

Treatment of non-union fractures with fetal cell therapy

Dominique P. Pioletti¹, Lee Laurent-Applegate², Pierre-Yves Zambelli³, Keita Ito⁴

¹ *Laboratory of Biomechanical Orthopedics, EPFL, Lausanne, Switzerland*

² *Orthopedic Cell Therapy Unit, UNIL, Lausanne, Switzerland*

³ *Hôpital Orthopédique de la Suisse Romande, CHUV, Lausanne, Switzerland*

⁴ *AO Research Institute, Davos, Switzerland*

Background in non-union fractures : This project has been developed in order to solve the clinical problem of *atrophic non-unions* (osseous fractures). This situation is observed in 5 to 7% of all tibial and femoral fractures and represents an important and difficult population to treat. Progressively, surgeons have come to realize that fracture healing is not only a mechanical problem but also a biological or a cellular challenge.

There are two major expected outcomes in this research program, one at the level of understanding wound healing and one at the clinical level. For wound healing, by specifically looking at differences in human fetal and adult protein production, we would like to identify proteins produced by fetal cells but not by adult cells in the context of wound healing. These results would be fundamental in our comprehension of the phenomenon involved in wound healing in general and in specific for bone and associated osteogenetic factors. This approach could open new avenues of research with the clear view of enhancing wound healing as it has been demonstrated recently for the skin. At the clinical level, the actual treatment of non-unions is challenging the orthopedic community. Developing new solutions for this clinical problem is of primary importance and the approach of using fetal cells, if suitable, may revolutionize the medical practice. Obvious enhancements will be obtained for the patients suffering from non-unions who often have their quality of life profoundly affected due to the associated handicap and especially due to the associated pain. Delivering fetal cells percutaneously would then be an easy, non-traumatic procedure with substantial improvement in morbidity to unhealed fractures.

Rational to use fetal cells : Fetal associated tissues such as placenta, amniotic liquid or umbilical cord are described to be potential sources of cells for tissue engineering¹. In contrast to embryonic tissue derived up to the end of the 8th week, fetal tissue begins at the 9th week and is considered as an organ donation. Human fetal liver cells have already been used for transplantation to treat severe immunodeficiencies, haematological disorders and inborn errors of metabolism when there was no perfectly matched donor for marrow transplantation². Neuronal affections such as Huntington's³ or Parkinson's Disease⁴ have been treated by transplantation of fresh fetal neuroblasts. Unfortunately, these cells are difficult to expand in culture and have to be transplanted freshly therefore needing large quantities of fresh tissue⁵. Recently,

human fetal skin cells derived from one cell bank (1-4 cm² tissue results in over 10.5 million fetal skin constructs) were used in clinical trials and new advances in tissue therapy are possible with cellular constructs obtained from *ex vivo* cultures⁶. Engineered regeneration of human skeletal adult tissues could be also developed using human fetal bone cells. To evaluate their potential integration in a bone engineering strategy, a biological characterization of these cells is necessary.

Age dependent biology of osteoblasts is generally accepted. The particular biology of human primary fetal bone cells was partially demonstrated with cells isolated from calvaria⁷. They were found to secrete primarily matrix constituent proteins in culture, whereas adult cells produce additional proteins involved in matrix turnover. Age dependent differences regarding osteoblastic synthesis of osteoanabolic peptides and their impact on the regeneration of osseous defects were observed with a rat calvaria model⁸.

Recently, we performed a study to specifically evaluate the characteristics of human primary fetal bone cells for a better comprehension of their biology *in vitro* and to evaluate their potential use for tissue engineering in comparison to adult bone cells and mesenchymal stem cells⁹. Compared to primary adult bone cells, it was shown that fetal bone cells could be of great interest for bone research, due to their rapid growth rate and their ability to differentiate into mature osteoblasts. Importantly, human primary fetal bone cells represent an interesting and promising potential for therapeutic use in the bone tissue engineering field as these cells can be easily stocked "frozen for use" when necessary.

REFERENCES: ¹A. Kaviani et al. (2003) *J Am Coll Surg* **196**:592-597.

²J.L. Touraine et al. (1993) *Bone Marrow Transplant* **11**:119-122.

³A.E. Rosser et al. (2003) *CNS Drugs* **17**:853-867.

⁴E.D. Clarkson (2001) *Drugs Aging* **18**:773-785.

⁵T.B. Freeman TB. (1997) *Exp Neurol* **144**:47-50.

⁶J. Hohlfeld et al. (2005) *Lancet* **366**:840-842.

⁷J.S. Johansen et al. (1992) *J Bone Miner Res* **7**:501-512.

⁸F.J. Kramer et al. (2000) *Mund Kiefer Gesichtschir* **4**:S485-489

⁹M.O. Montjovent et al. (2004) *Bone* **35**:1323-1333.

ACKNOWLEDGEMENTS: This research work is supported by a grant from the AO Foundation (Davos, Switzerland) through the Biotechnology Advisory Board.