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Margarida D. Amaral

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A Roadmap for the Treatment of Cystic Fibrosis: From Theratyping to Personalised Medicine

Margarida D. Amaral[1]

ABSTRACT

Cystic Fibrosis (CF) is a paradigmatic recessive monogenic disorder resulting from mutations in the CFTR gene, which encodes an anion channel essential for epithelial homeostasis. Since its discovery in 1989, scientific research has radically transformed the disease's prognosis, evolving from purely symptomatic treatments to modulator therapies targeting the underlying protein defect. This article describes the "roadmap" of this evolution, analysing the transition from cell-line-based theratyping to patient-derived theranostics, such as intestinal organoids. It discusses the four generations of modulators, the limitations of "one-size-fits-all" medicine, and future frontiers, including gene editing and mRNA therapies. Despite the success of triple therapies benefiting 80% of patients, critical challenges remain regarding global accessibility and the urgent need for solutions for the 20% with non-responsive mutations. CF currently serves as a model for translational and precision medicine.

RESUMO

A Fibrose Quística (FQ) é uma doença monogénica recessiva paradigmática, resultante de mutações no gene *CFTR*, que codifica um canal de aniões essencial para a homeostase epitelial. Desde a sua descoberta em 1989, a investigação científica transformou radicalmente o prognóstico da doença, evoluindo de tratamentos puramente sintomáticos para terapias moduladoras que visam o defeito proteico subjacente. Esta comunicação descreve o "roteiro" desta evolução, analisando a transição da teratipagem baseada em linhas celulares para o teranóstico baseado em modelos derivados de pacientes, como organoides intestinais. Discutem-se as quatro gerações de moduladores, as limitações da medicina de "solução única" para todos os pacientes, bem como futuras abordagens, incluindo a edição genética e as terapias de mRNA. Apesar do sucesso das terapias triplas que potencialmente beneficiam 80% dos pacientes, persistem desafios críticos de acessibilidade global e a necessidade urgente de soluções para os 20% de pacientes com mutações que não respondem aos moduladores. A FQ serve hoje como modelo para a medicina de translação e de precisão.

INTRODUCTION: THE LANDMARK OF GENE DISCOVERY

Cystic Fibrosis (CF) is the most common severe monogenic disorder in Caucasian populations, following an autosomal recessive inheritance pattern, thus requiring two pathogenic variants (one from each progenitor) for disease

[1] Academia das Ciências de Lisboa, BioISI – Biosystems & Integrative Sciences Institute, Faculty of Sciences, University of Lisbon, Portugal.

manifestation. The molecular basis of the pathology is the dysfunction of the CF transmembrane conductance regulator (CFTR) protein, a chloride (Cl^-) and bicarbonate (HCO_3^-) channel that regulates fluid homeostasis across epithelial surfaces.

The year 1989 marked a historic turning point with the identification of the CFTR gene by the teams led by Collins, Riordan, and Tsui. This discovery was paradigmatic not only for its clinical impact but also for its technical innovation: it was the first time a gene was isolated using "chromosome jumping" and "chromosome walking" techniques, without prior knowledge of the protein's structure. This feat transformed CF from a poorly understood clinical condition into a disease with a clear molecular foundation, enabling the start of targeted research into disease mechanisms.

THE CFTR PROTEIN: FROM ION CHANNEL TO MASTER REGULATOR

Understanding of CFTR function has evolved significantly. Initially identified as a Cl^- channel, subsequent studies revealed its crucial role in HCO_3^- transport. Bicarbonate secretion is essential for neutralizing acidic secretions, hydrating mucus, and facilitating mucin expansion; its absence in CF leads to the acidification of the airway surface liquid (ASL), which impairs mucociliary clearance and innate immunity.

Furthermore, CFTR is considered a "master epithelial regulator" of ion transport. It interacts with and regulates other channels, such as the epithelial sodium channel (ENaC). In CF, the loss of ENaC inhibition by CFTR results in the hyperabsorption of sodium and water, exacerbating mucus dehydration. This multisystemic nature affects the lungs, pancreas, liver, intestines, and reproductive system, with progressive pulmonary failure which is the primary cause of mortality.

CLASSIFICATION OF MUTATIONS AND THE CONCEPT OF THERATYPES

Since 1989, over 2,100 mutations have been reported in the CFTR gene. To organize this heterogeneity, mutations have traditionally been grouped into seven functional classes (I to VII):

- Class I: Defective protein production (protein absent).
- Class II: Defective traffic and processing (e.g., p.Phe508del, the most common mutation, occurring in ~80% of patients).
- Class III: Defective regulation/opening (channel gating).
- Class IV: Defective ionic conductance (flow of ions through the channel pore).
- Class V: Reduced amount of functional protein.
- Class VI: Protein instability at the cell surface.
- Class VII: Unrescuable mutations (e.g., large deletions).
- The term "theratype" was coined to represent a refined classification system that groups variants not only by their molecular defect but also by their expected response to specific therapeutic strategies. This "one-size-fits-all" grouping has allowed for drug label extensions, but it has limitations in capturing individual variability.

THE REVOLUTION OF CFTR MODULATORS

The transition from symptom management (pancreatic enzymes, antibiotics, and mucolytics) to targeted molecular therapy represents a major paradigm shift. Modulators are divided into correctors, which help the protein reach the plasma membrane, and potentiators, which increase its channel activity once there.

Therapeutic evolution has occurred across four main generations:

1. 1st Generation (2012): Ivacaftor (Kalydeco®), the first potentiator, effective for gating mutations like p.Gly551Asp (~5% of patients).
2. 2nd Generation (2015-2018): Double combinations like Lumacaftor/Ivacaftor (Orkambi®) and Tezacaftor/Ivacaftor (Symkevi®), focussed on p.Phe508del homozygotes, but evidencing modest efficacy (~70-80% of patients).
3. 3rd Generation (2019): Triple therapy Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®/Kaftrio®), which revolutionized treatment by benefiting ~70-80% of patients with at least one p.Phe508del copy.
4. 4th Generation (2024): Vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek®), designed for higher durability and superior efficacy in reducing sweat chloride.

THERATYPING VS. THERANOSTICS: THE SCIENTIFIC DEBATE

Currently the two approaches of cell-line-based theratyping and patient-oriented theranostics are considered complementary. The former has wider applicability for common mutations, while the latter should be applied for rarer genotypes which escape the scope of large clinical trials.

Cell-line-based Theratyping (e.g., FRT cells):

- Advantages: Convenient for high-throughput studies, cost-effective for common variants, and FDA-approved for label extensions.
- Disadvantages: Uses non-human or cancer-derived cells that do not capture human genetic diversity. It is prone to false results; for example, the p.Gly970Arg variant showed positive response in FRT cells but failed in the clinic because its real defect is alternative splicing, which cDNA models do not capture.

Patient-derived Theranostics (e.g., organoids and nasal cells):

- Advantages: A true "n-of-1" precision medicine approach. It uses intestinal organoids or nasal cells that maintain the individual's unique genetic background. The Forskolin-Induced Swelling (FIS) assay in organoids is a robust predictor of real-world clinical benefit.
- Disadvantages: Technically complex, resource-intensive, and requires tissue samples.

Integration of both approaches is thus recommended: theratyping for frequent variants and theranostics for ultra-rare or "orphan" genotypes, ensuring that patients without access to conventional clinical trials can still benefit from approved therapies.

GLOBAL ACCESS CHALLENGES AND EMERGING RISKS

A critical obstacle to personalized medicine is cost and accessibility. Trikafta® is priced at approximately $300,000 annually per patient, making it inaccessible in

most low- and middle-income countries (LMICs). Estimates suggest that only 12% to 19% of diagnosed people with CF worldwide have access to these life-changing drugs, exacerbating global mortality gaps. Nevertheless, modulators are improving enormously the quality of life of patients along with life expectancy.

Nevertheless, as life expectancy increases due to modulators, new clinical challenges emerge. Indeed, people with CF have an elevated risk of cancer (e.g., 5- to 7-fold higher for colorectal cancer) requiring rigorous screening protocols as this population ages. Furthermore, responses to drug vary for different individuals, and some patients have to discontinue treatment due to significant side effects or drug intolerance.

Importantly, and despite their high positive impact, these current treatments do not yet restore CFTR function to normal levels, as patients still have infections and exacerbations (although more sporadic and less intense).

THE FUTURE: GENOTYPE-AGNOSTIC THERAPIES AND THE CURE

For the 20% of patients who do not benefit from current modulators (Classes I and VII), research focusses on genotype-agnostic strategies:

- mRNA Therapies: Delivering functional CFTR transcripts to bypass genetic defects.
- Gene Editing (CRISPR-Cas9): Aiming for permanent correction of mutations at the genomic level.
- Stem Cell Therapy: Investigating lung cell regeneration to restore airway function.

Successful delivery of these therapies faces physical barriers, such as the thick mucus and chronic inflammation of the lung, as the main target organ. Nevertheless, CF remains the “model” for translational medicine, offering lessons for other genetic diseases which so far have not a path to a cure.

CONCLUSION

The roadmap for Cystic Fibrosis treatment is a testimony to the power of fundamental research. From the pioneering gene discovery in 1989 to today's personalized medicine, CF has moved from a disease which was fatal in childhood to a manageable adult condition for most. The future demands coordinated efforts to ensure global equity in access and the development of definitive curative solutions for all patients, regardless of their genotype.

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