1. PUBLISHABLE SUMMARY

1.1. Project Objectives

The **overall objective** of OptiStem is to leverage European scientific excellence through a collaborative project in order to develop new strategies that will enhance the efficacy of clinical trials with adult, tissue stem cells for degenerative deseases of epithelia and skeletal muscle. This synergistic approach will ensure that ongoing and future clinical trials have a greater chance of success. To this end, key actions have been identified:

1. Phase I and potentially Phase IIa cell therapy trials for patients with muscular, skin or ocular disorders
2. In-depth optimisation of cell therapy studies in large animal models
3. Systematic analysis of stem cells fate in these large animals to address *(i)* differentiation, *(ii)* molecular control and *(iii*) transplantation efficacy
4. Identification of novel therapeutic strategies based on clinical trials results and small animal modeling
5. Characterisation of *(i*) regulatory, *(ii)* transcriptional and *(iii)* signalling pathways that control stem cell activity *in vivo*
6. Stimulation of tissue regeneration through activation of angiogenesis, a key success factor in efficient cell therapy
7. Immunological studies both *in vitro* and *in vivo* in order to determine *(i)* any adverse or beneficial effect and *(ii)* factors that can modulate the immune response.

To achieve these stated goals, the programme of work focuses on six interrelated projects in which the partners bring in specific expertise and resources which are collectively leveraged.

The primary focus is on clinical trials (CT) with epithelial and muscle stem cells. CT represent the core of the OPTISTEM project : they will benefit from discoveries during preclinical trials in large animals and their results will lead to the identification of new therapeutic approaches through further studies in small animals. These clinical trials will move towards the treatment of *(i)* muscular dystrophies using allotransplantation of normal mesoangioblasts and intra-muscular transplantation of systemically deliverable stem cells, *(ii)* ocular disorders through an innovative, simultaneous transplantation of corneal and conjunctival cells and *(iii)* skin stem cells deficiencies *via* transplantation of cultured oral mucosal stem cells.

The second focus is on preclinical large animal models. It relies on results produced in small animals and constitutes a key translational interface between stem cell biology and the implementation of clinical protocols. In this regard, dystrophic dogs will be used to test long-term efficacy of wild-type and dystrophic mesoangioblasts transplantation using *(i)* lentiviral vectors or *(ii)* engineered small nuclear RNAs. Pigs will also be used as a model in experimental ophthalmology and we will develop single cell analysis and transplantation of transduced stem cells.

The third project focusses on developing mouse models for cell therapy including immune-deficient animals for human cell transplantation. The injection of human keratinocytes into immune-deficient mice will provide a quantitative assay for the effects of different signaling pathways on epidermal lineage selection. These xenografts of modified human epidermal cells will be used in conjunction with different transgenic mice in order to *(i)* modulate the Notch pathway involved in determining epidermal or hair follicle fate in the skin and *(ii)* to define the optimal conditions of neo-dermis formation.

The fourth focus is on the factors that control stem cell activation and renewal at a mechanistic level. Using cutting-edge molecular and cellular approaches we are studying the different signalling pathways and transcription factors that control *(i)* satellite cell behaviour and repair of skeletal cell muscle, *(ii)* muscle interstitial cells and *(iii)* mesoangioblasts.

The fifth project relates to tissue remodelling and engraftment of stem cells. Besides cells, modification of the muscle environment is crucial for the successful engraftment of donor cells. Here we shall aim to *(i)* unveil the mechanisms that control the induction of angiogenesis and permeability *(ii)* increase stem cell homing through pharmacological approaches and *(iii)* improve fiber survival by reducing fibrosis using plasminogen activation and pharmalogical depletion of fibrinogen.

Finally, we cover the immunological aspects that result from stem cell engraftment. The regulation of the immune response is a key success factor for stem cell therapy. Here we shall determine *(i)* to what extent mouse and human stem cells, prior or after manipulation, elicit or not an immune response, *(ii)* how this response is modulated and *(iii)* how we can induce tolerance.

1.2 Work performed since beginning of the project

The work performed since the beginning of the project covers all the areas mentioned above. The preliminary clinical trial for children affected by Duchenne muscular dystrophy has been completed. It enrolled 30 patients and demonstrated the feasibility of monitoring the evolution of the disease in DMD individuals undergoing experimental treatments.

A phase I/II clinical trial also started in March 2011, based on transplanting mesoangioblasts from HLA-identical sibling into DMD patients. Three patients have been transplanted and so far and no serious adverse events have been observed. Three more patients are eligible having an HLA-identical sibling and we are seeking funds to also treat them next year.

Another pilot clinical trial based on intra-arterial transplantation of autologous engineered muscle-derived CD133+ stem cells has been initiated in DMD boys as preclinical work these previous years gave encouraging results.

Furthermore, the first effective autologous cell therapy clinical trial of stem cell-derived cornea transplantation has also been completed finally demonstrating the real potential of stem cell therapeutics in treating a common disorder. A total of six patients with one or two blind eyes have been treated so far with stem cells from the eye or the oral mucosa and all had a substantial improvement of corneal transparency, an amelioration of the clinical signs and an improvement of visual acuity in the treated eye.

Stimulated regeneration capacity of myogenic precursor cells, reduced muscle necrotic damage and inflammation have been achieved through a combination of drugs already approved for humans hence improving stem cell homing enabling the path to encouraging clinical trials.

A major step forward has also been performed with an innovative device that successfully permits the transplantation of single stem cell on the ocular surface of the pig, rabbit or mouse. Stem cells including cells from the ocular surface, the thymus, the tooth and the hair follicle have been successfully transplanted and imaged.

Many new pathways have been uncovered that are involved in the mechanisms that control stem cell activation and differentiation. Also a number of tools including mouse and cell lines have been generated to conduct these studies that have already led to promising new stem cell therapy. For example, the Notch pathway was found to be implicated in atopic dermatitis

and in maintaining corneal integrity. A new bipotent stem cell population that can be purified from any tissue has also been identified opening perspectives that go even beyond the scope of the project since they might benefit to the entire regenerative medicine field.

1.3 Main results achieved so far

A number of advances have been reached so far in the project regarding clinical trials:

The preliminary study "Validation Outcome" for children affected by Duchenne muscular dystrophy has been completed. This study was necessary in order to predict efficacy of subsequent cell transplantation. The study showed that it is possible to establish tools to monitor the evolution of the disease in DMD individuals undergoing experimental treatments.

The phase I/II clinical trial based on transplanting mesoangioblasts from HLA-identical sibling into DMD patients started in March 2011 by Giulio Cossu's team (Milan). Three patients have been transplanted and so far and no serious adverse events have been observed. Three more patients are eligible having an HLA-identical sibling and we are seeking funds to also treat them next year.

A pilot clinical trial based on intra-arterial transplantation of autologous engineered muscle-derived CD133+ stem cells from DMD patients has been initiated by Yvan Torrente's team (Milan) as preclinical work these previous years gave encouraging results. Three DMD patients have been selected according to the inclusion/exclusion criteria of the study. All patients will be followed for 3 years. The main endpoint will be assessed at 12 months post transplantation.

Through formal authorization by the Italian Ministry of Health to continue with consolidated cell therapies (obtained in May 2011) and the need of accredit CMR in Regione Emilia-Romagna (process still ongoing) we have obtained the cGMP certificate of the Centre for Regenerative Medicine, necessary to initiate the clinical trial on epithelial reconstruction.

Furthermore, the first effective autologous cell therapy clinical trial of stem cell-derived cornea transplantation has also been completed by Michele De Luca's team (Modena) finally demonstrating the real potential of stem cell therapeutics in treating a common disorder. Three patients with massive unilateral destruction of the corneal surface have been treated with limbal-corneal cells, the eye stem cells, from their healthy eye and two more patients will be treated in the oncoming weeks. This type of autologous transplantation is however not possible in total bilateral limbal stem cell deficiency of both eyes. Therefore, the use of autologous oral mucosal epithelial cells as a source of cells for the reconstruction of the cornea was successfully investigated. Three blind patients with complete bilateral limbal stem cells deficiency due to chemical burn or to Lyell's syndrome were treated with autologous cultured buccal stem cells. So far, all patients treated had a substantial improvement of corneal transparency, an amelioration of the clinical signs and an improvement of visual acuity in the treated eye.

Preclinical data have been generated that will hopefully lead the way to further clinical trials:

Arianne Rochat and Yann Barrandon's groups (Lausanne) have integrated the principle of precaution early in their gene therapy approach and developed a clonal strategy that permits a thorough assessment of the transplantable progeny of the genetically corrected stem cell. They have fully characterized the progeny of the transduced stem cell on a number of criteria linked to stemness maintenance, production of type VII collagen and long-term generation of a genetically corrected epidermis, together with the formation of anchoring fibrils. They have also demonstrated that the progeny of the founding recombinant stem cell was not tumorigenic

and did not disseminate after transplantation onto SCID mice. The team aims at transplanting the first patient in early 2013.

A major step forward has also been performed thanks to an innovative device that allows the long-term maintenance of isolated pig eyes in organ culture. Mini-incubators for rabbit eyes are now available, while incubators for mouse eye are being designed. Yann Barrandon's group (Lausanne) also designed a lens that successfully permits the transplantation of a cell suspension onto a denuded cornea. Using the device and lentiviruses expressing fluorescent reported genes, the group has demonstrated that cells seeded in central part of a pig cornea entirely reconstruct the corneal epithelium in two weeks. This achievement allows the reliable and reproducible transplantation of cultured stem cells onto the cornea. Stem cells including cells from the ocular surface, the thymus, the tooth and the hair follicle have been successfully transplanted and imaged in pilot experiments.

The feasibility of single stem cell transplantation onto pig skin, a large animal model was assessed. It was found that autologous grafts of stem cells from the epidermis and the hair follicles of the pig, survived for several weeks. This result is very important for implementation of new clinical trials.

Another avenue to treat muscular dystrophy is to transplant genetically corrected mesoangioblasts. Giulio Cossu's team (Milan) performed in dogs, injection of autologous mesoangioblasts corrected with lentiviral vectors expressing either dog micro-dytrophin or small nuclear RNA engineered to skip the intron and adjacent exons containing the mutation in dog dystrophin gene. Results indicated a lack of immune response and persistence of dystrophin. In the same objective, Giulio Cossu's team (Milan) genetically corrected mesoangioblasts from dystrophic mdx mice with a human artificial chromosomes (HAC) vector containing the entire (2.4 Mb) human dystrophin genetic locus. The lab has shown that the mesoangioblasts transplanted into the arterial circulation were able to engraft in dystrophic muscles, express normal dystrophin, and produce functional muscle fibers with amelioration of dystrophic pathology. The team has now successfully transferred the same construct in human dystrophic mesoangioblasts.

To circumvent the fact that mesoangioblast from patients affected by limb-girdle muscular dystrophy 2D (LGMD2D, characterized by α-sarcoglycan deficit) could not be derived for cell therapy, LGMD2D fibroblasts and myoblasts were reprogrammed by Giulio Cossu's team (Milan) into induced pluripotent stem cells (iPSCs) and turned into mesoangioblast-like cells called HIDEMs. These cells were genetically corrected successfully with a muscle-specific lentiviral vector expressing human α-sarcoglycan. Upon transplantation into α-sarcoglycan-null immuno-deficient mice, myofibers expressing human α-sarcoglycan were generated.

A number of strategies using NO are also being exploited by Emilio Clementi (Milan). The long-term efficacy of a derivative of ibuprofen, NCX 320, in α-Sarcoglycan null mice has now analysed. Animals treated with NCX 320 showed a lower number of necrotic fibres, a reduced inflammatory reaction and an increased the number of newly-formed fibres. NCX320 has potent vasodilating effects that may be combined with other strategies including vascular permeabilisation to enhance homing of exogenous stem cells. In addition, in α-Sarcoglycan null mice, a combination of drugs approved for human use, isosorbide dinitrate (ISDN) and the NSAID ibuprofen was efficacious in slowing disease progression. The combination of ibuprofen and ISDN stimulated regeneration capacity of myogenic precursor cells, reduced muscle necrotic damage and inflammation hence improving stem cell homing. These preclinical experiments led the way to a clinical pilot study, part of the sister consortium EndoStem, designed to evaluate safety and tolerability of the combination in patients suffering from Duchenne, Becker and Limb Girdle muscular dystrophies. Furthermore, Emilio Clementi has shown that treatment with molsidomine of α-SG null mice leads to a long-term reduction of muscle damage with functional recovery and that molsidomine has beneficial effects also during embryonic myogenesis of α-SG null mice. The effect of NO on satellite cells appears to be complex and requires multiple pathways possibly converging on same mechanisms, such

as mitochondria. Emilio Clementi has up to now, identified two of such relevant pathways regulated by NO, the one inhibiting DRP1 activity and a second one stimulating the wnt signalling.

The mechanisms of disease and development have also been uncovered:

Muscle related research

Using the *Pax7* conditional transgenic mice generated during the first year of the project in different mutant backgrounds, Shahragim Tajbakhsh (Paris) established a model for the role of Notch in muscle stem cells and during regeneration. It appears that inhibition of Notch signalling provokes differentiation and bypass of S-phase in the majority of satellite cells. Notch activity is highest in satellite cells and it declines upon activation. A further decrease occurs during differentiation, whereas Notch activity is required for satellite cell self-renewal. During homeostasis, the majority of Rbpj null cells differentiate without executing S-phase.

Pura Muñoz-Cánoves (Barcelona) has generated a skeletal muscle conditional p38α mutant mouse by using the Pax7-cre mice. Thus, p38α was deleted in both in the satellite cell and myofiber compartments. The resulting mice have smaller muscle fiber size during normal postnatal development and during regeneration. Similarly, p38α was deleted in proliferating satellite cells by crosses with Myf5-Cre mice. These conditional mice are now being analysed.

Peter Zammit discovered that absence of signalling through S1PR3 increases satellite cell proliferation without drastically affecting myogenic progression, enhances muscle regeneration following acute injury and it ameliorates the dystrophic muscle phenotype in *mdx* mice.

A dissociation protocol and a flow cytometry based analysis of skeletal muscle cell subpopulations were established by Miltenyi (Cologne). The procedure was then automated based on usage of the gentleMACS device. Miltenyi also performed the development of a standardized and validated analysis method for analysis and enumeration of CD34+ and CD133+ stem cells. Furthermore, cytokines are under development for the proliferation and differentiation of stem cells with a focus on CD133+ stem cells. In addition Miltenyi is generating anti-Lgr5 antibodies for better understanding epithelial stem cells.

The role of Pitx2/3 and miRNA31 was further explored by Margaret Buckingham (Paris). Thus, the presence of miR31 antagonists increased the number of activated satellite cells and muscle hyperplasia. Furthermore, the appropriate crosses to generate conditional double *Foxc2/Foxc1* mutants are now all established and the examination of mutant embryos is underway.

David Sassoon (Paris) has made progress towards the generation of a conditional null allele for the PW1/Peg3 gene. The clones are presently being injected into blastocysts to generate chimeric mice that will soon be analyzed. PW1 silent mesoangioblasts are unable to cross the vessel wall and migrate into the fibers. This migration defect was investigated by Graziella Messina (Milan) using a transwell assay and microarray analysis, which identified down-regulation of a number of molecules important for cell adhesion, extravasation, invasion and migration. These results indicate that PW1 silent mesoangioblasts are able to move *per se*, but have an inability to modify their structure and morphology, to degrade the extracellular matrix and hence to cross the vessel wall. In addition, Graziella Messina has confirmed the existence of a post-translational inhibition of MyoD in these cells, by rescuing their myogenic defect using a proteasome-resistant form of MyoD. Thus, PW1 is essential in conferring identity and the proper potency to mesoangioblasts. PW1 could serve as a pre-screening molecule for the identification of powerful mesoangioblasts in the heterologous cell therapy of the Muscular Dystrophies.

Susanna Molinari (Modena) reported that MEF2C is expressed both in quiescent satellite cells and in the myonuclei but it is phosphorylated on Ser98 selectively in satellite cells.

The increase in permeability and/or the change in the overall architecture of cell to cell junctions induced by the absence of JAM-A, increases endothelial/myeloid progenitors mobilization from the bone marrow. Elisabetta Dejana (Milan) also generated data suggesting that JAM-A is a target molecule to improve stem cell homing and implantation. To explore the possibility to develop a JAM-A blocking antibody as therapeutic tool for human Duchenne Muscular Dystrophy treatment, Elisabetta Dejana examined mesoangioblast engraftment in muscles of *Sgca*-null mice upon JAM-A blocking antibody treatment (BV11). These data showed an increase of mesoangioblast engraftment into *Sgca*-null mice treated with JAM-A neutralizing antibody versus *Sgca*-null mice treated with rat IgG as control.

Pura Muñoz-Cánoves (Barcelona) has generated data suggesting that a certain level of pericellular PAI-1 is needed to avoid rapid fibrosis progression in injured and dystrophic muscle. Complete loss of PAI-1 results in unrestricted activation of uPA/plasmin in damaged and dystrophic muscle, leading to the unscheduled accumulation of collagen and fibrosis. In addition, the exaggerated levels of fibrotic signaling parameters and the functional deterioration of PAI-$1^{-/-}$ mdx muscle could be significantly reversed by pharmacological and genetic inhibition of uPA using amiloride (a specific uPA inhibitor). Unfortunately experiments from Giulio Cossu's team (Milan), showed that long term amiloride administration results in high lethality in immunodeficient aged mdx mice.

Last year Kathryn Wood showed that human mesoangioblasts are hypoimmunogenic and do not evoke an immune response *in vitro.* It appears that mesoangioblasts inhibits T cell proliferation in a dose and time dependent manner, but not their function (activation, cytokine production). Neutralising studies revealed a partial but significant role for IFN-γ in mesoangioblast suppression of T cell proliferation while cell contact was not required for suppression of T cell proliferation

To analyze the immunological response caused by stem cell transplantation into various organs, a protocol for the optimized isolation of lamina propria lymphocytes as well as intraepithelial lymphocytes (IELs) has been developed by Miltenyi. A further task in this project deals with the use of marrow stromal cells (MSC) to induce immunological tolerance. Foetal calf serum (FCS) containing cell culture media are used routinely for many preclinical and clinical studies in Europe but have to be replaced by animal component free media with regard to regulatory and safety reasons. Miltenyi has worked on the integration of the Miltenyi Flow Cytometer "MACS Quant Analyzer" into two liquid handling systems for automated analysis of MSCs and the development of a MSC expansion medium.

<u>Epithelial related research</u>

Regarding the epithelial part of the project, Fiona Watt (Cambridge) has performed grafts in nude mice using a mixture of neonatal mouse fibroblasts and human keratinocytes containing the dN-beta catenin ER construct under the control of the keratin 14 (K14) promoter or an empty vector control and all produced hair growth at the graft site.

After having shown that chronic inflammation is sufficient to induce conversion of the corneal epithelium to epidermis, Freddy Radtke (Lausanne) demonstrated that this is due to the down-regulation of the EGFR antagonist Lrig-1. Thus, plaque forming epithelial cells exhibit hyperactive EGFR signalling, which is now being investigated. Furthermore Deletion of c-jun in Notch1 deficient cornea resulted in delayed epidermal fate conversion and reduced inflammation after corneal wounding. To identify factors acting upstream of c-jun, the group has performed analysis on corneal epithelial cells isolated from mutant mice after corneal wounding, which demonstrates that the expression of the pro-inflammatory cytokine IL-1β is increased in the absence of both Notch1 and c-jun. Thus, it has been shown that c-myc and c-jun act co-operatively in the corneal epithelium to induce chronic inflammation in response to Notch1 ablation. In addition, simultaneous deletion of Notch1 and β-catenin prevents the

acquisition of epidermal markers in response to chronic inflammation. In addition, by isolating different populations of cells defined on the basis of *DLL1* and *LRIG1* expression, Fiona Watt (Cambridge) has identified a number of genes that showed strong expression in the basal layer of human epidermis and were downregulated during terminal differentiation. Thus, this dataset is likely to contain novel stem cell markers.

Ablation of Notch signalling in the adult mouse epidermis results in a chronic inflammatory disease resembling atopic-dermatitis (AD) and an accompanying myeloproliferative disease (MPD). This is mediated by high level expression of the cytokine TSLP. Freddy Radtke (Lausanne) further confirmed that TSLPR signalling elicits anti-tumor T cell mediated immunity and that these tumor development is dependent on Wnt/β-catenin activation.

Michele De Luca (Modena) has isolated a pure population of primary epithelial cells, based on the level of expression of the α6-integrin, for high-throughput screening experiments, using a magnetic microbeads strategy.

Yann Barrandon's group (Lausanne) demonstrated that all squamous epithelia of the rat contain clonogenic epithelial stem cells that can behave like bona fide hair follicle multipotent stem cells in absence of culture or genetic manipulation. To the opposite, stem/progenitors cells obtained from pseudo-stratified or transitional epithelia of the trachea and the bladder only generate an epidermis-like epithelium. Furthermore, the group has isolated clonogenic cells from human thymus and demonstrated the existence of three different types of clonogenic cells. They have identified a tripotent epithelial stem cell that can be serially cultured and that generates the two other types of clones.

As an indication of the volume and quality of the output, partners of the consortium have published more than 30 peer-reviewed articles in international journals such as *Cell, Nature* and *J. Cell Sciences.*

1.4 Expected final results & their potential impact and use

The proposed projects capitalize on combined expertise in different areas of regenerative medicine. The proposal involves collaborative interactions that allows us to merge our unique and complementary expertise in the field.

Impact on science

Our expertise in stem cell biology is already being translated into realistic strategies that will increase the efficacy of stem cell therapies. This project aims to develop and implement clinical trials for genetic and acquired diseases of epithelia and skeletal muscle, by transplantation of donor or genetically corrected, autologous adult stem cells. While transplantation of epithelial stem cells for skin and cornea are now routine clinical procedures, none of them is yet optimal as skin appendages are not restored and bilateral corneal damages cannot be treated. At the same time, a clinical trial with autologoous genetically modified stem cells has produced excellent results for a severe genetic disease (epidermolysis bullosa). In the case of muscle diseases, donor cell transplantation has produced encouraging results in a large animal, pre-clinical model of Duchenne muscular dystrophy (DMD); based on this result a first clinical trial is planned. The proponents of this proposal have pioneered this work and are world leaders in the field.

It is widely recognized that the efficacy of these trials relies on continuous optimization, based on in depth understanding of the biology of the stem cells used, of the pathology of the host tissue as well as the immune response against donor cells, viral vectors and transgenes. This project addresses coordinately all these issues, ranging from clinical experimentation, pre-clinical tests in large animals and in immune deficient mouse models, to cell biology of stem cells and targeted use of pharmacological tools. The project also addresses the biology of

epithelial and skeletal muscle regeneration, as well as the control of angiogenesis, inflammation and immune response in the host. The expertise of the participant groups, the documented long lasting collaboration among most of them and their prominent position in the field is already focusing toward a success for this project.

Economic benefits

The musculo-skeletal market globally is anticipated to be greater than € 262 million, while soft tissue and wound repair, for which epithelial stem cells are used, is anticipated to be greater than € 912 million.

The global muscular dystrophy market has been valued at $115 million in 2009 and is estimated to grow by 3.8% per year until 2016.

The global dermatology market was valued at $17.0bn in 2010. It was led by the US with a market share of 46%, accounting for sales of $7.8bn.
Atopic dermatitis for example is very common worldwide and increasing in prevalence. It affects males and females equally and affects between 10% and 20% of children around the world. Atopic dermatitis occurs most often in infants and children, and its onset decreases substantially with age. Scientists estimate that 65% of patients develop symptoms in the first year of life, and 90% develop symptoms before the age of 5. Onset after age 30 is less common and often occurs after exposure of the skin to harsh conditions. About 1% to 3% of adults have AD. This means that more than 15 million people in the United States have symptoms of the disease. In 2011, Galderma will continue to channel its efforts towards improving its R&D initiatives. In March 2011, AstraZeneca and Galderma Pharma S.A. (Galderma), initiated an R&D collaboration to develop new treatments for dermatological conditions including psoriasis, acne, and atopic dermatitis.

Alopecia areata is another example it affects 0.1%–0.2% of humans. It is common throughout the world and can occur at any age, but approximately 50 percent of cases are seen in children and young adults before the age of 20. Statistical data on the prevalence of alopecia areata in the United States, as determined from the First National Health and Nutrition Examination Survey conducted from 1971 through 1974, indicated that every 158 out of 100,000 persons, or roughly 0.1 to 0.2 percent of the population, was affected by alopecia areata. Some research literature has estimated that about 1.7% of the population presents at least one episode of Alopecia Areata during their life. In 2004, 19,503 hair transplantation procedures were carried out in the U.S. Source: American Society for Aesthetic Plastic Surgery (ASPS). In the last three years hair transplants have increased by 20% in India. A study carried out on the urban population of Bangalore found that 20% of people visit clinics and demand hair transplants.

Reilly estimates dystrophic epidermolysis bullosa afflicts 800-2,000 people in the U.S. and Europe combined. Considered together, the incidence of all types of dystrophic epidermolysis bullosa is estimated to be 6.5 per million newborns in the United States. The severe autosomal recessive forms of this disorder affect fewer than 1 per million newborns.

Chronic wounds mostly affect people over the age of 60. The incidence is 0.78% of the population and the prevalence ranges from 0.18 to 0.32%. As the population ages, the number of chronic wounds is expected to rise.

OptiStem and its European partners will demonstrate a proof of principle through the interaction and integration of the fundamental, pre-clinical and clinical partners which will boost the European biotechnology industry, especially the SME sector, and contribute to developing standards and regulations in the area. Industry, particularly SMEs, will be kept routinely informed of progress and therefore play a significant part: this is specifically pertinent in paving the way for the application of the diversity if cellular based products in development in the diverse pathologies that can be targeted via cell therapy.

Impact on society

Degenerative diseases create a life-altering experience for the person with injury, for their partner, parents, siblings, and children. The impact on and subsequent dimishment of body functions associated with the diseases can cause depression and loss of self-esteem. It has been considered essential, based on European policy consistent with human rights principles that people with disabilities should be treated with dignity, encouraged to have independence, be given equality of opportunity, encouraged to have an active participation, a full citizenship and a high quality of life.

Given the diversity of degenerative diseases indicated above, pathological manifestation can occur at any age: either as a child, during an individual's most productive years, or as an aged person. In most cases, patients require continuous physical and medical care depending on the disease, severity of manifesation, degree of disability, and location of injury. The burden of caregiving most frequently falls on the partner. Care giving partners are often severely stressed, particularly due to health issues that arise after tissue degeneration initiates and suffer emotional stress that is comparable to or greater than those of the injured partner. Caregivers have a higher incidence of physical stress, emotional stress, burnout, fatigue, anger, and resentment.

Hope is considered an important coping strategy for both the person and family with degenerative diseases. Goal-directed hope based on realistic perceptions of life, focusing on progress, positive interpretation of events, are important in helping people and families cope with the disease. Hope is also focused towards the society at large, that new therapeutics are developed.

In addition to imposing direct medical costs on society, degenerative diseases also result in indirect costs, primarily related to reduced productivity due to disability with a further loss of self-esteem of the sufferer and diminished integration into society.

OptiStem aims to provide more than hope: we aim to provide validated cell therapies.

1.5 Project Contact Details and Logo

Project Co-ordinator Contact details:

Professor Guilio Cossu, Universita degli Studi di Milano

Tel: +39 02 2643 4954

Fax: +39 02 2643 4951

E-mail: giulio.cossu@unimi.it

Project website[2] address: www.OptiStem.org

Opt!STEM
Optimization of Stem cell Therapy for degenerative Epithelial and Muscle diseases