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Human mesenchymal stem cell therapy: Potential advances for reducing cystic fibrosis infection and organ inflammation

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ABSTRACT

Innovation in cystic fibrosis (CF) supportive care, including implementing new antimicrobial agents, improved physiotherapy, and highly effective modulators therapy, has advanced patient survival into the 4th and 5th decades of life. However, even with these remarkable improvements in therapy, CF patients continue to suffer from pulmonary infection and other visceral organ complications associated with long-term deficient cystic fibrosis transmembrane conductance regulator (CFTR) expression. Human mesenchymal stem cells (MSCs) have been utilized in tissue engineering based upon their capacity to provide structural components of mesenchymal tissues. An alternative role of MSCs, however is their versatile utilization as cell-based infusion power-houses due to the unique capacity to deliver milieu specific soluble biologic factors, promoting immune supportive antimicrobial and anti-inflammatory potency. MSCs derived from umbilical cord blood, bone marrow, adipose and other tissues can be expanded in *ex vivo* using good manufacturing procedure facilities for a safe, unique therapeutic to reduce and limit CF infection and facilitate the resolution of multi-organ inflammation. In our efforts, we conducted extensive preclinical development and validation of an allogeneic derived bone marrow derived MSC product in preparation for a clinical trial in CF. In this process, potency models were developed to ensure the functional capacity of the MSC product to provide clinical benefit. *In vitro*, murine *in vivo* and patient tissue *ex vivo* potency models were utilized to follow MSC anti-infective and anti-inflammatory potency associated with the CFTR deficient environment. We showed in our "First in CF" clinical trial that the allogeneic MSCs obtained from healthy volunteer bone marrow samples were safe. The advent of improved CF care measures and exciting new small molecules has changed the survival and morbidity phenotype of patients with CF, however, there are CF patients who cannot tolerate or have genotypes that are non-responsive to modulators. Additionally, even with the small molecule therapy, CF patients are living longer, but without genetic correction, with the CF disease manifestation aggravated by the continuance of pre-existing CFTR-associated clinical issues such as ongoing inflammation. MSCs secrete bio-active factors that enhance and protect tissue function and can promote "self-immune" regulation. These properties can provide therapeutic support for the traditional and changing face of CF disease clinical complications. Further, MSC-derived bio-active factors can directly mitigate colonizing

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pathogens' survival by producing antimicrobial peptides (AMPs) which change the pathogen surface and increase host recognition, elimination, and sensitivity to antibiotics. Herein, we review the potential of MSC therapeutics for treating many facets of CF, emphasizing the potential for providing great additive therapeutics for managing morbidity and quality of life.

1. Introduction

Cystic fibrosis (CF) is an orphan disease that results from autosomal recessive genetic changes in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which impairs the chemical balance of mucosal fluids resulting in a multi-organ manifestation of inefficient hydration and tissue function. Although defects in CFTR are considered rare, CF is the most common genetic disorder in Caucasians and is estimated to affect 1 in every 2500 to 3500 neonates at the national level [1]. The frequency of incidence is lower in Black individuals at 1 per 17,000 and Asian Americans at 1 per 31,000. In Europe, the incidence ranges from 1 in 1353 whereas in Ireland to 1 in 25,000 and in Finland; in Australia and Canada, the rate is approximately 1 in 3000. Before the advent of small molecule therapy (also called modulators) to target the CFTR deficiency, most patients at most only survived into their second decade of life. Those affected experienced significant pulmonary and gastrointestinal morbidity often presenting at birth since deficient CFTR function alters the capacity of effected organs to maintain mucosal surface hydration, important for tissue and organ function and prenatal development [2]. The change in CFTR ion transport across the membrane of cells imparts metabolic and physiological cellular function globally in all cells that express CFTR [3]. The resultant anomaly leads to viscous secretions impacting mucociliary clearance and pulmonary sufficiency, gastrointestinal mobility, fertility, pancreatic function, liver homeostasis, neurophysiology, and

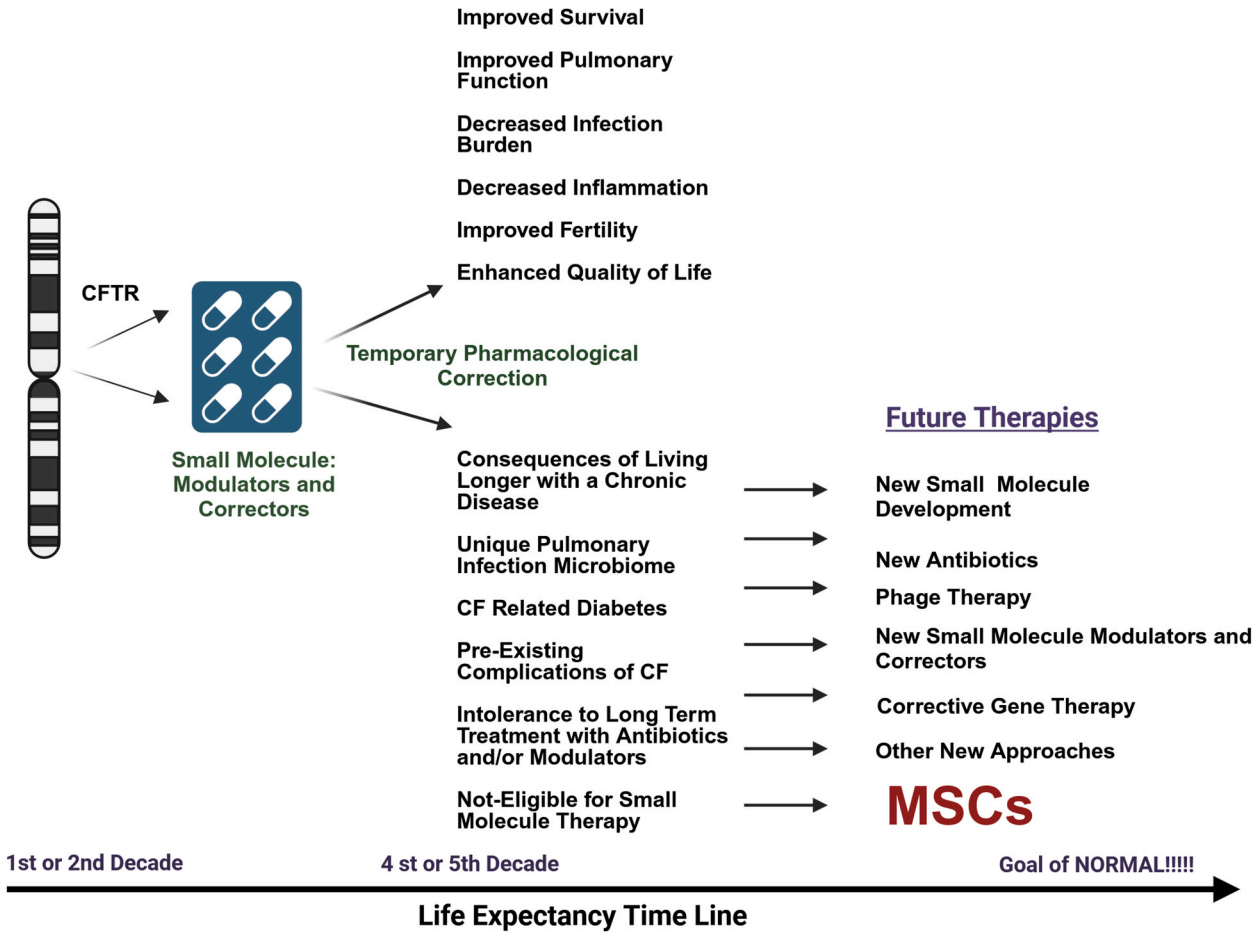

Fig. 1. Cystic Fibrosis, New Therapies and Advanced Care Progress and Deficits. The genetic manifestation of deficient CFTR which leads to CF, has benefited from the innovative production of small molecules which together can promote and enhance CFTR availability and function. This advance in clinical care has shifted the average life expectancy into the 3th decade of life, with improved lung function and quality of life. Even with the advancements made with small molecules, CF patients still struggle with infections, and inflammation, as well as the consequences of long-term CFTR dysfunction and modulator therapy. Figure created with BioRender.com.

cardiovascular and immune function, among other tissue-organ manifestations [4]. Genome-wide association studies (GWAS), which analyzed genetic variations between patients, have complicated the understanding of CF genotype and phenotype demonstrating the potential role of other genes and proteins in disease progression [5–7]. Environmental and access to care also impact patient morbidity and mortality supporting the role of physiotherapy, interventional care, compliance and daily living on CF disease presentation [8,9]. Individuals with CF are more susceptible to colonization by environmentally ubiquitous pathogens, which is attributed to the viscosity of the CFTR deficient airways and the inefficiency by which CF adaptive immunity, impairing management of chronic disease complications [2,10–12]. CF patients are not only more susceptible to infection, implying immune deficiency, but they also have an underlying robust, i.e. overzealous, initial immune response to infection which is not efficiently resolved [11,13–15]. This ongoing inflammatory state can result in significant visceral organ injury. The above deficiencies contribute to the descriptive "triad" in CF of pathogen colonization, dysfunctional inflammation, and tissue damage [16]. The essential role of CFTR in homeostasis has become very evident with the observation that carriers of genetic alterations in the CFTR gene have an increased susceptibility to infection and inflammation and other attributes of the CF pathophysiology, and that individuals with chronic obstructive lung disease have altered CFTR gene expression which correlates with disease severity [17–20]. It is also of interest that CFTR gene expression has been associated with aging in the general population, requiring further insight into the role of CFTR in human biology and disease.

2. Current advancements IN CF disease management

The pharmaceutical pipeline for CF has provided an expanded armamentarium of drugs to treat many of the consequences of deficient CFTR; however, changes in CF clinical disease phenotype associated with patients living longer have begun to present new challenges [16,21]. Even with the advancements in CF targeted and supportive care, CF patients remain susceptible to the unique spectrum of infecting pathogens and the overshooting of the threshold immune response, which continues the chronic inflammation "triad" process [12]. The conundrum continues with trying to balance the therapeutic management of inflammation versus concurrent infection since attenuating inflammation can hamper the eradication of the infection [22].

Before the advent of the targeted CFTR modulators, the focus of management was on the eradication of infection while attempting to reduce pulmonary inflammation and damage, the major contributors to patient morbidity and mortality [7]. These therapies included inhaled saline, protease inhibitors, and improved chest physiotherapy to battle inefficient mucociliary clearance. Such interventions provided only limited success as the structural changes resulted in decreased lung function, respiratory failure, and eventual mortality [23]. The availability of the small molecule agents such as Trikafta (elexacaftor, ivacaftor, and lumacaftor; Vertex Pharmaceuticals Incorporated, Boston, MA), changed the face of CF care and management for those individuals with eligible CFTR responsive genotypes (Fig. 1) [24]. These agents chemically induced the expression, function and availability of CFTR improving sodium and chloride membrane transport contributing to better mucociliary clearance and lung function [25]. However, even with the amazing advancements in CF provided by these modulator therapies, patients continue to experience morbidity associated with their chronic disease state and the consequences of previously damaged tissues [26,27]. The complexities of the aging process as well as drug intolerance, have brought to the spotlight of care hepatic dysfunction, CF-related diabetes mellitus, cardiovascular abnormalities, neurological changes, allergic reactions, and cataracts for enhance clinical focus and care [1,28,29]. Further, patients receiving modulator therapy still struggle with infections with complex combinations of traditionally microbes and inflammation, suggesting continued immune insufficiency, and potentially enhanced immune senescence and aging [21]. Immune aging is a known physiology and is associated with subtle immune suppression in individuals over 65 years of age, with changes in immunity [30,31]. Immune aging can also happen as a consequence of chronic disease due to the constant stress inflammation causes on tissue physiology [7,31,32]. Additionally, not all patients with CF are eligible or have tolerance to the new small molecule therapy emphasizing the need for alternative treatment and therapeutic pursuits [33,34]. Investigators continue to aggressively pursue solutions in gene therapy, infectious disease, medical microbiology, endocrinology, genetics, and immunology, among others, and have continued to work tirelessly to mitigate these consequences of CF pathophysiology. Further, research continues on the front small molecules to address patient tolerance, while the pursuit of gene therapy continues [28].

3. MSC biology

The initial phenotype of MSC multipotency was defined by *in vitro* studies that focused on differentiating MSC into different tissue types such as cartilage and bone. Dr. Arnold Caplan and his team, based upon embryologic development, utilized defined growth media containing biological effectors which specifically promote MSC differentiation along specific pathways of mesenchymal tissue end-points such as chondrocytes and cartilage [35–37]. These concepts were the foundation of an entire area of MSC of biology and tissue engineering [38,39]. Although the MSCs can differentiate when cultured *in vitro*, differentiation *in vivo* has never been realized even when tracking the, MSC *in vivo* using sophisticated technologies to label and follow cells longitudinally [40]. MSCs are short-lived, cell-based therapeutics targeted by host immunity and internalized by macrophages facilitating reprograming of the host response phenotype to better manage the tissue milieu, i.e. appropriately temper the immune response [41–44]. Even though the capacity to differentiate MSC *in vivo* was disappointing, the concept of MSC plasticity and the capacity to manipulate MSC phenotype and function became an additional advancement in how the MSC plasticity can be utilized clinically [45].

4. MSCS as medicinal signaling cells

The biological function of MSCs has evolved, emphasizing their cell-based therapeutic clinical potential. These cells are recognized

to be progenitors of pericytes which originate on the surface of blood vessels, exquisitely sensitive to changes in the tissue milieu during homeostasis and tissue damage [46]. The environmentally responsive pericyte transitions in response to injury to the phenotypic expression of MSCs [38]. Protocols have been established in which bone marrow aspirates (the original isolated source) to understand MSC function and phenotype [47–49]. Phenotypically, bone marrow derived adherent MSCs can be characterized by the surface expression of $CD73^{+}$, $CD90^{+}$, $CD105^{+}$ and $CD11b^{-}$, $CD14^{-}$, $CD19^{-}$, $CD34^{-}$, $CD45^{-}$, $CD79a^{-}$ and HLA-DR^{-} (outlined by the International Society for Cell & Gene Therapy, ISCT), as well as the capacity to differentiate into adipocytes, chondrocytes, and osteoblasts [46]. Importantly, these phenotypic cell surface signatures can change with MSC activation, age, and donor specificity which ultimately defines the ability to culture MSC *in vitro* and retain their functional capacity [50,51]. Suppressed HLA class II expression and the short-lived nature of MSCs, provide the immune evasion advantage of MSCs, which enables their therapeutic testing across species (xenografic) and allogeneic delivery in the clinic (allograft) [52–54]. However, differentiated and stressed MSCs have been shown to express HLA class II, emphasizing the essential importance of understanding MSC biology, source, and culture sustainability of the MSC product [55,56]. The ISCT distinction between mesenchymal "stromal" and "stem" cells focuses on these differences, requiring that advanced clarification emphasizing the tissue source and function of the MSCs product since phenotypically there are distinctions between phenotype and function between MSCs derived from different tissues [57]. The utilization of pre-clinical models are essential to minimize the concept of "stemness," as MSCs are not true "stem cells" due to the inability to regenerate tissue *in vivo*. The difference between mesenchymal "stromal cell" and mesenchymal "stem cell" lies with the inherent functional capacity of the stromal cell phenotype to differentiate *in vitro* into mesenchymal tissues lineages. The therapeutic "functional" power of MSCs is defined by their short-lived release of signaling molecules which can be harnessed to enhance cell-based therapeutic efficacy [58]. Even though a differentiated MSC product has not been established *in vivo*, the benefit of a short-lived allogeneic therapeutic artillery to treat disease cannot be underscored [41–44]. It became very apparent that the responsiveness of the MSCs to their environment defined their secretomes, which ultimately contributed to their therapeutic impact [59–62]. In CF, the development of MSCs as a therapeutic approach was based upon the capacity of the MSCs to respond to the unique environmental cues of the CF lung and theMSC capacity to secrete bioactive factors and extracellular vesicles (EVs) which can provide anti-inflammatory, anti-fibrotic, and anti-microbial tissue support (Fig. 2A) [63]. The balance of biological factors produced by the MSCs during infusion confers the therapeutic impact.

The breadth and depth of MSC secreted bio-factors continues to grow from the identified anti-inflammatory products such as interleukin 10, antimicrobial peptides such as cathelicidin (LL-37), human beta-defensin 2, and hepcidin, to small interfering RNAs; the diversity with which the MSCs can contribute to the effect is endless [64–67]. The combination of the secretome repertoire and functional responsiveness underlines the potency and potential efficacy of MSCs clinically. The malleability of hMSC defines the "response to the tissue milieu" induced a tissue specific MSC secretomes implicating an immune-like responsiveness to the environment that defines functional potency and potential efficacy *in vivo* [68]. The key in CF, is the combinational packaging, providing anti-inflammatory and antimicrobial secretomes concurrently mitigating the issue of providing anti-inflammatory therapeutics in patients who have constitutive and chronic pulmonary infections. The MSC power provides a network of resources to promote the outcomes for which they are developed, which in our efforts as coined by Dr. Caplan, resulted in the pursuit of a new name for MSCs "medicinal signaling cells (MSCs)", to minimize the confusion with the *in vitro* stemness of "stromal MSCs" used to create tissue scaffolds [40,64]. The concept of stemness for MSCs is associated with the capacity to differentiate into terminal mesenchymal tissues with unique phenotypes and structures, whereas MSCs do not differentiate but provide therapeutic "knowledge" to the tissue milieu based upon the bio-factors and response of the MSCs to the environment.

5. MSC BIO-FACTORS: Harnessing potency for clinical impact

Although the MSCs can provide a pathway for host response, it is intriguing to think of the concept of "response specific to the

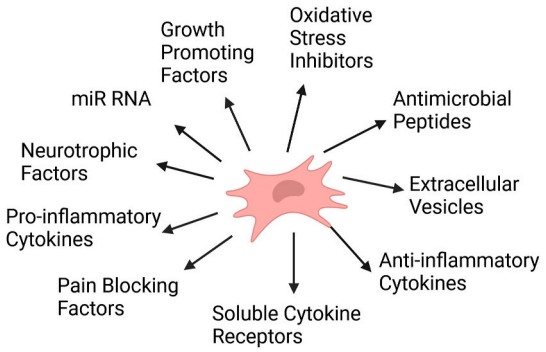

Fig. 2A. The Ever-Expanding Understanding of the MSC Secretomes. The depth and breadth of hMSC products define the unique identity of each MSC preparation and its potential to contribute to different facets of disease in CF. Harnessing the repertoire of MSC potency secretomes for functionally optimal targeted delivery provides the opportunity to streamline MSC therapeutic development to treat the unique attributes of CF pathophysiology. Figure created with BioRender.com.

environment", which begs the question of how the MSCs are being manipulated *in vivo* by the tissue milieu [22,46]. The infancy of MSC development, translated from preclinical *in vivo* models to patient subjects, was designed, executed and published in the first-in-human clinical trials by Dr. Hillard Lazarus and associates [69,70]. Subsequently, the potential immunomodulatory investigations of MSCs were designed to promote engraftment and attenuate graft-versus-host disease, while others used MSCs in diseases such as adult respiratory distress syndrome, osteogenic imperfecta and bronchopulmonary dysplasia [36,54,71–74]. In these studies, data were generated for how to grow hMSCs, whether to infuse the cells fresh or after cryopreservation and thawing, what route of administration to use, and how many infusions would impact the clinical outcome [61]. Fast forward to SARS-CoV2, and many other diseases, the use of MSC has demonstrated both dramatic as well as suboptimal clinical benefits, depending on the trial and the endpoints measured [75,76]. The complexity of the "MSC" malleability and the uniqueness of each patient and disease have no doubt impacted the variability in the clinical trials and contributed to the reluctance of the FDA to approve MSCs until the recent groundbreaking acceptance of remestemcel-L (trade name RYONCIL, Mesoblast, Inc., Melbourne Australia), for steroid-resistant acute GVHD(SR-aGVHD) [77,78]. In the clinical trial (NCT02336230) remestemcel-L was given twice weekly over 4 weeks in 54 children with primary SR-aGVHD. MSC treatment response correlated with improved survival with no identified infusion-related toxicities or safety concerns. The FDA approval of remestemcel-L for SR-aGVHD provides the platform in which to circumvent the plateau of MSC therapeutics development and translation to improve clinical outcomes to push MSCs into the FDA-approved category. The focus is on MSC malleability as a resource instead of a deficit, utilizing strategic algorithms that can be established to optimize MSCs potency for enhanced clinical outcomes (Fig. 2B) [44,79–81]. The innovation comes from conceptualizing where the MSC product will go and what it will encounter, to begin to define what the MSC needs to look like in the given clinical scenario [46,66,81–83]. Standardized protocols take into consideration the MSC product, how it adapts to culture, time to senescence, cell phenotype, and cell function. We used this approach to align with clinical impact, utilizing *in vitro* validated potency models enhanced by *in vivo* modeling and potential patient *ex vivo* tissue sample pre-clinical analysis. In our models, we utilized murine and human cells, both healthy and CF phenotypes, to bridge *the in vivo* murine mouse model of infection and inflammation to human *ex vivo* tissue potency outcomes. This detailed analysis compares the MSC functional attributes to ensure that the best possible product can be created to manage CF-specific infections and inflammation pathophysiology. The concept of pharmacological manipulation of MSC phenotype promises to not only streamline MSC product selection but also to enhance the potential power of MSCs as cell-based delivery "drug stores", as visualized by Dr. Caplan and other giants of the MSC frontier [84,85].

6. The MSC advantage IN CF

The utilization of MSCs has been the focus of clinicians who have treated a broad spectrum of diseases for many years due to their diverse properties and excellent safety profiles with the capacity to use allogeneic or autologous sources (Table I) (ClinicalTrials.gov). Although an autologous product is always the first preference, in many cases, this approach may not provide optimal clinical care, either due to the complexities of the genetic manifestations of disease or disease severity of the patient in the clinical setting. In our studies, blocking CFTR function in MSCs completely changed their capacity to provide antimicrobial and anti-inflammatory potency, implicating the necessity for using an allogeneic, rather than an autologous MSC product [80,86]. MSCs provide an attractive and very safe therapeutic for CF, due to their excellent safety profile and their capacity to selectively control inflammation while at the same time facilitating infection management. At the same time, MSCs can provide therapeutic support for many of the other clinical manifestations that impact CF patient quality and duration of life, especially as patients live longer with the advancements in CF management [87]. MSCs are readily available for clinical use from a variety of tissue sources, many of them vetted already in a clinical setting. Additionally, MSCs are amenable to efficient and stable gene transduction and transfection and subsequently can be used to treat cardiovascular, gastrointestinal, pancreatic, liver, bone, and complications like neuropathy and autoimmunity [88–90]. MSCs can also be derived from discarded tissues and like other MSC sources, can be rapidly expanded exponentially *ex vivo* for clinical translation. Frozen hMSCs can be banked for future use, wherein cells can be shipped to clinical sites and thawed at infusion, thus providing opportunities for multicentered clinical trials, enabling the capacity to treat CF patients globally [91,92].

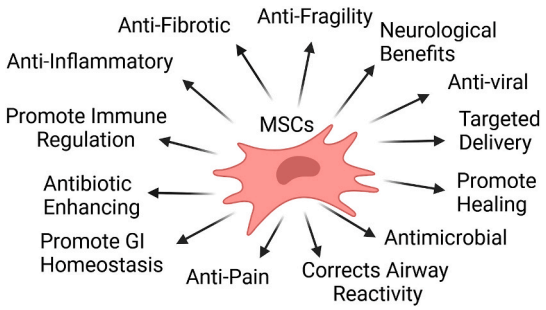

Fig. 2B. MSC Products with Clinical Potential for CF. MSCs can make a variety of products from proteins to interfering RNAs, extracellular vesicles, cytokines, growth factors, and oxidative metabolites. All these factors define the unique capacity of the hMSCs to provide a plethora of diversity in functional potency which has the potential to benefit individuals with CF. Further the utilization of MSCs as vehicles of delivery promises to enhance this perspective of hMSCs as a therapeutic powerhouse. GI: Gastrointestinal. Figure created with BioRender.com.

Table 1
FDA Clinical Trials using Mesenchymal Stem Cells in Diseases with Relevance to CF.

Trial ID #	Treatment Pursuit	Source	Country
NCT06149832	Treatment of Oral Chronic Graft-versus-host Disease with Human Umbilical Cord Mesenchymal Stem Cell Dressing	Human Umbilical Cord Allogenic MSCs	China
NCT02172885	Mesenchymal Stem Cell Based Therapy for the Treatment of Osteogenesis Imperfecta	Bone Marrow Derived Allogenic MSCs.	Spain
NCT02881476	Therapeutic Treatment of Amyotrophic Lateral Sclerosis	Human Umbilical Cord Allogenic MSCs	Poland
NCT03130374	Treatment of Laryngotracheal Stenosis Using Mesenchymal Stem Cells.	Olfactory mucosa derived Autologous MSCs	Belarus
NCT02387749	Effect of Mesenchymal Stem cells Transfusion of the Diabetic Peripheral Neuropathy Patents	Bone Marrow Derived Autologous MSCs	Cairo
NCT02530047	Safety and Efficacy of Human Mesenchymal Stem Cells for Treatment of Liver Failure	Human Umbilical Cord Allogeneic MSCs	Beijing
NCT01586312	Treatment of Knee Osteoarthritis with Allogenic Mesenchymal Stem Cells	Bone Marrow Derived Allogenic MSCs.	Spain
NCT03477942	Impact of Mesenchymal Stem Cells in Knee Osteoarthritis	Bone Marro Derived Autologous MSCs	United States
NCT03186417	Mesenchymal Stem Cells in Early Rheumatoid Arthritis	Bone Marrow Derived Autologous	MetroHealth Medical Center, University Hospitals Cleveland Medical Center
NCT04441658	Efficacy and Safety of Umbilical Cord Mesenchymal Stem Cells Transplantation in Patients with Type 2 Diabetes Mellitus	Human Umbilical Cord Allogeneic MSCs	Shanghai East Hospital
NCT01087996	The Percutaneous Stem Cell Injections Delivery Effects on Neo-myogenesis of cardiomyopathy.	Biological Autologous and Biological AllohMScs	University of Miami
NCT05095532	Autologous Mesenchymal Stromal Cells and Islet Co-transplantation in TP-IAT	Bone Marrow Derived Autologous MSCs	Medical University of South Carolina
NCT06205342	Safety and Efficacy of Mesenchymal Stem Cells Associated with Chronic Pancreatitis Pain.		
NCT02866721	Safety and Tolerability of Allogeneic Mesenchymal Stem Cells in Adults with Cystic Fibrosis	Bone Marrow Derived Allogeneic MSCs.	University Hospital Cleveland Medical Center.
NCT00294112	Prochymal™ Adult Human Mesenchymal Stem Cells for Treatment of Moderate to Severe Crohn's Disease.	Prochymal™ Adult Bone Marrow Derived Allogeneic MSCs.	Mesoblast, Inc.
NCT0316231	Phase IIbTrial to Evaluate Longeveron Mesenchymal Stem Cells to Treat Aging Fragility	Bone Marrow Derived Allogeneic MSCs (Longeveron).	Longeveron.
NCT04047810	Mesenchymal Stem Cells in the treatment of Subjects with Advanced Chronic Obstructive Pulmonary Disease	Bone Marrow Derived Allogeneic MSCs.	Mayo Clinic
NCT02181712	Mesenchymal Stem Cell Therapy for Lung Rejection.	Bone Marrow Derived Allogeneic MSCs	Mayo Clinic

The MSC therapeutic delivery in disease has been established in a diverse range of diseases including CF, SAR-CoV2-induced COVID-19, acute respiratory distress, bronchopulmonary dysplasia, interstitial pulmonary fibrosis, osteoarthritis, rheumatoid arthritis, graft-versus-host disease, cardiovascular disease, fragility concurrent with aging, Crohn disease, multiple sclerosis, and Parkinson disease, to name just a few. The repertoire of these targeted diseases has, at the very basics, inflammation, but the spectrum of disease pathophysiology is complex, emphasizing the broad-spectrum attributes of MSC as diverse and safe cell-based therapeutics. The adaptability of the MSCs to the CF disease milieu setting provides the unique power of MSC for disease management, designing the product to provide the most beneficial therapeutic potency (Fig. 3). Responsive to local tissue cues, MSCs cannot only attenuate the destructive chronic inflammation that plagues CF patients but can concurrently combat infection and manage immune dysregulation. This therapeutic balance is essential in CF and has traditionally been the major hurdle in managing the progression to significant life-impacting morbidity and eventual respiratory failure. Even in the current era of using small molecule modulator therapy, the insidious presence of diverse microbes such as *Pseudomonas aeruginosa*, *Mycobacterium avium* complex, *Mycobacterium abscessus*, *Burkholderia cepacia complex*, methicillin-sensitive and resistant *Staphylococcus aureus* and *Aspergillus fumigatus* continue to adversely impact the clinical management of many patients [93]. The capacity of MSCs to provide concurrent management of inflammation and infection while enhancing antibiotic efficacy is a promising directive.

7. MSC and enhancing CF management and quality of life

The question becomes the relevance of MSC as a therapeutic pursuit for CF, and what the data are to support this directive. When we undertook the introduction of allogeneic human mesenchymal stem cell (hMSC) therapeutics in our "First in CF" Phase I clinical trial (CEASE CF: NCT02866721), our goal was to demonstrate safety. The hypothesis of treating CF (like those listed in Table 1), was based upon the multifaceted nature of the MSCs to manage infection an inflammation. [42,94]. As we strive toward a Phase II, the focus becomes the unique capacity of MSCs to provide clinical benefit towards managing the multi-organ complications of CF, especially with a focus on airway infection inflammation with the unique pulmonary microbiome of colonizing pathogens [95]. The

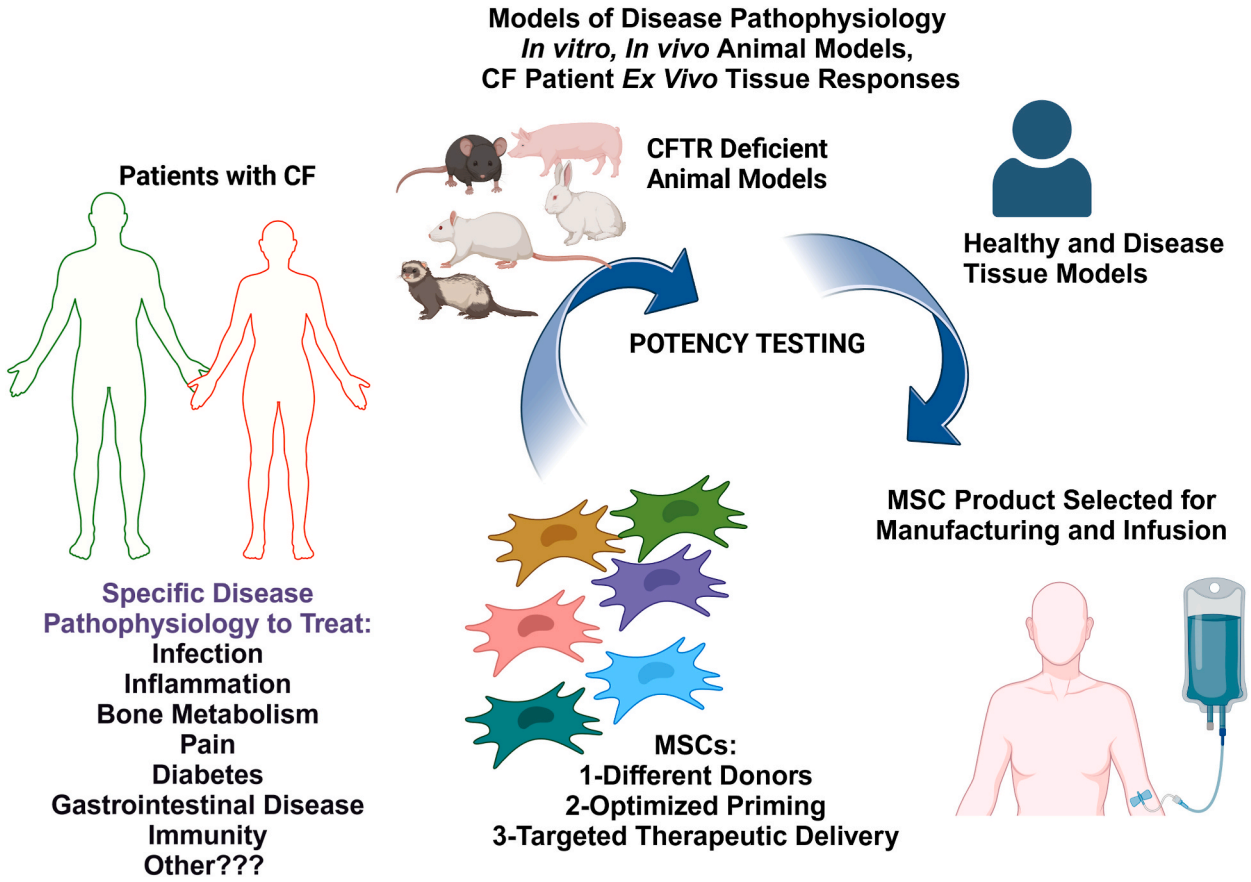

Fig. 3. MSC Therapeutic Development for Future CF Clinical Trials. Each donor MSC preparation has its own unique capacity to provide potency, defined by the function in models. This functional quantification of the MSCs can be harnessed for efficiency and therapeutic efficacy using models that represent aspects of the pathophysiology of CF. Animal models deficient in CFTR, including the mouse, rat, rabbit, ferret, and pig can be used to analyze the functional specificity and capacity of MSCs for therapeutic selection. Analysis of MSC potency in each assay, provides a score that are validated in both mouse and human functional assays to ensure the potency translates from animal models to human disease. All through the process, cell lines recapitulating both animal models and human tissue are used to bridge the gap between the pre-clinical and clinical translation. The goal is the identification of the ideal MSC product for infusion and clinical care. Figure created with BioRender.com.

advent of modulator therapy has improved pulmonary morbidity and delayed the mortality in CF, but patients continue to struggle with CF-related diabetes, cardiovascular diseases, gastrointestinal complications, pancreatic, liver, and even sleep and behavior consequences, all of which have been targeted successfully by MSCs in other diseases with similar manifestations.

In our phase I clinical trial, we have demonstrated that allogeneic human MSC infusions are safe in CF. We treated fifteen patients in a 3/3 dose escalation model, and each dose was equally well tolerated. In the trial, we infused a single dose of MSCs to CF patients suffering from mild or moderate disease. Patients were followed by a survey, phone call follow-ups, sputum expectoration bacteriology, and serum markers of inflammation, along with other serum biomarkers and clinical endpoints, including pulmonary function. Statistical significance of efficacy was not achieved, in part due to the small sample size. However, we demonstrated the potential to pursue the optimal MSC dose and number of infusions with the ideal product, vetted for *in vivo* functional potency with molecular and functional characterization. As a result, we believe this approach represents a tangible, attainable, and highly beneficial potential therapeutic resource for CF patients [61,96]. Since our initial trial, we have been diligently pursuing the next product for the follow-up phase II study. The changing repertoire of CF patient morbidity has defined the need for complex potency models, i.e., optimizing the product to have the capacity to efficiently manage the ongoing pathophysiology *in vivo*. Strategizing the development of the MSC clinical product based on the current landscape of infection, inflammation, and morbidity is our focus and goal (Fig. 3). In our work and the work of others it has been demonstrated *in vitro* the antimicrobial potency of MSCs against a variety of pathogens known to colonize individuals with CF including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *Mycobacterium avium*, *Mycobacterium intracellulare* and *Mycobacterium abscessus* [22,62,79,97]. Further, the MSCs promote a more efficient microbial inhibition capacity of antibiotics. hMSCs can improve immune cell function, minimize fibrotic tissue deposition, and attenuate airway reactivity [22,42,74,98–101]. Harnessing these diverse MSCs properties clinically and the capacity to deliver concurrently within the context of the current standard of care or having adverse effects is based on the thousands of hMSCs clinical trials documented by the FDA, highlighted in Table 1 (ClinicalTrials.gov).

Innovations in hMSC therapeutics also implicate additive directionality to clinical care in CF. In recent years, the focus on extracellular vesicles has become more intent with the potential to provide a product that possesses the same "bang" for therapeutic impact without the added concern on delivery of allogeneic MSC cells [102,103]. The EVs can be targeted, and they can be used as defined delivery vehicles [104,105]. The EV field, however, is impacted by product purity and sustainability, which continues the development of more active protocols for EV technologies [67,106,107]. Targeted product delivery has also been pursued with the MSCs themselves, pursuing transfection protocols that can provide sustained accessibility to products important in managing infection and inflammation in CF [108–111]. The forefront of all these studies, however, goes back to the concept of MSC malleability and to the idea that EVs and the directed product delivery can be refined by optimization strategies. Such would provide a hMSC product that would adapt appropriately to the tissue milieu and provide the resources necessary to promote and support infection and inflammation resolution.

8. Conclusion

Advocating for MSC development in CF is based upon the multiple observations conducted in *in vitro*, in preclinical animal models, and *ex vivo* studies, which is further appreciated by the history of safety in greater than two thousand clinical trials worldwide (ClinicalTrials.gov). The diversity in hMSC cell-based therapy functional potency provides a unique platform that has the potential to provide CF patients with a supportive therapeutic that can circumvent a variety of consequences of the longitudinal impact of deficient CFTR. Product development, the optimal route of delivery and number of infusions, and EV development are all strategic avenues that promise to provide a unique forum for managing the many consequences of CF until an effective cure is available for all patients who suffer from the disease and the consequences of treatment maintenance.

Practice points

- Cystic fibrosis (CF) is an inherited disease with manifestations of multi-organ disease that result from the deficient expression and function of the cystic fibrosis transmembrane receptor in many cells.
- Innovative therapeutics have improved CF morbidity and mortality but have not achieved genetic correction.
- Some CF patients are not eligible for new small molecule modulator therapy due to the nature of their genetic mutation, while other CF patients cannot tolerate several new treatment modalities.
- As CF patients age, they continue to struggle with pulmonary infection and inflammation along with other consequences of aging, including chronic diseases such as CF-related diabetes mellitus, gastrointestinal disease, and cardiovascular diseases.
- Mesenchymal stem cells can provide a safe therapeutic resource that possesses both antimicrobial and anti-inflammatory secretomes which can improve the management of infection while reducing organ inflammation, thereby aiding in the management of other CF disease complications.
- Using such strategies as potency assays, mesenchymal stem cells can be optimized to produce the "ideal secretomes" for better managing CF pathophysiology and patient symptoms.

Research agenda

- Mesenchymal stem cells (MSCs) are a cellular product that can be optimized *in vitro* using several approaches, including potency assays to enhance the treatment of cystic fibrosis (CF) patients. To improve morbidity, quality of life, and survival, treatment with MSCs can be utilized in addition to standard vigorous supportive therapy.
- Advanced technological approaches to improve therapy using MSCs include RNAseq, secretomes analysis, and appropriate *in vitro* and *in vivo* functional potency assays, which can quantify the functional appropriateness and will provide MSC product selection for manufacturing and clinical translation.
- Identifying the MSC molecular signature and functional phenotype that aligns with efficient antimicrobial and anti-inflammatory activity for the CF diseased milieu will enhance efficacy and define the "target" for training strategies.
- Future phase II mesenchymal stem cell clinical trials will be designed to improve the cell product and dosing and have a high likelihood of advancing CF clinical care and management by reducing pulmonary infections as well as the complicating inflammation that affects several visceral organs.

CRediT authorship contribution statement

Tracey L. Bonfield: Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hillard M. Lazarus:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing

The authors have not used AI or AI-assisted technology in the manuscript.

Conflict of interest

The authors have no conflict of interest related to this review.

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