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4

# Human stem-cell research in gastroenterology: Experimental treatment, tourism and biobanking

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A B S T R A C T

The growing interest in the possibility of applying stem-cell therapies to gastroenterological diseases is outlined. Some promising results have been reported, but more research is needed in view of the uncertainties and knowledge gaps that still exist. The ethical issues raised by this kind of research are then indicated and classified. Three problematic kinds of situation are outlined: experimental treatments, stem-cell tourism and biobanking. A four-question approach – which is not to be confused with the well-known four-principle approach introduced by Beauchamp and Childress – is described and applied to these three challenging situations. In conclusion, it is pointed out that the analysis of these situations illustrates the interplay between definitions, empirical research and ethics. They are interrelated and need to be integrated.



## Background

For more than a decade there has been a growing interest in the possibility of applying stem-cell therapies to gastroenterological diseases, and in particular in the prospect that haematopoietic stem-cell transplantation might benefit patients with inflammatory bowel diseases (IBDs) and Crohn's

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disease (CD) [1]. Diabetes mellitus, coeliac disease and acute or chronic hepatopathies are also potential targets of the translation of basic stem-cell research into novel therapeutic strategies [2].

There is an interesting case report of a 36-year-old male with ileocolic CD [3]. It concludes that immunoablative chemotherapy followed by autologous peripheral blood stem-cell transplantation 'may be a beneficial therapeutic option in complicated refractory CD' [3, p. 340]. Burns and Thapar suggest that neural stem cells offer the prospect of a cure 'given their potential ability to replenish missing or dysfunctional neurons' [4]. The various sources of stem cells and their potential are explored in this paper, which also addresses the critical steps that remain to be taken before these therapies can be used in patients.

Promising results have been reported from a multi-centre, phase II trial [5] in connection with stem-cell therapies in intestinal diseases. There are also quite a few clinical trials of stem-cell therapy for liver diseases, although most are of limited significance because they use small groups of patients, with no controls, and refer to outcome parameters that are easily biased [6, p. 3875].

But the history of stem-cell research is not only a history of hope but also of hype. Clearly, more research is needed given the uncertainties and gaps in our knowledge that still exist. Precisely this is stressed in a study of mobilization of peripheral blood stem cells in 12 patients with refractory Crohn's disease [7], where it is argued that a randomized study will be needed to confirm the efficacy of this therapy. A paper on stem cell-based therapy in gastroenterology and hepatology reports that stem cells are already leaving the bench and reaching the bedside 'despite incomplete knowledge of the genetic control program driving their fate and plasticity' [2, p. 100].

Burra et al mention several types of stem cells which can be used for cell therapy, including mesenchymal stem cells (MSCs), haematopoietic stem cells (HSCs) and adult liver stem/progenitor cells (LPSCs) [6]. The authors focus on the use of stem cells to treat hepatic and intestinal diseases. Like the authors of [8] they stress that further studies are needed. We need to know more about the biology of stem cells. The paper also reports a discussion at a workshop on stem cells sponsored by the Italian Society of Gastroenterology. The rather cautious conclusion is that stem cells may have the potential to replace cells lost as the result of diseases such as acute or chronic liver disease and inflammatory or immune-mediated bowel disease [6, p. 3876].

Animal studies are obviously essential in the early stages of translational research. Adipose-derived MSCs have been checked for hepatocyte-specific markers and functions and then transplanted into nude mice with liver injury. The results reported in Ref. [9] indicate that these stem cells have a special affinity for hepatocyte differentiation *in vitro* and liver regeneration *in vivo*. The authors suggest that adipose-derived stem cells 'may be a superior choice for the establishment of therapy for an injured liver' [9, p. 77].

Recently, further animal studies have been carried out on mice to evaluate the effect and mechanisms of human umbilical cord-derived MSCs on immune responses in murine colitis [10]. Differences in the effects on rats, when MSCs are administered in the early and late phases of tumorigenesis have also been investigated [11]. It was concluded that early-phase administration inhibits colorectal tumour development under certain conditions in a rat model of colorectal tumours [11, p. 175]. However, as is well known, the results of studies using animal models may not translate to humans. Further studies are required.

The authors of a recent review paper discussing the choice of somatic cells to be reprogrammed using emergent new and non-integrative strategies conclude that the differentiation of human induced pluripotent stem cells (hiPSCs) towards hepatocyte-like cells continues to be very promising for applications in haematology [12]. Some problems are indicated, but it is concluded that recent publications have demonstrated 'that many research groups worldwide are displaying creative and original strategies to move the field forward' [12, p. 342]. Potential applications in haematology include liver development, disease modelling, host–pathogen interactions, drug metabolism and toxicity.

Some interesting research projects deserve to be mentioned in this context. These include MODHEP, with its focus on modelling hepatocellular carcinoma, and STELLAR, both of which are supported by the European Commission [13]. The general objective of MODHEP, as stated on its website, is a systems biology-based approach intended to provide an integrated understanding of the molecular changes that drive complex diseases such as cancer. STELLAR is a research consortium interested in developing an alternative to renal replacement therapy making use of newly discovered kidney mesenchymal stem cells.