Technical Seminar

Tittle: Epidermal Growth Factor (EGF) and the innovative intralesional infiltration for diabetic ulcers healing. Heberprot-P®: from the bench to the clinic.

Presenters: Jorge A. Berlanga Acosta DVM MS PhD; Boris Acevedo Castro MD PhD. Center for Genetic Engineering and Biotechnology, PO Box 6162, Havana City, Havana 10 600, Cuba

Place: Pan American Health Organization, Room. 525 23rd ST NW, Washington DC, 20037

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On-line Access: www.paho.org/virtual/chronicdiseases

Abstract: Epidermal Growth Factor (EGF) and the innovative intralesional infiltration for diabetic ulcers healing. Heberprot-P®: from the bench to the clinic. Correspondence to: jorge.berlanga@cigb.edu.cu

The factors that in diabetes "wipe away" from the cells the intrinsic mechanisms for a physiological repair and consequently lead to wound chronification remain unclear. Canonic findings invoke the concepts that diabetic wound biochemistry is a complex and hostile milieu in which inflammatory mediators, proteolysis and pro-oxidative ingredients prevail. Furthermore, advanced glycation end-products and their adjacent pathways have also proved to be cytotoxic for granulation tissue cells as for keratinocytes, thus hindering fibro-angiogenesis and wound re-epithelialization. Although a myriad of *in vitro* and animal experiments have largely documented the relevance of growth factors (GFs) for the events encompassed in the megaprocess of healing as for a its physiological trajectory; the clinical advent of GFs for topical administration was followed by medical disappointment. Conclusions derived from several pieces of knowledge from our group and others indicated that topical (GFs) pharmacodynamic deficiency may be related to diffusion/penetration limitations and a shortened local bioavailability. GFs are

degraded in diabetic foot ulcers (DFUs) but still tyrosine-kinase receptors' local agonistic stimulation is an instrumental factor to prevent wound chronification. Our Center for Genetic Engineering and Biotechnology in Havana, Cuba, manufactures recombinant human EGF since the early 80's while we have accrued seminal experimental findings and relevant clinical data in different settings. EGF has the privative ability to stimulate its receptor as to simultaneously trigger different signaling pathways involved in granulation tissue cells migration, anchoring, secretion, proliferation and importantly cyto-protection. Moreover, as opposed to other fibro-angiogenic GFs; EGF does not recruit inflammatory cells. Thus, EGF is endowed with the intrinsic biologically capability to resume wound healing and turn off chronicity phenotype. As we observed that wound deeper layers express far more EGF receptors, and that wound surface express far more cell-proliferation inhibitors; we set forth the rationale of infiltrating EGF down inside complex/terminal diabetic foot wounds as a replacement therapy to ensure a proper tyrosine-kinase fueling to the wound bed cells. The concept first emerged from two of our experimental evidences: (a) locally infiltrated EGF prevented trophic ulcers and limb necrosis upon denervation in rats, (b) pigs acute-controlled experimental wounds' clean exudate exhibited proteolytic activity. Depositing EGF in deep cells' responsive strata allows for two main pharmacological actions indispensable for chronic wounds healing: cyto-protection and proliferation of fibroblasts and endothelial cells, thus inducing progressive granulation.

This assertion has been progressively demonstrated along successive clinical trials, Heberprot-P® is an innovative Cuban product containing recombinant human epidermal growth factor for peri- and intralesional infiltration; it accelerates healing of deep and complex ulcers, both ischemic and neuropathic, and reduces diabetes-related amputations.

Several clinical trials of Heberprot-P in patients with diabetic foot ulcers have shown that repeated local infiltration of this product can enhance healing of chronic wounds safely and efficaciously. As a result, Heberprot-P was registered in Cuba in 2006, and in 2007 was included in the National Basic Medications List and approved for marketing. It has been registered in 15 other countries, enabling treatment of more than 120,000 patients.

Heberprot-P is a unique therapy for the most complicated and recalcitrant chronic wounds usually associated with high amputation risk. Local injection in complex diabetic wounds has demonstrated a favorable risk–benefit ratio by speeding out healing, reducing recurrences and attenuating amputation risk. Further testing and worldwide deployment of Heberprot-P would provide an opportunity to assess the product's potential to address an important unmet medical need.

Presenters:

Jorge A. Berlanga Acosta DVM MS PhD*; After completing his training in veterinary medicine, Dr Berlanga obtained a master's degree in medicine and comparative pathology and went on to earn a doctorate in pharmacology. A member of Cuba's Academy of Sciences, he has published more than 50 peer-reviewed articles on tissue repair and wound healing. Dr Berlanga is first author of the US patent for Heberprot-P.*

Boris Acevedo Castro MD PhD*; After completing his training as doctor in medicine, Dr Acevedo also obtained a doctorate in Medicine at Havana University. He is involved in the managing of innovative projects from the lab to registration, including Heberprot-P. He is author of more than 15 peer-reviewed articles and patents on innovative products.*