Biotechnology and Cytotherapeutics:The Swiss Progenitor-Cell Transplantation Program

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Historically, primary human progenitor cells (e.g., WI-38 and MRC-5 diploid-cell sources) have been industrially applied in research and in manufacturing processes for vaccines and for biologicals. Furthermore, tissue-specific primary progenitor-cell banks have recently been developed and exploited for the provision of safe, consistent, and effective cellular active pharmaceutical ingredients (API) in homologous allogeneic regenerative medicine applications. Notably, the modern legal and regulatory frameworks for novel therapeutic products and for progenitor-cell therapy development have been iteratively optimized to guarantee utmost product safety, quality, and efficacy. Over 50 years of global technical hindsight around progenitor-cell biotechnological substrates and over 30 years of in-house clinical experience around the therapeutic uses of standardized progenitor-cell sources in Switzerland have demonstrated the importance of such biological materials for public health. The aim of this entry work was to summarize the evolution of the industrial applications of selected primary progenitor-cell sources, ranging from the use as robust biotechnological substrates to standardized cellular API manufacture and their clinical uses in highly specialized regenerative medicine.

Keywords: biotechnological substrates ; cell therapies ; organ donation ; pharmacopeial monographs ; progen-itor cells ; quality requirements ; regenerative medicine ; regulatory compliance ; standardized transplants ; vaccine substrates

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Primary progenitor mammalian cells are characterized by extensive yet finite in vitro lifespans, defined tissue-specific phenotypes, and the technical potential for robust and extensive cell-batch-manufacture applications in controlled environments [1]. Primary progenitor cells are diploid cells, which are generally fibroblast-like in adherent in vitro monolayer cultures, and are non-modified, constituting cell types rather than cell lines [1][2]. Such cell sources were initially studied and were proposed as manufacturing substrates during the last third of the twentieth century, during the bold exploration of new frontiers in biotechnology for novel therapeutic-product development [3][4][5]. Specifically, the urgent global need for standardized substrates in the field of industrial vaccine-product manufacture had prompted the search for optimal and safe cell sources [6]. Therefore, notorious applied cellular-biology studies from the 1960s have laid the foundations of most modern biotechnology processes, with the original establishment and the subsequent thorough characterization of well-known diploid cell types (e.g., WI-38 and MRC-5 fetal lung fibroblast sources) [3][5]. Such specific biological materials, stabilized in cryopreserved form and in defined cell-bank systems, were soon proposed, confirmed, and were industrially adopted as technically optimal and high-quality biotechnological substrates. Thereafter, diversified and extensive industrial experience was gathered around these original diploid-cell sources, along with many demonstrated and tangible gains for global public health [7][8]. Notably, wide arrays of vaccine products were developed and/or produced using the WI-38 or the MRC-5 diploid cells, directly contributing to the effective prevention of, among other human diseases and affections, chickenpox, hepatitis A, poliomyelitis, smallpox, rabies, and rubella [6][7].

Interestingly, the direct and indirect use of such primary progenitor cell sources by scientific researchers and by pharmaceutical industries has constituted the basis for continued ethical and moral debates [9][10][11][12][13][14][15][16]. Despite the documentation of many proven public health benefits of using diploid cells for life-saving therapeutic-product development and manufacture, thorough discussions have been driven notably by religious scholars around the context of the original tissue procurement [7][14][15][16]. Nonetheless, the intensive industrial use and the global material demand for high-quality biotechnological substrates have currently never been higher, prompting the development of novel diploid-cell sources and the renewal of aging cell stocks [17][18][19]. Therefore, several sustainability and stability characteristics of appropriately established primary progenitor-cell sources are being set forth as critical attributes and as major technical advantages [1][17]. Based on such quality-oriented considerations, the development and the qualification of novel standardized progenitor-cellular substrates are of high current interest, for eventual valorization in the supply chain of modern biotechnological industries [6].

In parallel to the industrial manufacturing applications, where primary progenitor cells are used as ancillary biotechnological substrates, high interest has been recently set on the direct use of the same types of cells as starting

materials and as raw materials in cytotherapeutic products (**Figure 1**) [1][2]. Indeed, several technical and biological characteristics of such tissue-specific cell sources confer tangible advantages for the therapeutic uses thereof as active pharmaceutical ingredients (API) in homologous allogeneic regenerative-medicine applications [6][20]. Therefore, it has been reported that, when appropriately sourced and bioprocessed, primary progenitor-cellular APIs may be considered as optimally adapted for industrial transposition and for clinical translation in modern tissue-engineering applications [20]. In addition to the documented vast therapeutic potential and low risks of immunogenicity, the scalability and the robustness of selected primary progenitor-cell sources enable the eventual use of safe and consistent cytotherapeutic APIs [20][21][22][23][24][25][26][27]. Importantly, the use of stringent methodological workflows for progenitor-cell sourcing and for the subsequent clinical applications currently appear as central in the overall therapeutic approach, with specified ownership, rights, and obligations related to the defined cell sources [2][28][29].

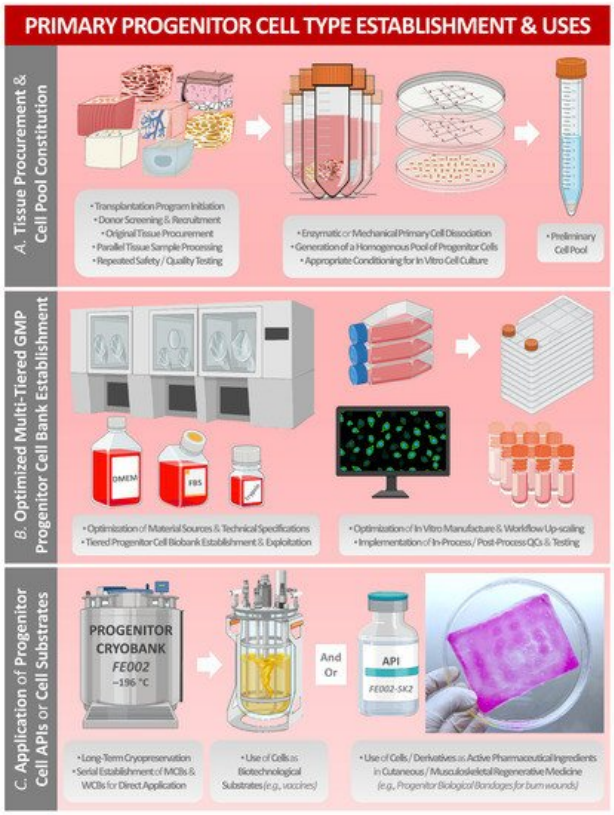

Figure 1. Schematic technical overview of the established workflows for optimized primary progenitor-cell-type establishment and of related industrial applications. (**A**) Using ad hoc and well-defined methodological processes for the original tissue procurement, the appropriate in vitro primary-cell-isolation procedures are applied to obtain a homogenous preliminary pool of primary progenitor cells. (**B**) Following stringent manufacture-optimization steps, the multi-tiered GMP cell banking is performed to constitute the primary progenitor-cell banks. (**C**) The established and qualified cell stocks of primary progenitor cells may then be used as biotechnological substrates or as cytotherapeutic APIs in specialized regenerative medicine. API, active pharmaceutical ingredient; DMEM, Dulbecco's modified Eagle medium; FBS, fetal bovine serum; GMP, good manufacturing practices; MCB, master cell bank; QC, quality control; WCB, working cell bank.

Despite several recent regulatory hurdles and bottlenecks affecting the global development of many cell-based therapeutic products, numerous efforts and vast resources have been allocated toward preclinical and clinical work around the therapeutic use of primary progenitor cells [30][31][32][33][34][35][36][37]. Specifically, almost three decades of specialized clinical experience with such progenitor-cell-based tissue-engineering products (TEP) have been gathered in pediatric burn-patient care [38][39][40][41]. Polyvalent use of skin-derived diploid progenitor fibroblasts as viable cellular APIs indicated for the promotion of cutaneous wound healing has revealed unique capacities for the obtention of structural and of functional restoration of the affected cutaneous structures [38][41]. In particular, the continued therapeutic management of pediatric burns and of chronic inflammatory cutaneous wounds in the Lausanne University Hospital using local homologous progenitor cell therapies since the 1990s may be considered as a landmark in the field [38][42][43].

Furthermore, the continued work in applied bioengineering and on diversified tissue-specific progenitor cell-therapeutic applications has revealed similar high potential for the allogeneic treatment of soft-tissue and of musculoskeletal-tissue affections [44][45][46][47][48][49][50]. Therefore, using evolutive process-based and conserved methodological aspects of diploid progenitor-cell sourcing, multi-tiered cell-bank establishment, and cellular API processing, it was shown that qualified progenitor cell sources were well-adapted for the establishment of safe and sustainable therapeutic-material

supply chains (**Figure 1**) [1][51][52][53]. Therefore, it can be summarily stated overall that selected primary progenitor-cell sources constitute scientifically and historically proven robust and polyvalent tools, to be indirectly or directly applied for the manufacture of therapeutic products, thereby tangibly contributing to the global betterment of public-health capitals [1].

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