BIOHYBRID - Biohybrid templates for peripheral nerve regeneration.

BIOHYBRID – Biohybrid templates for peripheral nerve regeneration

Dear Editor,

Peripheral nerve injuries represent a major cause for morbidity and disability in affected patients and cause substantial costs for society in a global perspective. It has been estimated that peripheral nerve injuries affect 2.8% of trauma patients, many of whom acquire life-long disability *(Noble et al., 1998)*. With respect to an incidence of nerve injuries of 13.9/100,000 inhabitants per year *(Asplund et al., 2009)* and the number of inhabitants in the EU (495,000,000 inhabitants in 2007), the number of peripheral nerve injuries requiring repair and reconstruction, excluding nerve injuries by amputations, may be 70,000 annually only in EU countries. Related to peripheral nerve injuries, the costs for society are substantial and consist of direct (costs for surgery, outpatient visits and rehabilitation) and indirect (lost production) costs. Individual median and ulnar nerve injuries in the forearm have total costs of EUR 51,000 and 31,000, respectively, where around 85% of the costs consist of loss of production *(Rosberg et al., 2005)*, still excluding costs for adjusted quality of life *(Eriksson et al., 2011)*. Thus, one may estimate that the annual costs only in the EU may be as high as EUR 2.2 billion, indicating that improved treatment strategies for peripheral nerve injuries may not only improve the situation for patients, but may also significantly reduce costs for society.

Based on these premises, the EU granted EUR 6,000,000 fund as part of the seventh Framework Program to the BIOHYBRID consortium that was built with the overall aim to develop, in a pre-clinical perspective, an innovative biohybrid artificial nerve device for improving the regenerative treatment of severe traumatic injuries of peripheral nerves.

BIOHYBRID is a 4-year collaborative project that started on October 1, 2011, and involves 10 partners from 5 European Countries (Germany, Italy, Portugal, Spain and Sweden) and 1 Associate Country (Israel) (Fig. 1). The Consortium, coordinated by Claudia Grothe from Hannover Medical School and supported by a coordination board composed of Stefano Geuna from Turin University, Thomas Freier from Medovent GmbH, and Kirsten Haastert-Talini also from Hannover Medical School, includes three active and well-integrated small and medium-sized enterprises (SMEs) as well as seven academic partners covering all the scientific areas of interest for this project.

Figure 1. The BIOHYBRID Consortium as a whole.

The work program includes an integrated experimental approach bringing together the main aspects of regenerative medicine: (1) reconstructive microsurgery, (2) regenerative scaffolds, and (3) cell transplantation. This approach aims at the biological pre-fabrication of biohybrid nerve devices, their grafting into nerve gaps in various animal models, and the comprehensive evaluation of the regenerative outcome. The SME involvement is not limited to production and supply of materials and services but also includes active participation in conduction of the experiments for *in vivo* pre-clinical assessment and follow-up.

The project is built on seven work packages (WPs). The first (WP1) is focused on the optimization and evaluation of chitosan-based hollow tubes with different characteristics, including porosity, biocompatibility, and biodegradability. Following initial material assessment according to standardized ISO/EN 109935 guidelines, different primary cell types

(sensory, motor neurons, Schwann cells, human mesenchymal stem cells) will be seeded into the hollow devices and analyzed with regard to cell survival, neurite outgrowth, cell differentiation, and myelination under standardized conditions.

Selected conditions will then be used in a standardized *in vivo* rat model for peripheral nerve regeneration (10 mm gap in sciatic nerves of adult rats) studied with regard to morphological and functional regeneration under standardized conditions (e.g., behavioral tests, electrophysiology, nerve morphometry, immunohistochemistry, biochemistry, molecular biology, etc.).

The following two steps (WP2/WP3) aim at defining efficient strategies for improving the effectiveness of the tubular devices obtained in WP1. This will be obtained either along two strategies: (1) functionalization by luminal fillers/biomatrices and/or trophic factors conjugated to nanoparticles (WP2); (2) enrichment with primary cell types (Schwann cells and mesenchymal stem cells) genetically engineered to promote neurite outgrowth by the production of neurotrophic factors (WP3). Based on extensive *in vitro* testing, the combined devices that prove to perform best will be selected for *in vivo* evaluation following the same experimental protocols used in WP1.

As a final comparative evaluation aiming at defining the best approach among those that emerged as the most effective in WP1-3, WP4 is focused on their *in vivo* assessment in more complex sciatic nerve repair animal models, including (1) a rat model with long gap (15 mm), with/without delayed repair; (2) a diabetic rat model with moderate increased glycemic levels; and (3) a rabbit model with 4 cm sciatic nerve gap.

Furthermore, the presence of substantiated expertise to meet the regulatory work for ATMP development inside the Consortium will result in the continuous supervision of the facilitation of product transfer into future clinical trials (WP5). This WP includes the development of new documentation models, health economy calculations, standard operation protocols, consultation of the Innovation Task Force and the Committee for Advanced Therapies (CAT) for scientific advice and for classification of the product, design of Common Technical Documents for GMP manufacture and of dossiers for clinical trial authorization by the national regulatory authorities, and preparation of submission of quality and non-clinical data (conducted under good laboratory practice (GLP) conditions) to EMA/CAT for ATMP certification.

Finally, management of the project activities as well as the dissemination and exploitation of the project results will be carried out according to two dedicated WPs (WP6 and WP7).

BIOHYBRID is an academic–industrial partnership reaching to significant innovation in peripheral nerve tissue engineering with considerable funding from the EU. A side objective of this project is also to generate a protocol that can serve as a template for future clinical trials for tissue engineering of damaged peripheral nerves. Considering the interdisciplinary expertise of the project partners, the BIOHYBRID project stands on the front line of regenerative medicine research and it is expected that it can lead to significant advancements regarding not only the biology of nerve regeneration but also the clinical treatment of patients suffering from peripheral nerve damage.

Sincerely,Claudia Grothe [1] , Kirsten Haastert-Talini [1] , Thomas Freier [2] , Xavier Navarro [3] , Lars B. Dahlin [4] , Antonio Salgado [5] , Shimon Rochkind [6] , Abraham Shahar [7] , Luis Filipe V. Pinto [8] , Martin Hildebrandt [9] , and Stefano Geuna [10]

References

Asplund M, Nilsson M, Jacobsson A, von Holst H (2009). Incidence of traumatic peripheral nerve injuries and amputations in Sweden between 1998 and 2006. Neuroepidemiology 32:217–228.

Eriksson M, Karlsson J, Steen Carlsson K, Dahlin LB, Rosberg HE (2011). Economic consequences of firewood machnery accidents to the hand and forearm - a cost of illness study. J Plast Surg Hand Surg 45:28–34.

Noble J, Munro CA, Prasad VS, Midha R (1998). Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. J Trauma 45:116–122.

Rosberg HE, Carlsson KS, Hojgard S, Lindgren B, Lundborg G, Dahlin LB (2005). Injury to the human median and ulnar nerves in the forearm–analysis of costs for treatment and rehabilitation of 69 patients in southern Sweden.JHandSurg Br 30:35–39.