Primary Chondroprogenitors: Standardized & Versatile Allogeneic Cytotherapeutics

Subjects: Orthopedics

Contributor: Alexis Laurent, Annick Jeannerat, Cédric Peneveyre, Corinne Scaletta, Virginie Philippe, Philippe Abdel-Sayed, Wassim Raffoul, Robin Martin, Nathalie Hirt-Burri, Lee Ann Applegate

Primary chondroprogenitors obtained from standardized cell sources (e.g., FE002 clinical grade cell sources) may be cultured in vitro and may be cytotherapeutically applied in allogeneic musculoskeletal regenerative medicine. Multicentric translational research on FE002 human primary chondroprogenitors under the Swiss progenitor cell transplantation program has notably validated their robustness and high versatility for therapeutic formulation in clinically compatible prototypes, as well as a good safety profile in diverse in vivo preclinical models. Therein, stringently controlled primary cell source establishment and extensive cell manufacturing optimization have technically confirmed the adequation of FE002 primary chondroprogenitors with standard industrial biotechnology workflows for consistent diploid cell biobanking under GMP. Laboratory characterization studies and extensive qualification work on FE002 progenitor cell sources have elucidated the key and critical attributes of the cellular materials of interest for potential and diversified human cytotherapeutic uses. Multiple formulation studies (i.e., hydrogel-based standardized transplants, polymeric-scaffold-based tissue engineering products) have shown the high versatility of FE002 primary chondroprogenitors, for the obtention of functional allogeneic cytotherapeutics. Multiple in vivo preclinical studies (e.g., rodent models, GLP goat model) have robustly documented the safety of FE002 primary chondroprogenitors following implantation. Clinically, FE002 primary chondroprogenitors may potentially be used in various forms for volumetric tissue replacement (e.g., treatment of large chondral/osteochondral defects of the knee) or for the local management of chondral affections and pathologies (i.e., injection use in mild to moderate osteoarthritis cases). Overall, standardized FE002 primary chondroprogenitors as investigated under the Swiss progenitor cell transplantation program were shown to constitute tangible contenders in novel human musculoskeletal regenerative medicine approaches, for versatile and safe allogeneic clinical cytotherapeutic management.

Keywords: bioengineering ; chondral/osteochondral defects ; chondrogenesis ; cytotherapeutics ; formulation ; musculoskeletal pathologies ; primary FE002 chondroprogenitors ; regenerative medicine ; safety ; translational research

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Musculoskeletal diseases in general and chondral/osteochondral affections, in particular, are highly incident in aging patient populations [1][2][3][4]. While conservative orthopedic best practices enable the successful clinical management of critical cases of cartilage injury or degeneration (e.g., prosthetic replacement), effective regenerative medicine interventions and solutions are necessary in the cases of moderate to severe affections [3][5][6][7][8]. Therefore, many natural and artificial biomaterials or bioengineered constructs have been successfully clinically applied for chondropathies and cartilage tissue defects, with extensive available hindsight (i.e., intervention safety, quality, efficacy) [5][9][10][11][12][13][14][15][16][17][18]. Parallelly, important translational efforts, deployed over the past 40 years, have led to the implementation of diverse clinical protocols for several generations of autologous chondrocyte implantation (ACI) [1][4][8][19][20][21][22][23][24][25][26][27][28]. While initial and successful approaches to ACI may have relied on the use of cultured cells or minimally manipulated chondrocyte suspensions, current commercially available clinical approaches to cartilage regenerative medicine often comprise the use of a matrix/scaffold component (i.e., combination products, e.g., cells in a hyaluronan-based hydrogel scaffold or bilayer collagen constructs) [1][10][11][28][29][30][31][32][33][34][35][36][37].

Vast arrays of potential cell sources (e.g., various stem and progenitor cells, somatic cells, platelets, etc.) and processing methods (e.g., preparation of cell suspensions, spheroids) have been investigated for the high-quality cytotherapeutic management of chondropathies and chondral/osteochondral defects [7][11][38][39][40][41][42]. Recently, multiple genetically modified cell lines, designed for enhanced chondrogenic function, have been studied and clinically proposed for cartilage tissue engineering [6][43][44][45]. From a technical standpoint, the scientific knowledge of the in vitro behavior and functional evolution (i.e., transiently reduced chondrogenesis potential in monolayer cellular expansion) of cultured chondrocytes has rapidly increased [5][8][14][31][46][47][48][49][50][51][52][53][54][55]. For therapeutic cell manufacturing purposes, numerous studies have enabled and have validated (i.e., from technical, quality, and functional standpoints) the substitution of fetal bovine serum (FBS) by human platelet lysates (HPL) as cellular growth medium supplements [28][56][57][58][59][60][61][62][63].

Notwithstanding, despite enormous progress in the biotechnological and bioengineering approaches to cell-based combination products for cartilage repair and regeneration, important regulatory and clinical bottlenecks have recently been documented [28][40][64][65][66][67][68][69][70]. Indeed, specific quality-oriented and process-based approaches to cell therapy manufacturing have become the norm (e.g., application of cGMPs for cellular active substances and finished cell-based product manufacture) [28]. Importantly from the clinical standpoint, the cartilage lesion localization, the surgical approach, and the patient follow-up management plan have been identified as critical factors for consistently attaining long-term clinical success with cytotherapies for cartilage tissue affections [14][65][69].

Human primary chondroprogenitors (e.g., FE002 clinical grade cell sources) have been extensively investigated under the Swiss progenitor cell transplantation program as a potential cytotherapeutic solution for the optimal homologous allogeneic management of diverse cartilage tissue disorders [38][71][72]. Human FE002 primary chondroprogenitors are cultured diploid cells, inherently pre-terminally differentiated, which display monomodal and stable phenotypes in vitro [38][72]. Homogeneous and robust cryopreserved cell banks and cell lots of FE002 primary chondroprogenitors may be exploited as highly sustainable tools and material sources for allogeneic musculoskeletal cytotherapeutic applications under modern restrictive quality requirements [71][72]. Importantly, human FE002 primary chondroprogenitors are highly biocompatible with diverse biomaterials, possess an inherent immune privilege, and present no known tumorigenic behaviors [38][72].

Such standardized biological materials are biotechnologically manufactured and are formulated following best practices in pharmaceutical sciences and cell-based bioengineering, with the central therapeutic objectives of rapidly and optimally restoring chondral tissular structures and functions [72]. Overall, the FE002 primary chondroprogenitors investigated under the Swiss progenitor cell transplantation program were shown to present high robustness and versatility in an array of potential therapeutic uses (e.g., fresh or off-the-freezer cell therapies) in human musculoskeletal regenerative medicine [71][72]. A succinct overview of the currently published body of knowledge (i.e., scientific peer-reviewed elements) on FE002 primary chondroprogenitors is presented in **Table 1**.

Table 1. Summary of the published peer-reviewed reports describing the collaborative and multicentric translational work (i.e., characterization, qualification, validation) on FE002 primary chondroprogenitors under the Swiss progenitor cell transplantation program. This constantly evolving body of knowledge has established FE002 primary chondroprogenitors as standardized and versatile cytotherapeutic contenders for human musculoskeletal regenerative medicine, for repair promotion and/or regeneration support in chondral/osteochondral affections. CAM, chorioallantoic membrane model; GLP, good laboratory practices; HA, hyaluronic acid.

Study Subject/Domain	Scope of the Study/Investigated Parameters/Main Data	References
1. Progenitor Cell Source Establishment	**Biological starting material procurement (i.e., controlled organ donation within the Swiss progenitor cell transplantation program) and establishment of FE002 primary progenitor cell sources in a cryogenically preserved multi-tiered cell bank system.**	[71]
2. In Vitro Cell Type Characterization	**Characterization of progenitor cell type key and critical attributes (e.g., cellular proliferative behavior in culture, cellular lot homogeneity and purity, cell genetic and phenotypic stability, proteomics, chondrogenic potential, in vitro safety parameters).**	[38][72]
3. Characterization of In Vitro Mechanobiological Cellular Behavior	**Study of the influence of physical (i.e., mechanical) parameters on cellular biology and functional attributes [1]. Optimization of physical processing workflows for cytotherapeutic material lots.**	[73][74][75]
4. In Vitro Cell Banking & Biotechnological Manufacturing	**Optimization and standardization of in vitro progenitor cell manufacturing workflows (i.e., industrial-scale cellular lots). Confirmation of progenitor cell source sustainability at passage levels for clinical use [2].**	[72]
5. Formulation Studies for Functional Cytotherapeutic Products	**Formulation and translational characterization/qualification of hydrogel-based (e.g., modified HA-based gels) standardized transplants and polymeric scaffold-based tissue engineering products yielding viable/functional progenitor cells.**	[76][77][78][79][80]
6. In Vivo Preclinical Safety Assessments	**Study of progenitor cellular material or cytotherapeutic combination product safety in ovo (i.e., standardized CAM model) and in vivo (e.g., subcutaneous rodent implantation models, GLP study of knee chondral defect management in goats).**	[72][76][77][79]

[1] It is noteworthy that the considered tissue engineering products/prototypes were reported to be characterized by endpoint mechanical attributes which did not match those of native chondral tissues. This aspect has not been interpreted negatively, based on the fact that such orthopedic cell-based approaches aim to stimulate repair and/or support

regeneration processes, rather than exclusively structurally replacing the damaged cartilage. Therefore, while the implanted constructs must be able to bare weight, sufficient potential for mechanical adaptation to the local healing environment must remain, for optimal graft integration and therapeutic deployment of functional attributes. [2] The established models have outlined that a single clinical grade primary chondroprogenitor cell source could potentially yield several million therapeutic bioengineered cartilage grafts or injectable viable cell suspensions, without the need for repetition of the cell type establishment phase.

Notably, multiple in vivo preclinical studies (e.g., in rodent and goat models) have robustly documented the safety of FE002 primary chondroprogenitors following implantation, which may therefore be safely considered for investigational human cytotherapeutic use (i.e., international first-in-man clinical trials) [72][76][77][79]. From a clinical indication standpoint, such cellular materials and combinations thereof may potentially be used for volumetric tissue replacement (e.g., treatment of extensive chondral/osteochondral defects of the knee) or the local management of mild to moderate chondral affections and pathologies (i.e., injectable hydrogels in osteoarthritis patients) [72]. Overall, the aggregated multicentric translational work on FE002 primary progenitor cell sources, performed over the past decade in Switzerland, has confirmed their high versatility and safety for application as cellular active ingredients within the development of novel cytotherapeutic products and standardized transplants for human use (**Table 1**) [38][72][76][77][78][79][80].

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