 strategy to knock out the gene in airway epithelial cells and evaluate the consequences on airway surface properties.

Regarding TRPV4, we are investigating the mechanisms linking this channel to CFTR and to Ca^{2+}-activated dual oxidases that produce H_2O_2 as a bactericidal agent.

Essential methods

We are using differentiated human bronchial epithelia (HBE) in which TMEM16A and TRPV4 function are altered with genetic and/or pharmacological approaches. We carried out a panel of experiments to evaluate intracellular calcium mobilization. We are evaluating the airway surface liquid properties, mucin secretion, epithelial composition/morphology, and H_2O_2 production.

Preliminary results

TMEM16A-defective epithelia, generated by nucleofection of basal stem cells, showed a near total ablation of calcium-dependent chloride secretion without alteration of calcium signaling. Pharmacological TRPV4 activation leads to the release of ATP, which then activates CFTR through stimulation of adenosine and purinergic receptors. Bacterial supernatants elicited a significant calcium increase, possibly through TRPV4.

Conclusions

The results obtained so far show that we are able to ablate TMEM16A function in differentiated epithelia, which will allow us to assess its physiological role.
TRPV4 appears to regulate H_2O_2 and ATP release. It will be important now to determine how pharmacological modulation of TMEM16A and TRPV4 leads to improvements in airway surface hydration and innate defense mechanisms of the airway epithelium.

Identification of molecular mechanisms which underpin the activation of pathogenic pulmonary Th1/17 cells in cystic fibrosis

Moira Paroni (on the left) and Clelia Peano (on the right)

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Irene Dusetti[1], Simone Puccio[2], Matteo Chiara[1], Eugenia Ricciardelli[3], Javier Cibella[3], Elio Rossi[1], Paolo Landini[1], Andrea Gramegna[4,5], Francesco Blasi[4,5], Clelia Peano[3,6], Moira Paroni[1]

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(FFC#14/2023, ongoing)

Background and rationale

Persistent activation of the mucosal immune system and recurrent bacterial infections are major drivers of pulmonary decline in CF. Among airway pathogens, *Pseudomonas aeruginosa* (Pa) is a key inducer of immune dysregulation by altering dendritic cell (DC) functions and promoting the generation of pathogenic IFNγ-producing Th17 cells. However, the molecular mechanisms through which Pa-infected DCs drive this skewing remain elusive.

Hypothesis and objectives

We hypothesize that Pa persistence within CF-derived DCs reshapes both bacterial and host transcriptomes, establishing a proinflammatory environment that polarizes and reprograms protective Th17 into pathogenic IFNγ-producing Th17 cells. Our goal is to elucidate the dual host–pathogen transcriptional programs sustaining Th17-driven immunopathology, ultimately identifying microbial and immunological targets to selectively block detrimental inflammation and lung damage in CF.

Essential methods

We applied a dual-RNA sequencing approach to simultaneously analyse host and bacterial transcriptional profiles during Pa persistence within CF-derived DCs. In parallel, single-cell RNA sequencing of DCs isolated from sputum of CF patients with Pa pulmonary infection provided a high-resolution definition of Pa-induced immunomodulation within the lung microenvironment.

Preliminary results

Pa displays an intrinsic ability to persist within DCs, inducing the release of high levels of polarizing cytokines and highly driving the skewing of protective cTh17 into pathogenic IFNγ-producing Th17 cells, even at the early stage of the disease. Dual-RNAseq revealed that Pa persistence within CF-DCs profoundly rewired the transcriptional program: 307 bacterial genes were upregulated, largely linked to metabolic optimization for intracellular survival. Infected DCs exhibited 2040 up- and 1698 down-regulated genes. Among the host genes induced during Pa persistence, anti-apoptotic pathways were markedly upregulated, suggesting that Pa actively prevents DC death to establish its intracellular niche and sustain an exaggerated inflammatory response. Notably, pathway enrichment analysis revealed a robust activation of TNF, IL-17, and JAK–STAT signaling, together with Th17 differentiation programs, underscoring the emergence of a proinflammatory DC phenotype specifically primed to drive pathogenic Th17 responses.

Conclusions

Our study delineates a dual host–pathogen transcriptomic signature of Pa-infected DCs in CF, uncovering key mechanisms by which Pa orchestrates DC-mediated polarization of pathogenic Th17 subsets. By dissecting these pathways, we will identify novel immune checkpoints and druggable microbial and host targets. This provides a framework for next-generation immunotherapies aimed at selectively blocking detrimental inflammation, ultimately preventing lung damage and further improving clinical outcomes in CF.

Beyond the lung: the gut's role in the pathology of cystic fibrosis

Left to right: Alessandra Bragonzi, Federica Ungaro, Valeria Daccò

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Gloria Delmonte[2], Cristina Cigana[1], Marika Grasso[1], Laura Veschetti[2], Amanda Facoetti[2], Lisa Cariani[3], Beatrice Orena[3], Daniela Girelli[3], Valeria Daccò[3], Federica Ungaro[2], Alessandra Bragonzi[1]

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(FFC#5/2023, ongoing)

Background and rationale

Despite CFTR-modulator therapies, respiratory complications remain a concern for people with cystic fibrosis (pwCF), highlighting the need to understand the disease mechanisms for new diagnostic and treatment strategies. Beyond the lungs, the gut shares key structural features, including mucus-secreting epithelia and barrier dysfunctions, and manifests overlapping inflammatory changes.

Hypothesis and objectives

Emerging data support a gut-lung axis that may sustain persistent airway inflammation despite CFTR modulator therapy. Our aim is to establish the mechanistic links between gut pathology, microbiota, and pulmonary inflammation, which have largely remained unexplored due to the lack of genetically diverse animal models that fully represent the disease features observed in pwCF.

Essential methods

We used a Collaborative Cross CF mouse model with F508del mutation (CC037-F508del) and a new gastrointestinal *Pseudomonas aeruginosa* infection model. Pathological, transcriptomic, and immunological responses were studied in the lung, gut, and blood to characterize the host response. Microbial contributions were assessed using metatranscriptomics and culture-based approaches. A pwCF cohort was recruited to analyze sputum and stool microbiology.

Preliminary results

Immunophenotyping and single-nucleus RNA sequencing showed early lung and systemic inflammation, including responses to bacterial pathogens, preceding structural damage in CC037-F508del mice. Culture and metatranscriptomics revealed a substantial bacterial burden in the lungs. Remarkably, this included species typically associated with the gut, suggesting overlaps between lung and gut microbiota. Intestinal inflammation, dysbiosis, and impaired barrier function were observed alongside increased pulmonary and systemic immune activation. Following gut infection with *P. aeruginosa*, CC037-F508del mice exhibited persistent bacterial colonization in the gastrointestinal tract and stool, whereas CC037-wt mice were able to control the infection. The recovery of *P. aeruginosa* from the lung following gut colonization supports the cross-talk between these sites. Data from pwCF indicate that CF pathogens can also be recovered from stool samples, and potential correlations with sputum are under evaluation.

Conclusions

These findings provide evidence for a gut-lung axis in CF, highlighting its contribution to immune dysregulation and microbial dynamics. We suggest that gut pathology may drive and exacerbate lung disease and support new diagnostic and therapeutic strategies beyond lung-focused approaches.

Appendix 1

Recent publications (2021-2025) from studies funded by the Italian Cystic Fibrosis Research Foundation

1. Innovative therapies to correct the basic defect and CFTR genetics

FFC Project#3/2015 "***Relationship between mitochondria and F508del-CFTR in Cystic Fibrosis***" Hugo de Jonge (Dipartimento di Gastroenterologia ed Epatologia - Centro Medico, Erasmus University, Rotterdam), Sara Caldrer (Dipartimento di Patologia e Diagnostica, sezione di Patologia Generale - Università di Verona)

- Ciciriello F, Bijvelds JCM, Alghisi F et al. "Theratyping of the Rare CFTR Variants E193K and R334W in Rectal Organoid-Derived Epithelial Monolayers" J. Pers. Med. 2022, 12, 632
- Bijvelds MJC, Roos FJM, Meijsen KF et al. "Rescue of chloride and bicarbonate transport by elexacaftor-ivacaftor-tezacaftor in organoid-derived CF intestinal and cholangiocyte monolayers" J Cyst Fibros. 2022 May;21(3):537-543

FFC Project#1/2016 "***New generation trimethylangelicin (TMA) analogues for selective modulation of defective CFTR or inflammation***" Adriana Chilin (Dipartimento di Scienze Farmaceutiche e Farmacologiche, Università di Padova)

- Vaccarin V, Gabbia D, Franceschinis E et al. "Improved Trimethylangelicin Analogs for Cystic Fibrosis: Design, Synthesis and Preliminary Screening" Int. J. Mol. Sci. 2022, 23, 11528

FFC Project#5/2016 "***Implementation of a new imaged-controlled sweat test for in vivo quantification of CFTR function: value for diagnosis and efficacy of new therapies***" Teresinha Leal (Louvain Center for Toxicology and Applied Pharmacology, Institut de Recherche Expérimentale et Clinique; Université Catholique de Louvain, Brussels, Belgium), Stefano Ceri (Dipartimento di Elettronica, Informazione e Bioingegneria, Università di Milano); Nguyen-Khoa Thao (Necker-Enfants Malades Hospital, APHP Laboratory of General Biochemistry, Paris)

- Treggiari D, Kleinfelder K, Bertini M et al. "Optical Measurements of Sweat for *in vivo* Quantification of CFTR Function in Individual Sweat Glands" J Cyst Fibros. 2021 Sep;20(5):824-827.

FFC Project#6/2016 "***Understanding the mode of action of regulatory pathways controlling F508del-CFTR proteostasis and developing drugs that rescue F508del-CFTR by targeting these pathways synergistically***" Alberto Luini (Consiglio Nazionale delle Ricerche, Dipartimento Scienze Biomediche, Istituto di Biochimica delle Proteine, Napoli)

- Del Giudice S, De Luca V, Parizadeh S, Russo D, Luini A, Di Martino R. "Endogenous and Exogenous Regulatory Signaling in the Secretory Pathway: Role of Golgi Signaling Molecules in Cancer" Front Cell Dev Biol. 2022 Mar 23;10:833663
- Liccardo F, Luini A, Di Martino R. "Endomembrane-Based Signaling by GPCRs and G-Proteins" Cells. 2022 Feb 3;11(3):528
- Rizzo R, Russo D, Kurokawa K, et al. "Golgi maturation-dependent glycoenzyme recycling controls glycosphingolipid biosynthesis and cell growth via GOLPH3" EMBO J. 2021 Apr 15;40(8):e107238
- Pothukuchi P, Agliarulo I, Pirozzi M, et al. "GRASP55 regulates intra-Golgi localization of glycosylation enzymes to control glycosphingolipid biosynthesis" EMBO J. 2021 Oct 18;40(20):e107766

FFC Project#11/2016 "***Myriocin potential as a phenotype-modifyingt herapeutical in cystic fibrosis***" Paola Signorelli (Dipartimento di Scienze della Salute, Ospedale San Paolo, Università di Milano)

- Signorelli P, Pivari F, Barcella M et al. "Myriocin modulates the altered lipid metabolism and storage in cystic fibrosis" Cell Signal. 2021 May;81:109928.

FFC Project#12/2016 "***Properties of airway mucus in cystic fibrosis: their modification by changes in the activity of CFTR and after application of bicarbonate***" Loretta Ferrera (U.O.C. Genetica Medica, Istituto "G. Gaslini" , Genova)

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FFC Project#2/2022 "***Characterization of CFTR modulators mechanism of action via Photo-Affinity Labeling (PAL) approach***" Fabio Bertozzi (Istituto Italiano di Tecnologia – IIT Genova)

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FFC Project#4/2022 "***Esculentin-derived peptides as novel therapeutic agents with antimicrobial and CFTR potentiator activities to address cystic fibrosis lung disease***" Maria Luisa Mangoni (Dip. Scienze Biochimiche, Università La Sapienza, Roma), Arianna Venturini (Telethon Institute of Genetics and Medicine - TIGEM, Pozzuoli, NA), Mattia Mori (Dip. Biotecnologie Mediche, Università di Siena)

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FFC Project#2/2023 "***Exploring the cellular pathways to promote rescue of mutant CFTR protein in cystic fibrosis***" Carlos M. Farinha (BioISI – Biosystems and Integrative Sciences Institute, University of Lisboa, Portugal), Valeria Tomati (U.O.C. Genetica Medica, Istituto Giannina Gaslini, Genova)

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FFC Project#1/2024 "***Development of new potentiators active on (ultra)rare mutants of CFTR***", Giovanni Marzaro (Department of Diagnostic and Public Health, University of Verona, Italy), Gergely Lukacs (Department of Physiology, McGill University, Canada), Tamas Hegedus (Biophysical Virology Research Group, Hungarian Research Network, Budapest).

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2. PERSONALIZED THERAPIES - THERATYPING

FFC Project#12/2018 "***Establishment of Conditionally Reprogrammed Airway Epithelial Stem Cell cultures from nasal epithelia of Cystic Fibrosis patients: exploring response to CFTR-modulating drugs for correlation with genetic profile (theratyping) and restoring CFTR function through gene editing approaches***" Adriana Eramo (Dip. Oncologia e Medicina Molecolare, Istituto Superiore di Sanità), Marco Lucarelli (Dip. Biotecnologie Cellulari e Ematologia, La Sapienza, Roma)

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FFC Project#9/2019 "***Theratyping orphan mutations in Italian cystic fibrosis patients: efficacy of CFTR modulators and RNF5 inhibitors***" Nicoletta Pedemonte (IRCCS Istituto "G. Gaslini", UOC Genetica Medica, Genova), Andrea Cavalli (Istituto Italiano di Tecnologia, Biologia Computazionale e Chimica, Genova)

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FFC Project#5/2020 "***Intestinal organoids for assessment and pharmacological correction of abnormalities in fluid transport and anion currents in patients affected by pancreatitis";*** Luca Frulloni (Università degli Studi di Verona, Dip. di Medicina, Div. Gastroenterologia), Hugo De Jonge (Erasmus University Medical Center); Vincenzina Lucidi (Ospedale Pediatrico Bambino Gesù, Centro Fibrosi Cistica)

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FFC Project#8/2021 "***Theratyping of cystic fibrosis"*** Marco Lucarelli (Dipartimento di Medicina Sperimentale, Sapienza Università di Roma), Adriana Eramo (Istituto Superiore di Sanità, Dip. di Oncologia e Medicina Molecolare, Roma)

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FFC Project#10/2021 "***Theratyping orphan mutations in Italian cystic fibrosis patients: meeting unmet needs"*** Nicoletta Pedemonte (IRCCS Istituto Giannina Gaslini, UOC Genetica Medica, Genova), Renata Bocciardi (Dip. di neuroscienze, riabilitazione, oftalmologia, genetica e scienze materno-infantili - DINOGMI, Università degli Studi di Genova)

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3. MICROBIOLOGY

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FFC Project#19/2017 "***A longitudinal metagenomic analysis to uncover microbial signatures of CF lung disease: unravelling host-microbial community interactions in humans and animal models"*** Annamaria Bevivino (ENEA, Divisione Biotecnologie e Agroindustria, Lab. Sostenibilità, Qualità e Sicurezza delle Produzioni Agroalimentari, Centro Ricerche Casaccia, Roma), Alessio Mengoni (Dip. di Biologia, Università degli Studi di Firenze), Nicola Segata (CIBIO, Laboratorio di Metagenomica computazionale, Università di Trento)

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FFC Project#18/2018 ***"In vitro and in vivo efficacy of an antimicrobial and antibiofilm designed peptidomimetic against CF lung pathogens"*** Eugenio Notomista (Università degli Studi di Napoli Federico II, Dip. di Biologia), Eliodoro Pizzo (Università degli Studi di Napoli Federico II, Dip. di Biologia)

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FFC Project#20/2018 ***"Biocompatible and inhalable antimicrobial-loaded nanoparticles for the counteraction of biofilm formation and antibiotic resistance: towards a potential new therapy for CF related infections"*** Maurizio Sanguinetti (Divisione Microbiologia clinica, Università Cattolica del Sacro Cuore, Roma), Alberto Vitali (Istituto di Chimica del Riconoscimento Molecolare CNR-ICRM); Michele Iafisco (Istituto di Scienza e Tecnologia dei materiali ceramici ISTEC CNR, Faenza), Daniele Catalucci (Istituto di Genetica e Ricerca biomedicale -IRGB, Milano)

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FFC Project#19/2019 ***"Gallium as an antibacterial agent in cystic fibrosis: animal studies for the delivery of inhalable formulations to the clinic"*** Paolo Visca (Dipartimento di Scienze, Lab. Microbiologia Clinica e Virologia, Università Roma Tre), Raffella Sorrentino (Dip. di Farmacia, Università di Napoli Federico II)

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FFC Project#13/2020 ***"Can old and new sweet glycomimetics act as antibacterial and antibiofilm agents in the treatment of CF lung disease infections?"*** Annalisa Guaragna (Università degli Studi di Napoli Federico II, Dip. di Scienze Chimiche), Eliana De Gregorio (Università degli Studi di Napoli Federico II, Dip. di Medicina Molecolare e Biotecnologie Mediche)

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FFC Project#15/2020 ***"Targeting the STING/Transglutaminase 2-regulated Interferon response as a novel host-direct approach to fight bacterial infections in cystic fibrosis"*** Mauro Piacentini (Università di Roma Tor Vergata, Dip. di Biologia), Valeria Raia (Università degli Studi di Napoli, Dip. di Scienze Mediche Traslazionali)

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FFC Project#13/2021 ***"Probiotics: an emerging strategy to fight bacterial pulmonary infections in CF"*** Giovanna Batoni (Dipartimento di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa)

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FFC Project#16/2021 ***"Linking elexacaftor/tezacaftor/ivacaftor to infections in cystic fibrosis lung disease"*** Cristina Cigana (Unità Infezioni e Fibrosi Cistica, divisione di Immunologia, Trapianti e Malattie Infettive, Istituto San Raffaele Milano), Daniela Girelli (Lab. Microbiologia FC, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano); Ersilia Vita Fiscarelli (Lab. Microbiologia FC, Ospedale Bambino Gesù, Roma)

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FFC Project#17/2021 ***"New drug combinations against non-tuberculous Mycobacteria infections in cystic fibrosis"*** Lanfranco Fattorini (Istituto Superiore di Sanità, Dipartimento Malattie infettive, Roma)

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FFC Project#18/2021 ***"New weapons against Mycobacterium abscessus and other nontuberculous mycobacteria"*** Maria Rosalia Pasca (Università degli Studi di Pavia, Dip. di Biologia e Biotecnologia "Lazzaro Spallanzani" , Lab. Microbiologia molecolare), Vladim Makarov (Federal Research Center, Moscow), Santiago Ramón-García (University of Zaragoza), Enrico Tortoli (Div. di Immunologia, Trapianti e Malattie Infettive HSR, Milano)

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FFC Project#5/2022 ***"Nontuberculous Mycobacteria in cystic fibrosis: scouting molecules against M. abscessus iron acquisition pathways"*** Chiarelli Laurent Roberto (Lab. Microbiologia molecolare, Dip. Biologia e Biotecnologia "Lazzaro Spallanzani", Università di Pavia)

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FFC Project#7/2022 ***"Genomic and phenotypic characterization of Mycobacterium abscessus and detection of host biomarkers to define mycobacterial infection in cystic fibrosis"*** Nicola Lorè (Unità Patogeni Batterici Emergenti, Istituto Scientifico San Raffaele, Milano), Lisa Cariani (Fondazione IRCCS, Cà Granda Ospedale Maggiore Policlinico di Milano)

- Lorè NI, Gramegna A, de Pretis S et al. "Single-Cell RNA Sequencing Shows that Circulating Monocytes Enriched in IFN Signaling Are Associated with Nontuberculous Mycobacteria Pulmonary Disease in Cystic Fibrosis" Am J Respir Crit Care Med. 2024 Sep 15;210(6):834-837.

FFC Project#8/2022 ***"Targeting the STING/Transglutaminase 2-regulated Interferon response as a novel host-direct approach to fight bacterial infections in cystic fibrosis"*** Mauro Piacentini (Dip. Biologia, Università Roma Tor Vergata), Valeria Raia (Dip. di Scienze Mediche Traslazionali, Università di Napoli Federico II)

- Rossin F, Ciccosanti F, D'Eletto M et al. "Type 2 transglutaminase in the nucleus: the new epigenetic face of a cytoplasmic enzyme" , 2023, Cell Mol Life Sci. 80:52.

FFC Project#6/2023 ***"Using a Virtual Screening approach to find new drugs against Pseudomonas aeruginosa and Staphylococcus aureus"*** Silvia Buroni (Dip. Biologia e Biotecnologie "Lazzaro Spallanzani", Università di Pavia), Antonio Coluccia (Dip. Chimica e Tecnologie del Farmaco, Università La Sapienza, Roma)

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FFC Project#9/2023 ***"Evaluation of the efficacy of the "VOMG" new antibiotic against Mycobacterium abscessus"*** Maria Rosalia Pasca (Dip. di Biologia e Biotecnologie Lazzaro Spallanzani, Università degli Studi di Pavia), Riccardo Manganelli (Dip. di Medicina Molecolare, Università di Padova), Fabio Saliu (Infection and Cystic Fibrosis Unit San Raffaele Scientific Institute, Milano)

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FFC Project#10/2023 ***"Drug repurposing to inhibit Pseudomonas aeruginosa adaptation to the CF lung environment"*** Giordano Rampioni (Dip. di Scienze, Università Roma Tre)

- Caruso L, Mellini M, Catalano Gonzaga O et al. "Hydrogen sulfide production does not affect antibiotic resistance in *Pseudomonas aeruginosa*" Antimicrob Agents Chemother. 2024 Apr 3;68(4):e0007524.
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FFC Project#8/2024 ***"A combined therapy against Pseudomonas aeruginosa-Staphylococcus aureus co-infections in cystic fibrosis"*** Annalisa Guaragna (Department of Chemical Sciences, University of Naples Federico II, Naples, Italy), Eliana De Gregorio (Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy)

- Esposito A , Stabile M, Migliaccio A et al. "Synthesis and preliminary biological evaluation of novel steroidal compounds as antibacterial agents", Steroids, Volume 223, November 2025, 109686
- Esposito A, D'Alonzo D, Stabile M et al. "Synthesis of a di-O-acylated deoxynojirimycin (DNJ) derivative and evaluation of its antibacterial and antibiofilm activity against *Staphylococcus aureus* and Stenotrophomonas maltophilia", Carbohydr Res 2025 Apr:550:109379.

4. INFLAMMATION

FFC Project#21/2011 ***"Phosphodiesterases type-4 (PDE4) as a novel target to reduce neutrophilic lung inflammation in cystic fibrosis"*** Virgilio Evangelista (Laboratorio di Biologia Vascolare e Farmacologia, Fondazione Mario Negri Sud Santa Maria Imbaro, Chieti), Mario Romano (Dip. di Scienze Sperimentali e Cliniche, Lab. di Medicina Molecolare, Università G. D'Annunzio, Chieti-Pescara)

- Totani L, Amore C, Piccoli A, et al "Type-4 Phosphodiesterase (PDE4) Blockade Reduces NETosis in Cystic Fibrosis" Front Pharmacol. 2021 Sep 8;12:702677

FFC Project#16/2013 ***"Phosphodiesterases type-4 (PDE4) inhibitors and β 2-adrenergic agonists to reduce neutrophilic lung inflammation in cystic fibrosis. Preclinical studies and identification of biomarkers of efficacy"*** Virgilio Evangelista (Laboratorio di Biologia Vascolare e Farmacologia, Fondazione Mario Negri Sud Santa Maria Imbaro, Chieti)

- Totani L, Amore C, Piccoli A, et al "Type-4 Phosphodiesterase (PDE4) Blockade Reduces NETosis in Cystic Fibrosis" Front Pharmacol. 2021 Sep 8;12:702677

FFC Project#17/2014 ***"TRPA1 channels as novel molecular targets for anti-inflammatory therapies in CF lung"*** Giulio Cabrini (Laboratorio di Patologia Molecolare, Dip. di Patologia e Diagnostica, Università di Verona), Romina Nassini (Dip. di Scienze Sanitarie, Unità di Farmacologia Clinica e Oncologica, Università di Firenze)

- Ribeiro CMP, McElvaney NG and Cabrini G "Editorial: Novel Anti-Inflammatory Approaches for Cystic Fibrosis Lung Disease: Identification of Molecular Targets and Design of Innovative Therapies" Front. Pharmacol. 2021 Nov 4;12:794854

FFC Project#19/2014 ***"Mitochondrial Ca2+-dependent inflammasome activation exacerbates the P. aeruginosa-driven inflammatory response"*** Paolo Pinton (Dip. di Morfologia, Chirurgia e Medicina Sperimentale, Lab. Trasduzione del Segnale, Università di Ferrara)

- Rimessi A, Vitto VAM, Patergnani S et al. "Update on Calcium Signaling in Cystic Fibrosis Lung Disease" Front Pharmacol. 2021 Mar 11;12:581645.

FFC Project#22/2014 ***"Targeting pathogenic pathways leading to inflammatory Th17 responses in cystic fibrosis: from drug discovery to preclinical validation"*** Luigina Romani (Dip. di Medicina Sperimentale, Università di Perugia)

- Pariano M, Pieroni S, De Luca A et al. "Anakinra Activates Superoxide Dismutase 2 to Mitigate Inflammasome Activity" Int J Mol Sci. 2021 Jun 18;22(12):6531.
- Van de Veerdonk FL, Renga G, Pariano M et al. "Anakinra restores cellular proteostasis by coupling mitochondrial redox balance to autophagy" J Clin Invest. 2022 Jan 18;132(2):e144983.
- Pariano M, Costantini C, Santarelli I et al. "Defective Glyoxalase 1 Contributes to Pathogenic Inflammation in Cystic Fibrosis" Vaccines 2021, 9, 1311.

FFC Project#21/2017 ***"Testing the anti-inflammatory effects of matrix metalloprotease inhibitors in P. aeruginosa-infected CFTR-knockout mice by in vivo imaging techniques"*** Federico Boschi (Dipartimento di Informatica, Università degli Studi di Verona)

- Sandri A, Lleo MM, Boschi F et al. "Protease inhibitors elicit anti-inflammatory effects in mice with *Pseudomonas aeruginosa* acute lung infection" Clin Exp Immunol. 2021 Jan;203(1):87-95.

FFC Project #21/2018 ***"Thymosin alpha 1 in cystic fibrosis: from the lung to the gut"*** Marina Maria Bellet (Dipartimento di Medicina Sperimentale, Università degli Studi di Perugia, Perugia)

- Bellet MM, Borghi M, Pariano M, et al "Thymosin alpha 1 exerts beneficial extrapulmonary effects in cystic fibrosis" Eur J Med Chem. 2021 Jan 1;209:112921

FFC Project#22/2018 ***"Preclinical testing in cystic fibrosis of a repurposed molecule targeting HMGB1"*** Marco Emilio Bianchi (Divisione Genetica e Biologia Cellulare, Unità dinamica della cromatina, Ospedale San Raffaele, Milano)

- De Leo F, Rossi A, De Marchis F et al. "Pamoic acid is an inhibitor of HMGB1·CXCL12 elicited chemotaxis and reduces inflammation in murine models of *Pseudomonas aeruginosa* pneumonia" Molecular Medicine (2022) 28:108

FFC Project#23/2018 ***"Evaluation of anti-inflammatory treatments for CF lung disease in murine models of lung infection in vivo"*** Maria Cristina Dechecchi (Dip. Patologia e Diagnostica, Lab. Patologia Molecolare, AOUI Verona), Annalisa Guaragna (Università degli Studi di Napoli Federico II, Dip. Scienze Chimiche)

- Esposito A, Rossi A, Stabile M et al. "Assessing the potential of N-Butyl-l-deoxynojirimycin (l-NBDNJ) in models of cystic fibrosis as a promising antibacterial agent" ACS Pharmacol Transl Sci. 2024 May 10;7(6):1807-1822.

FFC Project#24/2018 ***"Pharmacology and therapeutics of inhaled indoles, as aryl hydrocarbon receptor ligands, in cystic fibrosis"*** Luigina Romani (Università degli Studi di Perugia, Dip. Medicina Sperimentale)

- Puccetti M, Pariano M, Renga G et al. "Targeted Drug Delivery Technologies Potentiate the Overall Therapeutic Efficacy of an Indole Derivative in a Mouse Cystic Fibrosis Setting" Cells. 2021 Jun 25;10(7):1601
- Pariano M, Puccetti M, Stincardini C et al. "Aryl Hydrocarbon Receptor Agonism Antagonizes the Hypoxia-driven Inflammation in Cystic Fibrosis" Am J Respir Cell Mol Biol. 2022 Oct 17.

FFC Project#25/2018 ***"Enabling pulmonary delivery of siRNA in cystic fibrosis lung inflammation: therapeutic potential of hybrid lipid/polymer nanoparticles"*** Francesca Ungaro (Università degli Studi di Napoli Federico II, Dip. Farmacia), Olivia Monica Merkel (Dept. Pharmazie, Ludwig-Maximilians Universität, München)

- Conte G, Costabile G, Baldassi D et al. "Hybrid Lipid/Polymer Nanoparticles to Tackle the Cystic Fibrosis Mucus Barrier in siRNA Delivery to the Lungs: Does PEGylation Make the Difference?" ACS Appl. Mater. Interfaces 2022, 14, 7565−7578

FFC Project#18/2019 ***"Investigating Achromobacter xylosoxidans pathogenicity and clinical role in CF lung infection"*** Maria M. Lleò (Dip. Diagnostica e Sanità Pubblica, Università di Verona)

- Veschetti L, Sandri A, Patuzzo C et al. "Genomic characterization of Achromobacter species isolates from chronic and occasional lung infection in cystic fibrosis patients" Microb Genom. 2021 Jul;7(7):000606
- Veschetti L, Sandri A, Patuzzo C et al. "Mobilome Analysis of Achromobacter spp. Isolates from Chronic and Occasional Lung Infection in Cystic Fibrosis Patients" Microorganisms. 2021 Jan 8;9(1):130.

FFC Project#20/2019 ***"Evaluation of anti-inflammatory treatments for CF lung disease in murine models of lung infection in vivo: insights on the anti-inflammatory effect of β-sitosterol and anti-inflammatory/anti-infective activity of L-miglustat"*** Maria Cristina Dechecchi (Azienda Ospedaliera Universitaria Integrata di Verona, Laboratorio di Patologia Molecolare-Laboratorio Analisi), Annalisa Guaragna (Università di Napoli Federico II, Dip. di Scienze Chimiche)

- Esposito A, Rossi A, Stabile M et al. "Assessing the potential of N-Butyl-l-deoxynojirimycin (l-NBDNJ) in models of cystic fibrosis as a promising antibacterial agent" ACS Pharmacol Transl Sci. 2024 May 10;7(6):1807-1822.

FFC Project#22/2019 ***"Multi-task evaluation of TMA analogues as anti-inflammatory treatments for CF lung disease"*** Ilaria Lampronti (Dip. Scienze della vita e biotecnologie, Sez. biochimica e biologia molecolare, Università di Ferrara)

- Tupini C, Chilin A, Rossi, A et al "New TMA (4,6,4'-Trimethyl angelicin) Analogues as Anti-Inflammatory Agents in the Treatment of Cystic Fibrosis Lung Disease" Int. J. Mol. Sci. 2022, 23, 14483

FFC Project#23/2019 ***"Potential action of phages as immunomodulators in cystic fibrosis"*** Anna Silvia Pistocchi (Dip. Biotecnologie Mediche e Medicina Traslazionale, Università degli Studi di Milano)

- Cafora M, Chanson M, Pistocchi A "Restoring airway epithelial homeostasis in Cystic Fibrosis" J Cyst Fibros. 2023 Mar;22 Suppl 1:S27-S31

- Cafora M, Poerio N, Forti F et al. "Evaluation of phages and liposomes as combination therapy to counteract *Pseudomonas aeruginosa* infection in wild-type and CFTR-null models" 2022 Front. Microbiol. 13:979610.

FFC Project#17/2020 ***"Oral and pulmonary delivery platforms for anakinra repurposing in cystic fibrosis"*** Stefano Giovagnoli (Università degli Studi di Perugia, Dip. di Scienze Farmaceutiche)

- Pariano M, Costantini C, Santarelli I et al. "Defective Glyoxalase 1 Contributes to Pathogenic Inflammation in Cystic Fibrosis" Vaccines 2021, 9, 1311
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- Puccetti M, Costantini C, Ricci M, Giovagnoli S "Tackling Immune Pathogenesis of COVID-19 through Molecular Pharmaceutics" Pharmaceutics. 2021 Apr 5;13(4):494

FFC Project#20/2020 ***"Harnessing selective histone deacetylase 6 (HDAC6) inhibition to tackle inflammation and fibrotic remodeling in cystic fibrosis"*** Vincenzo Summa (Università degli Studi di Napoli Federico II, Dip. di Farmacia), Lucia Altucci (Università degli Studi della Campania Luigi Vanvitelli, Dip. di Medicina di Precisione)

- Barone S, Cassese E, Alfano AI et al. "Chasing a Breath of Fresh Air in Cystic Fibrosis (CF): Therapeutic Potential of Selective HDAC6 Inhibitors to Tackle Multiple Pathways in CF Pathophysiology" Published as part of the Journal of Medicinal Chemistry special issue "Epigenetics 2022" , J Med Chem. 2022 Feb 24;65(4):3080-3097
- Brindisi M, Barone S, Rossi A, et al "Efficacy of selective histone deacetylase 6 inhibition in mouse models of *Pseudomonas aeruginosa* infection: A new glimpse for reducing inflammation and infection in cystic fibrosis" Eur J Pharmacol. 2022 Dec 5;936:175349

FFC Project#19/2021 ***"Exploring the dual targeting of host and microbial sphingosine-1-phosphate lyase as antimicrobial strategy in cystic fibrosis"*** Barbara Cellini (Università degli Studi di Perugia, Dipartimento di Medicina Sperimentale)

- Cellini B, Pampalone G, Camaioni E et al. "Dual species sphingosine- 1-phosphate lyase inhibitors to combine antifungal and anti- inflammatory activities in cystic fibrosis: a feasibility study" Sci Rep. 2023 Dec 20;13(1):22692.

FFC Project#20/2021 ***"Nanotechnology-based Resolvin D1 as Proresolving Therapy in Cystic Fibrosis: Preclinical Studies for the Delivery of Innovative Formulations to the Clinic"*** Antonio Recchiuti (Università G. d'Annunzio Chieti-Pescara, Dip. di Scienze Mediche, Orali e Biotecnologiche), Alessandra Aloisi (Istituto per la microelettronica e microsistemi - IMM, Consiglio Nazionale delle Ricerche, Lecce)

- Sousa T, Pinho D, Recchiuti A et al. "Editorial: Specialized proresolving mediators: Benefits within and beyond inflammation resolution in cardiometabolic, neurological and psychiatric disorders" Front Physiol. 2023 Apr 4;14:1176700.
- Ferri G, Serano M, Isopi E et al. "Resolvin D1 improves airway inflammation and exercise capacity in cystic fibrosis lung disease" FASEB J. 2023 Nov;37(11):e23233.

FFC Project#10/2022 ***"Towards the development of GY971a as anti-inflammatory drug in Cystic Fibrosis"*** Ilaria Lampronti (Dip. di Scienze della vita e biotecnologie, Università degli Studi di Ferrara)

- Vaccarin C, Gabbia D, Franceschinis E et al. "Improved Trimethylangelicin Analogs for Cystic Fibrosis: Design, Synthesis and Preliminary Screening" , Int J Mol Sci 2022;23:11528.
- Tupini C, Chilin A, Rossi A et al. "New TMA (4,6,4'-Trimethyl angelicin) Analogues as Anti-Inflammatory Agents in the Treatment of Cystic Fibrosis Lung Disease, Int J Mol Sci 2022; 23a:14483.
- Ribeiro CMP, Higgs MG, Muhlebach MS et al. "Revisiting Host-Pathogen Interactions in Cystic Fibrosis Lungs in the Era of CFTR Modulators" , Int J Mol Sci. 2023 Mar 5;24(5):5010.

FFC Project#11/2022 ***"Targeting platelet activation with pro-resolving mediators: an innovative strategy to dampen lung inflammation in cystic fibrosis"*** Domenico Mattoscio (Dip. Scienze Mediche, Orali e Biotecnologiche, Univ. Chieti-Pescara)

- D'Orazio S, Mattoscio D "Dysregulation of the arachidonic acid pathway in cystic fibrosis: implications for chronic inflammation and disease progression" Pharmaceuticals (Basel) 2024, 17(9).
- Mattoscio M, Baeza LA, Bai H et al. "Inflammation and epithelial-mesenchymal transition in a CFTR-depleted human bronchial epithelial cell line revealed by proteomics and human organ-on-a-chip", FEBS J. 2025 Mar 3.

FFC Project#12/2022 ***"Evaluation of phage interactions with host immune system in models of cystic fibrosis: one step toward phage therapy application"*** Anna Silvia Pistocchi (Dip. di Biotecnologie Mediche e Medicina Traslazionale - Biometra, Università degli Studi di Milano)

- Cafora M, Brix A, Forti F et al. "Studying Bacteriophage Efficacy Using a Zebrafish Model" Methods Mol Biol. 2024:2734:151-169.
- Cafora M, Poerio N, Forti F et al. "Evaluation of phages and liposomes as combination therapy to counteract *Pseudomonas aeruginosa* infection in wild-type and CFTR-null models" Front Microbiol. 2022 Sep 15:13:979610.
- Cafora M, Chanson M, Pistocchi A "Restoring airway epithelial homeostasis in Cystic Fibrosis" J Cyst Fibros. 2023 Mar;22 Suppl 1:S27-S31
- Cafora M, Dobi D, William JNG et al. "Anti-inflammatory activity of *Pseudomonas aeruginosa* DEV phage in cystic fibrosis models", J Cyst Fibros. 2025 Mar 6:S1569-1993(25)00069-4

FFC Project GMSG#1//2023 ***"Developing a new respiratory 3D model as an innovative strategy to study the inflammation pathology in cystic fibrosis"*** Roberto Plebani (Dip. di Scienze Mediche, Orali e Biotecnologiche, Università G. d'Annunzio di Chieti-Pescara)

- Mattoscio M, Baeza LA, Bai H et al. "Inflammation and epithelial-mesenchymal transition in a CFTR-depleted human bronchial epithelial cell line revealed by proteomics and human organ-on-a-chip", FEBS J. 2025 Oct;292(19):5086-5104.

FFC Project GMRF#1//2024 ***"Airway surface as a battleground against bacteria"*** Daniela Guidone TIGEM, Pozzuoli (NA, Italy)

- Guidone D, de Santis M, Pesce E et al. "The apical mucus layer alters the pharmacological properties of the airway epitheliumy", J Physiol. 2025 Mar 6.

FFC Project#13//2024 ***"Unraveling proresolving effects of CFTR modulators on lung inflammation and infection"*** Antonio Recchiuti (Department of Medical, Oral, and Biotechnology Science, University G. D'Annunzio Chieti-Pescara, Chieti, Italy)

- Muccia M, Colarellia M, Ripani P et al. "Development and application of a multimatrix LC–MS/MS method for quantifying elexacaftor–tezacaftor–ivacaftor: Expanding therapeutic drug monitoring in cystic fibrosis from systemic circulation to airways and sweat", Biomedicine & Pharmacotherapy

5. CLINICAL AND EPIDEMIOLOGICAL RESEARCH

FFC Project#29/2015 ***"Testing CFTR repair in cystic fibrosis patients carrying nonsense and channel gating mutations"*** Claudio Sorio (Dipartimento di Patologia e Diagnostica Università di Verona), Monica Averna (Dip. di Medicina Sperimentale, sez. di Biochimica Università di Genova)

- Bergamini G, Stellari F, Sandri A et all. "An IL-8 Transiently Transgenized Mouse Model for the *In vivo* Long-term Monitoring of Inflammatory Responses" J Vis Exp. 2017 Jul 7;(125)
- Pedrazzi M, Vercellone S, Barberis E et al. "Identification of Potential Leukocyte Biomarkers Related to Drug Recovery of CFTR: Clinical Applications in Cystic Fibrosis" Int J Mol Sci. 2021 Apr 10;22(8):3928

FFC Project#20/2016 ***"Italian multicenter study of glucose tolerance defects in cystic fibrosis"*** Alberto Battezzati (Centro Internazionale per Inquadramento dello Stato Nutrizionale-ICANS, DeFENS, Università degli Studi di Milano)

- Colombo C, Foppiani A, Bisogno A et al. "Lumacaftor/Ivacaftor in Cystic Fibrosis: Effects on Glucose Metabolism and Insulin Secretion" , J Endocrinol Invest. 2021 Oct;44(10):2213-2218

FFC Project#27/2018 ***"Use of multivolume MRI instead of ionizing imaging techniques for surveillance in young patients after lung transplantation for cystic fibrosis"*** Alessandro Palleschi (Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milano)

- Pennati F, Salito C, Borzani I et al. "Quantitative Multivolume Proton-Magnetic Resonance Imaging in Lung Transplant Recipients: Comparison With Computed Tomography and Spirometry" Acad Radiol. 2021 Oct;28(10):e297-e305.

FFC Project#28/2018 ***"Identification of early molecular biomarkers of acute and chronic rejection in cystic fibrosis patients with lung transplant through the application of omics technologies"*** Federico Rea (Dip. Scienze Cardiologiche, Toraciche e Vascolari, Div. Chirurgia toracica, AOU Padova), Francesco Paolo Schena (Schena Foundation – Omics Research)

- Lunardi F, Abbrescia DI, Vedovelli L et al. "Molecular Profiling of Tissue Samples with Chronic Rejection from Patients with Chronic Lung Allograft Dysfunction: A Pilot Study in Cystic Fibrosis Patients" Biomolecules 2023, 13(1), 97;

FFC Project#30/2018 ***"Cystic Fibrosis screen positive inconclusive diagnosis (CFSPID): an italian multicenter survey evaluating prevalence, clinical data, management and outcome"*** Vito Terlizzi (Centro FC, AOU Meyer, Firenze), Rita Padoan (Centro supporto FC, Spedali Civili, Brescia); Antonella Tosco (Centro FC, Università Federico II, Napoli), Laura Elisabetta Claut (IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano)

- Terlizzi V, Claut L, Tosco A et al. "A survey of the prevalence, management and outcome of infants with an inconclusive diagnosis following newborn bloodspot screening for cystic fibrosis (CRMS/CFSPID) in six Italian centres" J Cyst Fibros. 2021 Sep;20(5):828-834.
- Terlizzi V, Padoan R "Infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis and acute recurrent pancreatitis: what definition?" J Med Screen. 2021 Jul 13;9691413211031613.
- Botti M, Terlizzi V, Francalanci M et al. "Cystic fibrosis in Tuscany: evolution of newborn screening strategies over time to the present" Ital J Pediatr. 2021 Jan 6;47(1):2.
- Terlizzi V, Claut L, Colombo C et al. "Outcomes of early repeat sweat testing in infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/CF screen-positive, inconclusive diagnosis" Pediatr Pulmonol. 2021 Sep 22.
- Dolce D, Claut L, Colombo C et al. "Different management approaches and outcome for infants with an inconclusive diagnosis following newborn screening for cystic fibrosis (CRMS/CFSPID) and *Pseudomonas aeruginosa* isolation" J Cyst Fibros. 2023 Jan;22(1):73-78

FFC Project#24/2019 ***"Early Derangements of Glucose Tolerance in Cystic Fibrosis: effect of CFTR Modulators"*** Alberto Battezzati (Centro Internazionale per lo Studio della Composizione Corporea, DeFENS, Università di Milano), Carla Colombo (Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Clinica Pediatrica De Marchi, Centro Regionale FC, Milano), Vincenzina Lucidi (Ospedale pediatrico Bambino Gesù, Unità Operativa Fibrosi Cistica, Roma), Maria Cristina Lucanto (AOU Messina, Unità di Gastroenterologia Pediatrica e Fibrosi Cistica); Andrea Mari (Istituto di Neuroscienze, CNR, Padova)chimica Università di Genova)

- Battezzati A, Foppiani A, Alicandro G et al. "Prepuberal insulin secretory indices are long-term predictors of short adult stature in cystic fibrosis" Endocr Connect. 2022 May 10;11(5):e220056.
- Andrea F, Ciciriello F, Bisogno A et al. "Distribution of OGTT-Related Variables in Patients with Cystic Fibrosis from Puberty to Adulthood: An Italian Multicenter Study" , J Pers Med. 2023 Mar 3;13(3):469.
- Colombo C, Foppiani A, Bisogno A et al. "Lumacaftor/Ivacaftor in Cystic Fibrosis: Effects on Glucose Metabolism and Insulin Secretion" , J Endocrinol Invest. 2021 Oct;44(10):2213-2218

FFC Project#27/2019 ***"Right ventricle dysfunction in cystic fibrosis patients undergoing lung transplantation"*** Vittorio Scaravilli (Dipartimento Anestesia, Rianimazione ed Emergenza, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano)

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FFC Project#22/2020 ***"Role of viable but non culturable (VBNC) bacterial forms in CF patients in a clinical setting: a translational research"*** Natalia Cirilli (Ospedali Riuniti, Dip. Materno Infantile, Centro FC, Ancona), Luca Tiano (Università Politecnica delle Marche, Dip. di Scienze della Vita e dell'Ambiente), Rosaria Gesuita (Università Politecnica delle Marche, Centro di Epidemiologia, Biostatistica e Informatica Medica)

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6. FFC RICERCA FACILITIES

Cystic Fibrosis animal Core facility (CFaCore) Alessandra Bragonzi (Istituto di Ricerca San Raffaele, Milano)

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Primary Cell Cultures Facility Valeria Capurro (U.O.C. Genetica Medica, Istituto "G. Gaslini" , Genova), Luis J. V. Galietta (Telethon Institute of Genetics and Medicine - TIGEM, Pozzuoli, NA)

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7. STRATEGIC PROJECTS

TFCF Task Force for Cystic Fibrosis, Tiziano Bandiera (Istituto italiano di tecnologia, Genova), Nicoletta Pedemonte (Lab. Genetica Medica, Istituto G. Gaslini, Genova), Luis J. V. Galietta (Telethon Institute of Genetics and Medicine - TIGEM, Pozzuoli, NA)

- Capurro V, Tomati V, Sondo E et al. “Partial Rescue of F508del-CFTR Stability and Trafficking Defects by Double Corrector Treatment” Int J Mol Sci. 2021 May 17;22(10):5262

Molecole 3.0, Paola Barraja (STEBICEF - Laboratorio di sintesi degli eterocicli, Università di Palermo), Luis J.V. Galietta (Telethon Institute of Genetics and Medicine - TIGEM, Pozzuoli, NA)

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1 out 30 and You Don’t Know It, Carlo Castellani, (Centro Fibrosi Cistica, Istituto Giannina Gaslini), Cinzia Colombo, Paola Mosconi (Lab. di Ricerca per il Coinvolgimento dei Cittadini in Sanità - Istituto Mario Negri); Chiara Gerardi, Rita Banzi (Centro Politiche Regolatorie in Sanità - Istituto Mario Negri); Emanuela Foglia, Lucrezia Ferrario, Daniele Bellavia, Elisabetta Garagiola, Fabrizio Schettini (LIUC Università Carlo Cattaneo); Giulia Candiani, Dania Puggioni (Zadig srl)

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GenDel-CF, Anna Cereseto (Dipartimento CIBIO dell’Università di Trento), Sheref S. Mansy (Università dell’Alberta, Canada); Luis J. V. Galietta(Tigem di Pozzuoli, Napoli); Serena Zacchigna (International Center for Genetic Engineering and Biotechnology (ICGEB) di Trieste); Sven Even Borgos, (Stiftelsen for INdustriell og TEknisk Forskning (SINTEF) di Trondheim, Norvegia)

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Appendix 2

Institutes and Laboratories involved in FFC Ricerca projects

ITALY

ABRUZZO

- Dipartimento di Scienze Mediche, Orali e Biotecnologiche, Università "G. d'Annunzio" di Chieti-Pescara
- Dipartimento di Medicina e Scienze dell'Invecchiamento, Università "G. d'Annunzio" di Chieti-Pescara
- Centro FC Teramo
- Dipartimento di Farmacologia Traslazionale, Consorzio Mario Negri Sud, Chieti
- Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, DISCAB - Università degli Studi dell'Aquila
- Laboratorio di Biologia Vascolare e Farmacologia, Fondazione Mario Negri Sud Santa Maria Imbaro (CH)

CAMPANIA

- Dipartimento di Scienze Mediche Traslazionali, Università Federico II, Napoli
- Dipartimento di Biologia Strutturale e Funzionale, Università Federico II, Napoli
- Telethon Institute of Genetics and Medicine - TIGEM, Pozzuoli, NA
- Dipartimento di Scienze Chimiche, Università di Napoli Federico II
- Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università di Napoli Federico II
- CABH - IIT, Napoli
- CEINGE Biotecnologie Avanzate Franco Salvatore, Napoli
- Cystic Fibrosis Regional Center, Paediatric Unit, Department of Maternal and Child health, A.O.U. Federico II, Napoli
- Dipartimento di Chimica Organica e Biochimica, Università Federico II, Napoli
- Dipartimento di Farmacia, Università di Napoli Federico II, Napoli
- Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Napoli
- Dipartimento di Farmacia, Università Federico II, Napoli
- Istituto di Biochimica e Biologia Cellulare (IBBC), CNR, Napoli
- Istituto di Biostrutture e Bioimmagini, CNR, Napoli
- Istituto per l'Endocrinologia e l'Oncologia Sperimentale "Gaetano Salvatore" (IEOS), CNR, Napoli

EMILIA ROMAGNA

- Dipartimento di Scienze della Vita e Biotecnologie, Università degli Studi di Ferrara
- Dipartimento di Farmacia e Biotecnologie (FABIT), Università degli Studi di Bologna
- Dipartimento di Chimica, Scienze delle Vita e della Sostenibilità ambientale, Università degli Studi di Parma
- Centro di Ricerca sulle Terapie Innovative per la Fibrosi Cistica, Università degli Studi di Ferarra
- Department of Electrical, Electronic and Information Engineering "Guglielmo Marconi" (DEI), Università di Bologna
- Dipartimento di Chimica, Università di Bologna
- Dipartimento di Medicina e Chirurgia, Università di Parma
- Dipartimento di Morfologia, Chirurgia e Medicina Sperimentale, Signal Transduction Lab, Università di Ferrara
- Dipartimento di Oncologia, Ematologia e Malattie respiratorie, Università di Modena
- Dipartimento di Pediatria, Università di Parma
- Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna
- Istituto di Genetica Molecolare "Luigi Luca Cavalli-Sforza" (IGM), CNR, Bologna

FRIULI VENEZIA GIULIA

- Istituto di Cristallografia, CNR, Trieste
- International Center for Genetic Engineering and Biotechnology (ICGEB), Trieste
- Dipartimento di Scienze della Vita, Università degli Studi Trieste
- IRCCS, "Burlo Garofolo", Trieste

LAZIO

- Dipartimento di Biologia e Biotecnologie "Charles Darwin", Università La Sapienza, Roma
- Dipartimento Chimica e Tecnologie del Farmaco, Università La Sapienza, Roma
- Dipartimento di Medicina Molecolare, Università La Sapienza, Roma
- Dipartimento di Biomedicina e Prevenzione, Università di Roma "Tor Vergata"
- Dipartimento di Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma
- Dipartimento di Biologia, Università di Roma "Tor Vergata"
- Dipartimento di Scienze e Tecnologie Chimiche, Università di Roma "Tor Vergata"
- Dipartimento di Scienze, Università Roma Tre, Roma
- Dipartimento di Salute Pubblica e Malattie Infettive, Istituto Superiore di Sanità (ISS), Roma
- Ospedale pediatrico Bambino Gesù, Laboratorio Microbiologia Fibrosi Cistica, Roma
- Ospedale pediatrico Bambino Gesù, Unità Operativa Fibrosi Cistica, Roma
- Dipartimento di Malattie Infettive, Istituto Superiore di Sanità
- ENEA Centro Ricerche Casaccia
- Facoltà di Medicina, Università Cattolica Sacro Cuore, Roma
- Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Santa Lucia Foundation
- Istituto Superiore di Sanità, Roma
- Laboratorio di Microbiologia FC, Ospedale Bambino Gesù

LIGURIA

- Centro Fibrosi Cistica, Istituto "G. Gaslini", Genova
- UOC Genetica Clinica, Istituto "G. Gaslini", Genova
- Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGMI)
- Dipartimento di Farmacia, Università degli Studi di Genova
- Dipartimento di Medicina Sperimentale, Università degli Studi di Genova
- Dipartimento di Farmacia, Sezione di Chimica Medica - Scuola di Scienze Mediche e Farmaceutiche, Università degli Studi di Genova
- Dipartimento di Scienze Pediatriche, Centro FC, Università di Genova, Istituto "G. Gaslini"
- Istituto Italiano di Tecnologia, Analytical Chemistry Facility, Genova
- IRCCS, Istituto "G. Gaslini", Terapia Intensiva Neonatale e Pediatrica, Genova
- IRCCS Ospedale Policlinico San Martino, Genova
- Istituto di Biofisica, CNR, Genova
- Istituto per la microelettronica e microsistemi (IMM), CNR

LOMBARDIA

- Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano
- Laboratorio di Microbiologia molecolare, Dipartimento di Biologia e Biotecnologia “Lazzaro Spallanzani”, Università degli Studi di Pavia
- Dipartimento di Biotecnologie mediche e Medicina translazionale (BioMeTra), Università degli Studi di Milano
- Dipartimento di Bioscienze, Università degli Studi di Milano
- Dipartimento di Biologia e Genetica per le Scienze Mediche, Università degli Studi di Milano
- Dipartimento di Biochimica Medica e Medicina Traslazionale, Università degli Studi di Milano
- Dipartimento di Biotecnologie e Bioscienze, Università degli Studi di Milano
- Dipartimento di Biotecnologie e Bioscienze, Università di Milano-Bicocca
- Dipartimento di Chimica, Università degli Studi di Milano
- Dipartimento di Elettronica, Informazione e Bioingegneria, Università di Milano
- Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia
- Dipartimento di Psicologia - Engage Minds Hub Center, Università Cattolica Sacro Cuore, Milano
- Dipartimento di Scienze della Salute, Università degli Studi di Milano
- Dipartimento di Ingegneria Strutturale, Politecnico Milano
- Dipartimento di Medicina Clinica e Prevenzione, Università di Milano-Bicocca
- Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia
- Dipartimento di Scienze Farmacologiche e Biomolecolari (DiSFeB) , Università di Milano
- Dipartimento di Chirurgia e Medicina Traslazionale, Università di Milano-Bicocca, Laboratorio di Epatologia
- Laboratorio di Biochimica e Biologia Molecolare, Dip. Medicina, Osp. S. Paolo, Università di Milano
- Laboratorio di Biologia Clinica Molecolare e Citogenetica, Università Vita-Salute HSR, Milano
- Laboratorio di Tecnologie Biomediche, Dipartimento di Elettronica, Informazione e Bioingegneria (DEIB), Politecnico Di Milano
- Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico, Laboratorio Microbiologia FC, Milano
- Istituto di Ricerca Genetica e Biomedica (IRGB), CNR, Milano
- Istituto Nazionale Genetica Molecolare (INGM), Milano
- IRCCS Istituto Auxologico Italiano, Milano
- Istituto di Ricerche Farmacologiche Mario Negri, Centro Politiche Regolatorie in Sanità, Milano
- Istituto di Ricerche Farmacologiche Mario Negri, Laboratorio Ricerca per il Coinvolgimento dei Cittadini in Sanità, Milano
- LIUC - Università Carlo Cattaneo, Varese
- Fondazione IRCCS Istituto Nazionale dei Tumori, Milano
- Infection and Cystic Fibrosis Unit San Raffaele Scientific Institute, Milano
- Istituto di Biofisica, CNR, sede di Milano
- Istituto di Chimica del Riconoscimento Molecolare (ICRM) - CNR, Milano
- Istituto di Ricerche Farmacologiche Mario Negri IRCSS, Bergamo
- Istituto di Scienze e Tecnologie Chimiche “Giulio Natta” (SCITEC), CNR
- Istituto di Tecnologie Biomediche (ITB), CNR
- Istituto Europeo per Ricerca in Fibrosi Cistica-IERFC, Istituto San Raffaele, Milano
- Universita di Brescia, Ospedale dei Bambini, AO Spedali Civili
- Università Vita e Salute, San Raffaele, Milano
- IRCCS Humanitas Research Hospital
- IRCCS Ospedale San Raffaele
- Centro Alta Tecnologia "Istituto di Ricerche Chimiche e Biochimiche G. Ronzoni" Srl
- Centro Diagnostico Italiano, Milano
- Computational Sciences Chemical Core Technologies Department Nerviano Medical Sciences, Srl
- Zadig

MARCHE
- Dipartimento di Scienze Biomolecolari e Biotecnologiche, Università degli Studi di Urbino “Carlo Bo”
- Dipartimento Materno Infantile, Centro Regionale FC, Ospedali Riuniti, Ancona
- Centro di Epidemiologia, Biostatistica e Informatica Medica, Università Politecnica delle Marche, Ancona
- Dipartimento di Scienze della Vita e dell’Ambiente, Università Politecnica delle Marche, Ancona
- Università di Camerino

PIEMONTE
- Dipartimento di Biotecnologie molecolari e Scienze per la Salute, Università degli Studi di Torino
- Dipartimento di Scienze Mediche, Università di Torino
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- Dipartimento di Biologia, Università degli Studi di Pisa
- Dipartimento di Biotecnologie Mediche, Università di Siena
- Dipartimento di Biologia dell'Evoluzione, Università Firenze
- Dipartimento di Biologia, Università di Firenze
- Dipartimento di Scienze della Salute, Università degli Studi di Firenze
- Dipartimento di Scienze Sanitarie, Unità di Farmacologia Clinica e Oncologica, Università di Firenze
- Dipartimento di Medicina Pediatrica, Ospedale dei Bambini "A. Meyer"
- Dipartimento di Scienze Farmaceutiche, Università di Firenze
- Meyer Children's Hospital IRCCS, Cystic Fibrosis Regional Reference Centre
- Unità Infezione e Malattie Tropicali, Azienda Ospedaliero-Universitaria Careggi, Firenze

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- Dipartimento di Medicina e Chirurgia, Università degli Studi di Perugia

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- Dipartimento di Scienze Biomediche, Università degli Studi di Padova
- Dipartimento di Scienze del Farmaco, Università di Padova
- Dipartimento di Scienze Biomediche, Università di Padova
- Laboratorio di Patologia Molecolare, Azienda Ospedaliera Universitaria Integrata di Verona
- Campus Agripolis, Università degli Studi di Padova
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- Newcastle University
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- Stiftelsen for INdustriell og TEknisk Forskning (SINTEF), Trondheim

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- Erasmus University Medical Center Department of Gastroenterology & Hepatology
- Sophia Children's Hospital

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- McGill University Department of Physiology, Montreal
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- Joe DiMaggio Cystic Fibrosis, Pulmonary and Sleep Center, Hollywood, Florida

Appendix 3

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Aknowledgment

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Appendix 4

FFC Ricerca Projects (2023-2025) adopted by Supporters

PROGETTO STRATEGICO FFC RICERCA 2024-2027. GENDEL-CF. Strategie di trasferimento genico nei polmoni per il trattamento della fibrosi cistica
Responsabile: **Anna Cereseto** (Dipartimento CIBIO dell'Università di Trento)
Finanziamento: 1.870.207 €
Adottato da: **Lascito Anna Cantelli** (€ 490.000); **Delegazione FFC Ricerca di Imola e Romagna** (€ 100.000); **Gruppo di sostegno FFC Ricerca "Insieme per Giulia Sofia"** (€ 20.000); **Delegazione FFC Ricerca di Alberobello** (€ 30.000), **Delegazione FFC Ricerca di Torino** (€ 30.000), **Delegazione FFC Ricerca di Verbania e V.C.O.** (€ 10.000), **Doniamoci - Fundraising Dinner** (€ 42.000), **Delegazione FFC Ricerca di Reggello Firenze** (€ 30.000), **Associazione Fibrosi Cistica Alto Adige ODV** (€ 35.000), **Delegazione FFC Ricerca di Vicenza** (€ 50.000), **Loifur Srl** (€ 14.000), **Lega Italiana Fibrosi Cistica Emilia - Onlus** (€ 30.000), **Project Hope - Rosa Pastena** (€ 12.000), **Delegazione FFC Ricerca Val d'Alpone** (€ 60.000), **MinervaHub per la ricerca** (€ 10.000), **Parker** (€ 27.650), **Delegazione FFC Ricerca di Palermo e Trapani** (€ 50.000), **Delegazione FFC Ricerca di Bolzano** (€ 20.000), **Imprese unite per la ricerca** (€ 19.557), **Delegazione FFC Ricerca di Vercelli** (€ 30.000), **Delegazione FFC Ricerca di Imola e Romagna** (€ 80.000), **Delegazione FFC Ricerca della Valpolicella** (€ 45.000), **Antonio Guadagnin & Figlio srl** (€ 10.000), **Delegazione FFC Ricerca di Verbania** (€ 14.000), **Delegazione FFC Ricerca di Napoli con il Gruppo di Sostegno FFC Ricerca di Vitulazio** (€ 50.000), **Associazione Trentina "Dedicato a Efrem Gottoli"** (€ 60.000), **Delegazione FFC Ricerca di Messina** (€ 15.000) **La Chiave della Vita – In ricordo di Laura** (€ 50.000); **Delegazione FFC Ricerca del Lago di Garda** (€ 200.000); **Doniamoci – Fundraising Dinner** (€ 86.000); **Delegazione FFC Ricerca "Insieme per Giulia Sofia" – Cuneo** (€ 20.000); **Delegazione FFC Ricerca Melilli Siracusa** (€ 40.000); **Asta stellare Dallara – Intesa Sanpaolo** (€ 70.000); **Ass. Fino all'ultimo respiro ODV ETS** (€ 10.000); **CrowdForLife – Crédit Agricole Italia** (€ 10.000).

PROGETTO STRATEGICO FFC RICERCA 2025. 1 SU 30 E NON LO SAI. FASE 4. Una campagna di informazione e sensibilizzazione sul test del portatore sano di fibrosi cistica
Responsabile: **Jara Bombana** (Responsabile comunicazione istituzionale FFC Ricerca), **Carlo Castellani** (Centro Fibrosi Cistica, Istituto Giannina Gaslini, Genova)
Adottato da: **Fondazione Corrado e Bruno Maria Zaini** (€ 30.000); **Delegazione FFC Ricerca di Campiglione Fenile – Torino** (€ 20.000).

PROGETTO STRATEGICO FFC RICERCA 2023-2025. MOLECOLE 3.0 PER LA FIBROSI CISTICA. FASE 4. Nuovi modulatori farmacologici per il recupero della proteina CFTR mutata
Responsabili: **Paola Barraja** (STEBICEF - Laboratorio di sintesi degli eterocicli, Università di Palermo); **Luis Galietta** (Istituto Telethon di Genetica e Medicina – TIGEM, Pozzuoli, Napoli)
Adottato totalmente da: **Delegazione FFC Ricerca di Palermo e Trapani** (€ 50.000); **Rotary Distretto 2060** (€ 28.000); **Gruppo di sostegno FFC Ricerca di Matera** (€ 12.000); **Delegazione FFC Ricerca di Treviso Montebelluna** (€ 20.000); **Imprese Unite per la Ricerca** (€ 20.000); **I migliori amici della ricerca 2024** (€ 27.792,60); **Associazione Un sogno per vincere** (€ 8.000); **Rotary Distretto 2060** (€ 21.000); **I migliori amici della ricerca 2025** (€ 3.257,40).

PROGETTO STRATEGICO FFC RICERCA 2023-2025. ESPERTI INSIEME. Migliorare l'integrazione e la condivisione degli obiettivi fra la comunità FC e il mondo della scienza e della ricerca
Responsabile: **Michele Gangemi** (Fondazione Ricerca Fibrosi Cistica)
Finanziamento: 45.000 €.
Adottato totalmente da: **UniCredit** (€ 20.000); **Delegazione FFC Ricerca di Campiglione Fenile** (€ 10.000); **Latteria Montello S.p.A.** (€ 15.000).

PROGETTO STRATEGICO FFC RICERCA 2023-2025. KAFTRIO NELLA VITA REALE. Efficacia e si curezza di Kaftrio nella vita reale: studio italiano osservazionale e multicentrico
Responsabile: **Cesare Braggion** (Direzione Scientifica, Area Ricerca Clinica FFC Ricerca)
Ricercatore principale: **Maria Cristina Lucanto** (Centro Regionale di Riferimento per la Fibrosi Cistica di Messina)
Finanziamento: 328.000 €
Adottato totalmente da: **Gruppo di sostegno FFC Ricerca Miriam Colombo – Ospedaletti** (€ 50.000); **Delegazione FFC Ricerca di Genova** (€ 50.000); **Delegazione FFC Ricerca di Brindisi Torre** (€ 30.000); **Delegazione FFC Ricerca di Milano** (€ 100.000); **Delegazione FFC Ricerca di Napoli** (€ 52.000); **Delegazione FFC Ricerca Cosenza Sud** (€ 8.000); **Delegazione FFC Ricerca della Valpolicella** (€ 30.000); **Delegazione FFC Ricerca di Roma Pomezia** (€ 8.000).

- **GMSG#1/2022 - Sviluppo di sistemi di trasporto per la tecnologia CRISPR-Cas per la cura della fibrosi cistica**
Responsabile: **Giulia Maule** (Dip. di Biologia Cellulare, Computazionale e Integrata CIBIO, Università di Trento)
Finanziamento: 149.000 €
Adottto totalmente da: **Delegazione FFC Ricerca Val d'Alpone** (€ 80.000); **Together for Life** (€ 69.000).

- **FFC#7/2022 - Identificazione dei tipi di *Mycobacterium abscessus* presenti in Italia e dei biomarcatori dell'ospite per caratterizzare l'infezione da micobatteri in fibrosi cistica**
Responsabile: **Nicola Ivan Lorè** (Unità Patogeni Batterici Emergenti, Istituto Scientifico San Raffaele, Milano)
Finanziamento: 128.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Morbegno** (€ 25.000); **Kymos Srl SB** (€ 9.000); **Antonio Guadagnin & Figlio Srl** (€ 8.000); **Gruppo di sostegno FFC Ricerca di Martinsicuro Teramo** (€ 22.000); **LIFC Toscana Onlus** (€ 10.000); **Delegazione FFC Ricerca di Cecina e Rosignano** (€ 54.000).

- **FFC#15/2022 - Usare gli anticorpi come potenziali biomarcatori per la diagnosi e la terapia dell'aspergillosi broncopolmonare allergica nei bambini con fibrosi cistica**
Responsabile: **Teresa Zelante** (Dip. di Medicina e Chirurgia, Università degli Studi di Perugia)
Finanziamento: 130.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Verbania e V.C.O.** (€ 10.000); **Delegazione FFC Ricerca di Fermo** (€ 12.000); **Delegazione FFC Ricerca di Fabriano Ancona** (€ 12.000); **Delegazione FFC Ricerca della Valpolicella** (€ 36.000); **Delegazione FFC Ricerca di Tradate Gallarate** (€ 60.000).

- **GMSG#1/2023 - Messa a punto di un modello 3D di tessuto respiratorio per studiare l'infiammazione in fibrosi cistica**
Responsabile: **Roberto Plebani** (Dip. di Scienze Mediche, Orali e Biotecnologiche, Università G. d'Annunzio di Chieti-Pescara)
Finanziamento: 159.162 €
Adottato totalmente da: **Together for life**

- **GMRF#1/2023 - Espianti di polmone di maiale come nuovo modello per testare la terapia fagica contro infezioni da *Pseudomonas aeruginosa* in fibrosi cistica**
Responsabile: **Marco Cafora** (Dip. Biotecnologie mediche e Medicina translazionale, Università degli Studi di Milano)
Finanziamento: 105.000 €
Adottato da: **Donatori regolari FFC Ricerca** (€ 70.000), **Delegazione FFC Ricerca di Novara** (€ 8.000), **Delegazione FFC Ricerca di Belluno** (€ 27.000).

- **FFC#1/2023 - Studio degli effetti secondari del Kaftrio sui grassi che compongono le cellule**
Responsabile: **Andrea Armirotti** (Istituto Italiano di Tecnologia - IIT Genova)
Finanziamento: 73.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Acqui Terme** (€ 53.500); **Gruppo di Sostegno FFC Ricerca Palo del Colle** (€ 20.000).

- **FFC#2/2023 - Esplorare i percorsi cellulari della proteina CFTR mutata per potenziarne il recupero**
Responsabile: **Carlos M. Farinha** (BioISI - Biosystems and Integrative Sciences Institute, University of Lisboa, Portugal)
Finanziamento: 136.465 €
Adottato totalmente da: **Gruppo di sostegno FFC Ricerca di Vimerca-**

te - in ricordo di Gloria (€ 94.000); **Armito Teatro - Delegazione FFC Ricerca di Genova "Mamme per la ricerca"** (€ 12.000); **Delegazione FFC Ricerca di Nichelino e Moncalieri** (€ 30.465).

- **FFC#3/2023 - Studio dei meccanismi alla base della variabilità di risposta ai modulatori di CFTR della mutazione N1303K su cellule nasali primarie**

Responsabile: **Renata Bocciardi** (Dip. di neuroscienze, riabilitazione, oftalmologia, genetica e scienze materno-infantili - DINOGMI, Università degli Studi di Genova)
Finanziamento: 135.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Genova "Mamme per la ricerca"** (€ 60.000); **Delegazione FFC Ricerca di Tradate Gallarate** (€ 76.500).

- **FFC#4/2023 - Strategia del cavallo di Troia per migliorare il trattamento delle infezioni polmonari da *Pseudomonas aeruginosa***

Responsabile: **Andrea Battistoni** (Dip. di Biologia, Università di Roma "Tor Vergata")
Finanziamento: 73.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Boschi Sant'Anna Minerbe "Alla fine esce sempre il sole"** (€ 35.000); **Associazione Trentina Fibrosi Cistica Odv - In ricordo di Luciano Rossi** (€ 20.000); **Delegazione FFC Ricerca di Sondrio Valchiavenna** (€ 18.500).

- **FFC#5/2023 - Oltre il polmone: studiare il ruolo dell'intestino nella fibrosi cistica**

Responsabile: **Alessandra Bragonzi** (Unità Infezioni e Fibrosi cistica, Divisione di Immunologia, Trapianti e Malattie Infettive, Istituto Scientifico San Raffaele, Milano)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Palermo e Trapani - #8maggioèpersempre2023 in memoria di Costanza (8.000€).**

- **FFC#6/2023 - Individuare nuovi farmaci contro *Pseudomonas aeruginosa* e *Staphylococcus aureus* mediante l'approccio di screening virtuale**

Responsabile: **Silvia Buroni** (Dip. Biologia e Biotecnologie "Lazzaro Spallanzani", Università di Pavia)
Finanziamento: 210.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Campiglione Fenile** (€ 40.000); **Delegazione FFC Ricerca Valle Scrivia Alessandria** (€ 16.000); **Delegazione FFC Ricerca di Vigevano** (€ 30.000), **Delegazione FFC Ricerca di Boschi Sant'Anna Minerbe "Alla fine esce sempre il sole"** (€ 40.000), **Delegazione FFC Ricerca di Lecco Valsassina** (€ 59.000), **Delegazione FFC Ricerca di Padova** (€ 25.000).

- **FFC#7/2023 - Valutazione del potenziale dell'antibiotico cefiderocol su *Pseudomonas aeruginosa* per il trattamento delle infezioni polmonari in fibrosi cistica**

Responsabile: **Barbara Citterio** (Dip. Scienze Biomolecolari e Biotecnologiche, Università di Urbino)
Finanziamento: 126.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Ferrara** (€ 10.000); **Delegazione FFC Ricerca di Belluno** (€ 12.000); **Adare Pharma Solutions** (€ 12.000), **Delegazione FFC Ricerca di Cecina e Rosignano** (€ 24.000); **Amici della ricerca** (€ 20.000); **Delegazione FFC Ricerca di Prato** (€ 28.000); **Delegazione FFC Ricerca di Pavia** (€ 20.000).

- **FFC#8/2023 - Nanoparticelle inalabili per la somministrazione di combinazioni di molecole antimicrobiche nel trattamento delle infezioni polmonari in fibrosi cistica**

Responsabile: **Eugenio Notomista** (Dip. Biologia Strutturale e Funzionale, Università Federico II, Napoli)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Napoli** (€ 32.000); **Gruppo di sostegno FFC Ricerca di Vitulazio** (€ 8.000); **Associazione Trentina Fibrosi Cistica Odv - In ricordo di Maria Gardumi e Alba Leveghi** (€ 20.000); **Delegazione FFC Ricerca di Vittoria Ragusa e Siracusa** (€ 76.500).

- **FFC#9/2023 - Valutazione dell'efficacia del nuovo antibiotico "VOMG" contro *Mycobacterium abscessus***

Responsabile: **Maria Rosalia Pasca** (Dip. di Biologia e Biotecnologie Lazzaro Spallanzani, Università degli Studi di Pavia)
Finanziamento: 136.500 €
Adottato totalmente da: **Donazione Carolina Sabatini** (€ 35.000); **Delegazione FFC Ricerca di Siniscola Nuoro** (€ 50.000); **Gruppo di sostegno FFC Ricerca di Casale Monferrato** (€ 8.000); **Delegazione FFC Ricerca della Valdadige** (€ 18.000); **Delegazione FFC Ricerca di Crevalcore** (€ 25.500).

- **FFC#10/2023 - Riposizionamento di farmaci per inibire l'adattamento di *Pseudomonas aeruginosa* all'ambiente polmonare nelle persone con fibrosi cistica**

Responsabile: **Giordano Rampioni** (Dip. di Scienze, Università Roma Tre, Roma)
Finanziamento: 66.150 €
Adottato totalmente da: **Associazione Trentina Fibrosi Cistica Odv - In ricordo di Otello Pegoretti** (€ 20.000); **Delegazione FFC Ricerca di Morbegno** (€ 36.000); **Delegazione FFC Ricerca di Ferrara** (€ 10.150).

- **FFC#11/2023 - Risoluzione delle infezioni da *Mycobacterium abscessus* con una terapia ispirata ai fagi**

Responsabile: **Loris Rizzello** (Istituto Nazionale Genetica Molecolare - INGM, Milano)
Finanziamento: 73.500 €
Adottato totalmente da: **Associazione Trentina Fibrosi Cistica Odv - In ricordo di Silvio Pellegrini** (€ 20.000); **Antonio Guadagnin & Figlio Srl** (€ 8.000); **Gruppo di sostegno FFC Ricerca Grottaglie** (€ 10.000); **Gruppo di sostegno FFC Ricerca di Magenta Milano** (€ 10.000); **Delegazione FFC Ricerca di Lecce** (€ 15.500); **Gruppo di sostegno FFC Ricerca di Casarile Milano** (€ 10.000).

- **FFC#12/2023 - Rieducare il sistema immunitario dell'ospite a neutralizzare l'infezione da *Mycobacterium abscessus***

Responsabile: **Edoardo Scarpa** (Dip. di Scienze Farmaceutiche, Università degli Studi di Milano)
Finanziamento: 136.500 €
Adottato da: **Delegazione FFC Ricerca di Firenze** (€ 15.000); **Delegazione FFC Ricerca di Ascoli Piceno** (€ 30.000) ; **"Respiri" charity dinner Voce – Aimo e Nadia** (€ 47.000); **Delegazione FFC Ricerca di Fabriano Ancona (€ 24.500)**.

- **FFC#13/2023 - Costruire strutture derivate da *Pseudomonas aeruginosa* per stimolare il sistema immunitario dell'ospite contro il batterio**

Responsabile: **Marco Sette** (Dip. di Scienze e Tecnologie Chimiche, Università di Roma "Tor Vergata")
Finanziamento: 210.000 €
Adottato totalmente da: **Delegazione FFC Ricerca del Lago di Garda.**

- **FFC#14/2023 - Identificazione dei meccanismi molecolari che portano all'attivazione delle cellule immunitarie Th1/17 patogeniche in fibrosi cistica**

Responsabile: **Moira Paroni** (Dip. di Bioscienze, Università degli Studi di Milano)
Finanziamento: 210.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Codogno e Piacenza** (€ 10.000); **Delegazione FFC Ricerca di Vercelli** (€ 30.000); **Delegazione FFC Ricerca della Franciacorta e Val Camonica** (€ 50.000); **Gruppo di sostegno FFC Ricerca di Ghedi** (€ 40.000); **Gruppo di sostegno FFC Ricerca "Il Sogno di Aiden"** (€ 40.000); **Amici della Ritty** (€ 40.000).

- **FFC#15/2023 - Melanocortine per controllare l'infiammazione nella fibrosi cistica**

Responsabile: **Mario Romano** (Dip. di Scienze Mediche, Orali e Biotecnologiche, Università G. d'Annunzio di Chieti-Pescara)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Treviso Montebelluna** (€ 30.000); **Delegazione FFC Ricerca di Pesaro - Delegazione FFC Ricerca di Parma Fidenza - Delegazione FFC Ricerca di Torino Rivarolo Canavese** (€ 80.000); **Delegazione FFC Ricerca di Pescara - Gruppo di sostegno FFC Ricerca della Valle Peligna e della Marsica** (€ 10.000); **LIFC Abruzzo** (€ 16.500).

- **FFC#16/2023 - Affrontare la resistenza alla terapia fagica di batteri *Pseudomonas aeruginosa* isolati da persone con fibrosi cistica**

Responsabile: **Federica Briani** (Dip. di Bioscienze, Università degli Studi di Milano)
Finanziamento: 113.085 €
Adottato totalmente da: **Gruppo di sostegno FFC Ricerca di Saviano** (€ 30.000); **Delegazione FFC Ricerca di Sondrio Valchiavenna** (€ 40.000); **Delegazione FFC Ricerca di Milano** (€ 43.085).

- **FFC#1/2024 - Ottimizzazione di nuovi potenziatori attivi su mutazioni (ultra)rare di CFTR che non rispondono alle terapie farmacologiche disponibili**

Responsabile: **Giovanni Marzaro** (Dip. di Scienze del farmaco, Università di Padova)
Finanziamento: 136.500 €

Adottato totalmente da: **Delegazione FFC Ricerca di Acqui Terme** (€ 100.000); **Delegazione FFC Ricerca di Vicenza** (€ 36.500).

- **FFC#2/2024 - Studio sulla sicurezza di Kaftrio in gravidanza e in giovane età**

Responsabile: **Andrea Armirotti** (Analytical Chemistry Facility, Istituto italiano di tecnologia, Genova)
Finanziamento: 208.425 €
Adottato totalmente da: **Delegazione FFC Ricerca Miriam Colombo Ospedaletti – Imperia** (€ 15.000); **Delegazione FFC Ricerca di Genova "Mamme per la ricerca"** (€ 100.000); **Delegazione FFC Ricerca di Rovigo** (€ 20.000); **Delegazione FFC Ricerca di Milano** (€ 40.000); **Delegazione FFC Ricerca di Catania Paternò** (€ 33.425).

- **FFC#3/2024 - Promuovere il corretto ripiegamento della proteina CFTR mutata per potenziare l'azione dei correttori**

Responsabile: **Mauro Salvi** (Dipartimento di Scienze Biomediche, Università degli Studi di Padova)
Finanziamento: 63.525 €
Adottato totalmente da: **Delegazione FFC Ricerca Fibrosirun Monza Brianza** (€ 63.525).

- **FFC#4/2024 - Un approccio di terapia personalizzata con antinfiammatori e antiossidanti per aumentare l'efficacia dei modulatori di CFTR**

Responsabile: **Onofrio Laselva** (Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Foggia)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca Valle Scrivia Alessandria** (€ 16.000); **Delegazione FFC Ricerca di Roma Pomezia** (€ 20.000); **Delegazione FFC Ricerca di Vicenza** (€ 45.500); **Delegazione FFC Ricerca di Alberobello con volontari di Noci** (€ 30.000); **Delegazione FFC Ricerca di Latina** (€ 25.000).

- **FFC#5/2024 - Sviluppo di terapie non tradizionali contro *Pseudomonas aeruginosa* agendo su piccoli RNA batterici**

Responsabile: **Giovanni Bertoni** (Dipartimento di Bioscienze, Università degli Studi di Milano)
Finanziamento: 73.290 €
Adottato totalmente da: **Delegazione FFC Ricerca della Franciacorta e Val Camonica** (€ 73.290).

- **FFC#6/2024 - Avanzamenti della terapia fagica per il trattamento di infezioni batteriche polmonari da *Mycobacterium abscessus* in persone con fibrosi cistica**

Responsabile: **Mariagrazia Di Luca** (Dipartimento di Biologia, Università degli Studi di Pisa)
Finanziamento: 135.450 €
Adottato totalmente da: **Delegazione FFC Ricerca di Napoli con Gruppo di sostegno FFC Ricerca di Vitulazio** (€ 30.000); **Delegazione FFC Ricerca di Saviano** (€ 30.000); **Iniziativa #CorrerePerUnRespiro promossa dalla Delegazione FFC Ricerca di Milano** (€ 75.450).

- **FFC#7/2024 - Interrompere la comunicazione tra batteri, o *quorum sensing*, per contrastare le infezioni di *Pseudomonas aeruginosa***

Responsabile: **Sandra Gemma** (Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena)
Finanziamento: 135.450 €
Adottato totalmente da: **Delegazione FFC Ricerca di Manciano Grosseto** (€ 12.000); **Delegazione FFC Ricerca di Verona** (€ 20.000); **Delegazione FFC Ricerca di Moncalvo Asti** (€ 35.000); **Delegazione FFC Ricerca di Crevalcore** (€ 28.450); **Delegazione FFC Ricerca di Fermo** (€ 10.000); **Delegazione FFC Ricerca di Milano - Milano Marathon** (€ 30.000).

- **FFC#8/2024 - Una terapia combinata contro le co-infezioni da *Pseudomonas aeruginosa* e *Staphylococcus aureus* in fibrosi cistica**

Responsabile: **Annalisa Guaragna** (Dipartimento Scienze Chimiche, Università Federico II, Napoli)
Finanziamento: 195.300 €
Adottato totalmente da: **Delegazione FFC Ricerca di Tradate Gallarate** (€ 100.000); **Delegazione FFC Ricerca "Un fiore per Valeria" Assemini – Cagliari** (€ 12.000); **Delegazione FFC Ricerca di Monterotondo Roma** (€ 20.000); **Delegazione FFC Ricerca di Benevento** (€ 8.000); **Delegazione FFC Ricerca di Cosenza Sud** (€ 8.000); **Gruppo di sostegno FFC Ricerca di Seregno** (€ 16.000); **Delegazione FFC Ricerca di Altamura** (€ 8.000); **Gruppo di sostegno FFC Ricerca di Isili – Cagliari** (€ 23.300).

- **FFC#9/2024 - Il contributo di Kaftrio alle terapie contro i micobatteri non tubercolari in fibrosi cistica**

Responsabile: **Santiago Ramón García** (ARAID Foundation, Dipartimento di microbiologia, Università di Zaragoza, Spagna)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca "Il sogno di Aiden"** (€ 50.000); **Amici della ricerca** (€ 16.000); **Delegazione FFC Ricerca di Vittoria Ragusa** (€ 35.250); **Delegazione FFC Ricerca di Catania Mascalucia** (€ 35.250).

- **FFC#10/2024 - Approcci chimico-farmaceutici per identificare nuovi agenti anti-*Mycobacterium abscessus***

Responsabile: **Stefano Sabatini** (Dipartimento di Scienze Farmaceutiche, Università degli Studi di Perugia)
Finanziamento: 89.250 €
Adottato totalmente da: **Delegazione FFC Ricerca di Alba Cuneo**

- **FFC#11/2024 - GY971 come agente anti-infiammatorio 2.0**

Responsabile: **Ilaria Lampronti** (Dipartimento di Scienze della vita e biotecnologie, Università degli Studi di Ferrara)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Treviso Montebelluna "Bottega delle donne"** (€ 40.000); **Delegazione FFC Ricerca di Ferrara** (€ 10.000); **Delegazione FFC Ricerca di Torino** (€ 20.000); **Delegazione FFC Ricerca di Massafra** (€ 66.500).

- **FFC#12/2024 - Agire sul sistema immunitario per spegnere l'infiammazione delle vie aeree in fibrosi cistica**

Responsabile: **Domenico Mattoscio** (Dipartimento di Scienze Mediche, Orali e Biotecnologiche, Università degli Studi "G. d'Annunzio" Chieti - Pescara)
Finanziamento: 210.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Como Dongo** (€ 80.000); **Delegazione FFC Ricerca di Codogno e Piacenza** (€ 20.000); **Gruppo di sostegno FFC Ricerca di Martinsicuro Teramo** (€ 12.000); **Delegazione FFC Ricerca di Novara** (€ 8.000); **Delegazione FFC Ricerca di Pavia** (€ 8.000); **Delegazione FFC Ricerca di Ascoli Piceno** (€ 20.000); **Gruppo di sostegno FFC Ricerca di Reggio Emilia** (€ 8.000); **Delegazione FFC Ricerca di Lecce** (€ 25.000); **Gruppo di sostegno FFC Ricerca di Asti** (€ 29.000)

- **FFC#13/2024 - Comprendere il ruolo dei modulatori di CFTR sulla risoluzione dell'infiammazione e delle infezioni nelle persone con fibrosi cistica**

Responsabile: **Antonio Recchiuti** (Università degli Studi "G. d'Annunzio" Chieti - Pescara, Dip. Scienze Mediche, Orali e Biotecnologiche)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Cerea "Il sorriso di Jenny"** (€ 8.000); **Gruppo di sostegno FFC Ricerca di Grado – Gorizia** (€ 8.000); **Gruppo di sostegno FFC Ricerca della Val Seriana** (€ 25.000); **Delegazione FFC Ricerca di Reggello con Delegazione FFC Ricerca di Siena** (€ 25.000); **Gruppo di sostegno FFC Ricerca di Vimercate – In ricordo di Gloria** (€ 8.000); **Gruppo di sostegno FFC Ricerca di Magenta** (€ 10.000); **Gruppo di sostegno FFC Ricerca di Sondrio Tresivio Ponte "In ricordo di Teresa"** (€ 8.000); **Delegazione FFC Ricerca di Franciacorta e Valcamonica** (€ 36.500); **Gruppo di sostegno Bari Santeramo in Colle** (€ 8.000).

- **FFC#14/2024 - Conseguenze a lungo termine della carenza di secrezione di insulina ed effetti dei modulatori di CFTR**

Responsabile: **Alberto Battezzati** (Dipartimento di Scienze per gli Alimenti, la Nutrizione e l'Ambiente, Università degli Studi di Milano)
Finanziamento: 42.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Palo del Colle** (€ 42.000).

- **FFC#15/2024 - Analisi dell'evoluzione dei fattori di virulenza e della resistenza antimicrobica di *Pseudomonas aeruginosa* in persone con fibrosi cistica**

Responsabile: **Martina Rossitto** (IRCCS Ospedale Pediatrico Bambino Gesù, Roma)
Finanziamento: 210.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Belluno** (€ 90.000); **Delegazione FFC Ricerca di Roma** (€ 30.000); **Delegazione FFC Ricerca di Sondrio Valchiavenna** (€ 30.000); **Delegazione FFC Ricerca di Lucca** (€ 45.000); **Latteria Montello** (€ 15.000).

- **GMSG#1/2024 - Studio di bersagli terapeutici alternativi per ripristinare la clearance mucociliare delle vie aeree FC**

Responsabile: **Michele Genovese** (TIGEM, Pozzuoli, Napoli)
Finanziamento: 189.000 €

Adottato totalmente da: **Delegazione FFC Ricerca di Siniscola Nuoro** (€ 50.000); **Delegazione FFC Ricerca di Lodi** (€ 16.000); **Delegazione FFC Ricerca di Bologna** (€ 123.000).

- **GMRF#1/2024 - La superficie delle vie aeree come campo di battaglia contro i batteri**

Responsabile: **Daniela Guidone** (TIGEM, Pozzuoli, Napoli)
Finanziamento: 52.500 €
Adottato totalmente da: **La Mano Tesa Onlus** (€ 52.500).

- **FFC#1/2025 - I meccanismi di danno e riparazione nei tessuti epiteliali della fibrosi cistica**

Responsabile: **Margarida Amaral** and Ines Pankonien (Cystic Fibrosis Research Lab, BioISI–Biosystems & Integrative Sciences Institute, Facoltà di Scienze, Università di Lisbona, Portogallo)
Finanziamento: 209.897 €
Adottato totalmente da: **Delegazione FFC Ricerca Miriam Colombo Ospedaletti – Imperia** (€ 15.000); **Gruppo di sostegno FFC Ricerca di Reggio Emilia** (€ 20.000); **Gruppo di sostegno di Seregno – Monza Brianza** (€ 15.000); **Delegazione FFC Ricerca Fibrosirun – Monza Brianza** (€ 80.352); **Delegazione FFC Ricerca "Il sogno di Aiden" Brescia** (€ 40.000); **Delegazione FFC Ricerca di Verbania e V.C.O** (€ 20.000); **Gruppo di sostegno FFC Ricerca di Matera** (€ 19.545,00).

- **FFC#2/2025 - Uso di oligonucleotidi antisenso per il recupero funzionale di CFTR con mutazioni stop e di splicing**

Responsabile: **Debora Baroni** (Istituto di Biofisica, CNR, Genova)
Finanziamento: 173.250 €
Adottato totalmente da: **Ass.ne Trentina Fibrosi Cistica ODV "In ricordo di Francesco Pelz"** (€ 90.000); **Delegazione FFC Ricerca di Vicenza** (€ 50.000); **Delegazione FFC Ricerca di Napoli** (€ 33.250).

- **FFC#3/2025 - Ottimizzazione della terapia genica e dei sistemi di trasporto per mutazioni ancora prive di terapia**

Responsabile: **Marianne Carlon** (Laboratory of Respiratory Thoracic Surgery, KU Leuven, Belgio)
Finanziamento: 209.998 €
Adottato totalmente da: **Delegazione FFC Ricerca "Alla fine esce sempre il sole" Boschi Sant'Anna Minerbe – Verona** (€ 40.000); **Delegazione FFC Ricerca "Il sorriso di Jenny" Cerea – Verona** (€ 8.000); **Delegazione FFC Ricerca di Torino** (€ 30.000); **Delegazione FFC Ricerca di Padova** (€ 35.000); **Delegazione FFC Ricerca di Alberobello – Bari con volontari di Noci** (€ 50.000); **Guadagnin Srl** (€ 8.000); **Delegazione FFC Ricerca di Vimercate - Monza Brianza** (€ 20.000); **Gruppo di sostegno FFC Ricerca di Martinsicuro - Teramo** (€ 18.998).

- **FFC#4/2025 - Approcci farmacologici per la correzione delle mutazioni stop in fibrosi cistica**

Responsabile: **Luis J. V. Galietta** (Università degli Studi di Napoli Federico II – Istituto Telethon di Genetica e Medicina TIGEM, Pozzuoli, Napoli)
Finanziamento: 210.000 €
Adottato totalmente da: **Piazzalunga srl** (€ 180.000); **Delegazione FFC Ricerca di Napoli** (€ 10.000); **Delegazione FFC Ricerca di Vitulazio – Caserta** (€ 10.000); **Gruppo di sostegno FFC Ricerca "Insieme per Costantino e Francesco" Serino – Avellino** (€ 10.000).

- **FFC#5/2025 - Caratterizzazione della proteina chinasi D1 come regolatore del traffico e della stabilità di CFTR**

Responsabile: **Emilio Hirsch** (Dipartimento di Biotecnologia Molecolare e Scienze della Salute, Università di Torino)
Finanziamento: 135.975 €
Adottato totalmente da: **Delegazione FFC Ricerca di Nichelino e Moncalieri** (€ 30.000); **Delegazione FFC Ricerca di Milano** (€ 50.000); **Delegazione FFC Ricerca di Campiglione Fenile – Torino** (€ 20.000); **Delegazione FFC Ricerca di Valpolicella** (€ 35.975).

- **FFC#6/2025 - Approfondire la doppia funzione dei peptidi Esc e loro derivati come potenziatori e agenti antimicrobici**

Responsabile: **Maria Luisa Mangoni** (Dipartimento di Scienze Biochimiche, Università La Sapienza, Roma)
Finanziamento: 136.500 €
Adottato totalmente da: **Gruppo di sostegno FFC Ricerca di Scauri – Minturno** (€ 8.000); **Delegazione FFC Ricerca di Moncalvo – Asti** (€ 20.000); **Delegazione FFC Ricerca di Dongo Como** (€ 108.500).

- **FFC#7/2025 - Sfruttare la dipendenza di *P. aeruginosa* dallo zinco per potenziare l'attività degli antibiotici**

Responsabile: **Andrea Battistoni** (Dipartimento di Biologia, Università di Roma Tor Vergata)
Finanziamento: 105.000 €
Adottato totalmente da: **Delegazione FFC Ricerca della Franciacorta e Val Camonica – Brescia**.

- **FFC#8/2025 - Sviluppo di una terapia combinata con antibiotici incapsulati in liposomi bioattivi per trattare l'infezione da *M. abscessus***

Responsabile: **Maurizio Fraziano** (Dipartimento di Biologia, Università di Roma Tor Vergata)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Pomezia – Roma** (€ 15.000); **Programma "I migliori amici della ricerca"** (€ 30.000); **Delegazione FFC Ricerca di Alba Cuneo** (€ 91.500).

- **FFC#9/2025 - Identificazione di nuovi bersagli nel trattamento delle forme persistenti di *Mycobacterium abscessus* in fibrosi cistica**

Responsabile: **Federico Giannoni** (Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Roma)
Finanziamento: 73.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Crevalcore** (€ 40.000); **Delegazione FFC Ricerca di Milano** (€ 25.000); **Gruppo di sostegno FFC Ricerca di Casarile - Milano** (€ 8.500).

- **FFC#10/2025 - Inibire i fattori di virulenza di *Pseudomonas aeruginosa* per contrastare le infezioni**

Responsabile: **Francesco Imperi** (Dipartimento di Scienze, Università Roma Tre)
Finanziamento: 63.000 €
Adottato totalmente da: **Delegazione FFC Ricerca di Imola e Romagna**.

- **FFC#11/2025 - Sviluppo di una nuova formulazione di VOMG per il trattamento delle infezioni da *Mycobacterium abscessus***

Responsabile: **Maria Rosalia Pasca** (Dipartimento di Biologia e Biotecnologia Lazzaro Spallanzani, Università degli Studi di Pavia)
Finanziamento: 73.500 €
Adottato da: **Delegazione FFC Ricerca di Napoli** (€ 46.826); **Delegazione FFC Ricerca di Latina** (€ 15.000).
Adottabile per 11.674 €

- **FFC#12/2025 - Studiare la risposta del sistema immunitario nelle infezioni polmonari da micobatteri non tubercolari**

Responsabile: **Nicola Ivan Lorè** (Unità Patogeni Batterici Emergenti, Divisione di Immunologia, Trapianti e Malattie Infettive, IRCCS San Raffaele, Milano)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca "Correre per un respiro"** (€ 75.000); **Delegazione FFC Ricerca di Roma Pomezia** (€ 30.000); **Delegazione FFC Ricerca di Morbegno - Sondrio** (€ 31.500).

- **FFC#13/2025 - Monitoraggio delle infezioni polmonari attraverso i microrganismi intestinali**

Responsabile: **Cristina Cigana** (Unità Infezioni e Fibrosi Cistica, divisione di Immunologia, Trapianti e Malattie Infettive, Istituto San Raffaele Milano)
Finanziamento: 136.500 €
Adottato totalmente da: **Delegazione FFC Ricerca di Mascalucia Catania** (€ 68.250); **Delegazione FFC Ricerca di Vittoria, Ragusa e Siracusa** (€ 68.250).

- **GMSG#1/2025 - Approcci non convenzionali per combattere i batteri della fibrosi cistica**

Responsabile: **Marta Mellini** (Laboratorio di Biotecnologie dei Microrganismi, Dipartimento di Scienze, Università Roma Tre)
Finanziamento: 177.450 €
Adottato da: **Delegazione FFC Ricerca "La bottega delle Donne" Montebelluna – Treviso** (€ 25.000); **Delegazione FFC Ricerca di Ghedi – Brescia** (€ 40.000); **Programma "I migliori amici della ricerca"** (€ 22.000).
Adottabile per 90.450 €

- **MindKids-CF - Indagine sulla salute mentale nei bambini con fibrosi cistica**

Responsabile: **Sonia Graziano** (Unità di Psicologia – Unità di Neuropsichiatria dell'infanzia e dell'Adolescenza, Ospedale Pediatrico Bambino Gesù IRCCS, Roma)
Finanziamento: 169.596 €
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Adottabile per 94.596 €

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