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stempeutics – A Leading Indian Stem Cell Company Developing Cellular Therapeutics for Global Consumers

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Stempeutics Research Pvt. Ltd. (www.stempeutics.com) is a leading Asian stem cell company developing stem cell based therapeutic products, with facilities in Bangalore and Manipal (India) as well as in Kuala Lumpur (Malaysia). Stempeutics was established in 2006 and has been funded by the Manipal group (http://www.manipalgroup.com). In 2009, Stempeutics entered into a strategic alliance with Cipla (http://www.cipla.com), one of the largest pharmaceutical companies in India. Stempeutics is in the process of bringing stem cell based therapeutics to India and South East Asia, and eventually to the global market. Stempeutics has taken an aggressive, focused and well thought-out scientific approach to understand the biology of human adult stem cells, and to harness the potential of these cells for the treatment of various types of degenerative diseases. The efforts are realized through innovative technologies and ideas, cutting edge R & D, patentable process development, large scale manufacturing and effective clinical trial design. Current areas of basic and clinical research are focused on adult mesenchymal stem cells (MSC) from bone marrow, Wharton's Jelly and adipose tissue, all of which are rich sources of stem cells. During the last five years we have published over 41 articles in peer reviewed journals and filed for 24 national and international patents. Recently, Stempeutics has received government funding from the Department of Biotechnology, to conduct a phase II clinical trial using our bone marrow MSC based product- Stempeucel®, and for performing basic R & D using Wharton Jelly derived MSC.

Mission:

Our mission is to ethically and scientifically explore the full potential of stem cells as new therapeutic interventions and offer hope to millions of people. Stempeutics is committed to delivering safe, effective and affordable stem cell therapies in a "Bench to Bedside" approach, by nurturing and developing novel stem cell based therapeutics for clinical applications and by matching customer satisfaction for "Regenerating Hope". Stempeutics endeavors to maintain scientific and ethical practices through a Quality Management System (QMS) in accordance with accepted national and international norms. Stempeutics is accomplishing this mission

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through dedicated efforts of its team to continually monitor and improve the effectiveness of the QMS to excel and innovate, thereby reflecting that we are truly “Inspired by Life”.

Stempeutics: Research and Product pipeline

The current focus of Stempeutics can be broadly divided into the following categories:

1. The on-demand off-the-shelf product range stempeucel®, based on allogeneic MSC derived from normal adult human bone marrow for curing various degenerative disorders;
2. On-demand personalized medicine based on autologous Stromal Vascular Fraction (SVF) cells isolated from fat tissue using Stempeutron™- a point-of-care medical device, intended for cosmetic and reconstructive procedures; and
3. The over-the-counter product Stempeucare™ based on stem cell derived bioactive factors for cosmetic applications.
4. On-demand off-the-shelf next generation product based on Umbilical cord Wharton’s jelly-derived MSC (WJ MSC)

To further supplement our R & D strength, Stempeutics actively collaborates with leading government and non-government research laboratories in India and around the world to develop novel technologies. Our collaborators include Syngene International, Bangalore, India; Dabur Research Foundation, New Delhi, India; National Institute of Nutrition, Hyderabad, India and Institute of Medical Research, Kuala Lumpur, Malaysia among others.

Stempeucel®:

The company’s lead product stempeucel® is ex-vivo cultured adult allogeneic human bone marrow MSC (BM MSC) derived through novel proprietary technology (Ref. 1) using multiple donors. Stempeucel® is manufactured inexpensively and can be used as an ‘off-the-shelf’ cryopreserved product. A unique xenofree cryopreservation solution is used to cryopreserve and store the BM MSC to maximize cell viability without compromising self renewal and multipotent capacity. Isolated and expanded BM MSC maintain their cellular and molecular phenotype throughout the passage period, and retain their differentiation ability to adipocytic, osteoblastic and chondrocytic lineages following cryopreservation and revival (Ref. 2-4). Stempeucel® has been designed and tested to be a safe product for cell therapy applications with the potential to regenerate diseased or damaged tissues of the aging human body (Ref. 3-5).

Stempeutron™:

Soft tissue reconstruction is a significant challenge in plastic and reconstructive surgery.
There are many clinical situations caused by congenital defects, trauma, lipodystrophy or cancer related surgery that result in a lack of soft tissue. Fat is natural filler, and has been used as dermal filler in aesthetic surgery for a few decades. However the survival of autologous fat grafts is mostly unpredictable due to lack of vascularization and graft resorption. Recent evidence suggests that survival of the fat graft is dependent on the stem and progenitor cells (Ref. 6) contained within the stromal vascular fraction (SVF) of the fat tissue. This has led to the scientific rationale for the supplementation of fat grafts with SVF cells for superior engraftment. SVF enriched fat grafts have applications in procedures such as breast reconstruction post mastectomy, breast augmentation, facial restructuring, deformity correction, scar and wrinkle reduction and other soft tissue repair.

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The use of SVF in aesthetic and reconstructive procedures is quickly becoming a clinical reality and has significant implications for the field as it would overcome the many challenges associated with artificial fillers. The manual procedure for obtaining SVF has several limitations, which calls for developing a fully automated point-of-care device for isolation of clinical grade SVF cells from lipoaspirate. Such a device would significantly facilitate the use of SVF in cosmetic and reconstructive procedures, and make it affordable for patients and healthcare providers.

Stempeutron™ is a medical device being developed jointly by Stempeutics R & D and Vignani technologies, a Bangalore based engineering solutions company. Stempeutron™ is a stand-alone, fully automated, point of care system/device to isolate SVF cells from adipose tissue. For automation in Stempeutron™, we have developed a proprietary process and technology (Ref. 7) which would allow gentle processing and aseptic isolation of clinical grade cells (Fig. 1). This will be enabled in the device through a uniquely designed, mechanically controlled, closed and aseptic, single-use flow path. Stempeutron™ will be the first indigenously developed device for stem cell isolation and is poised to place Stempeutics as the market leader in applying fat-derived cell therapy in India and abroad.

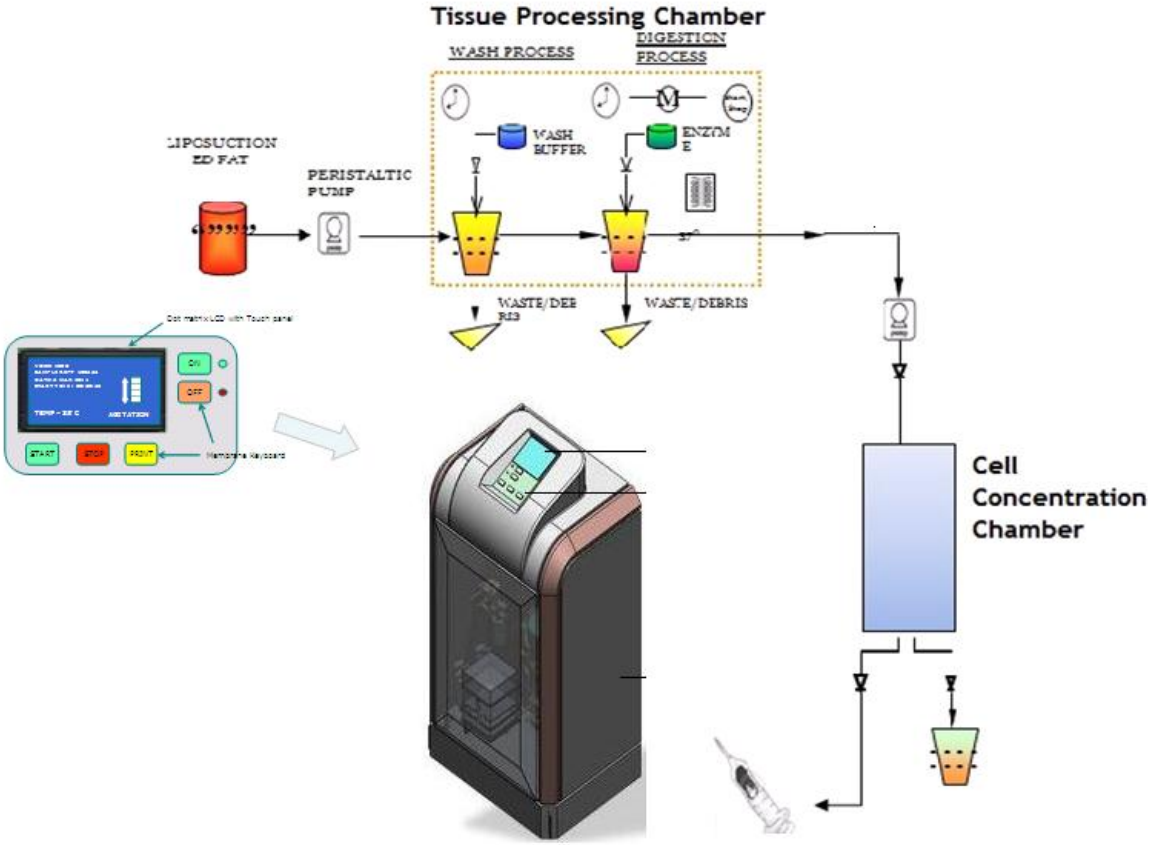

Figure 1: The figure illustrates the process and device for isolation of SVF from adipose tissue lipoaspirate. The device is fully automated, with a user friendly programmed interface to carry out the entire process from tissue loading to SVF collection in an aseptic environment.

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Stempeucare™:
Stempeucare™ is in the pipeline as an over-the-counter product for cosmetic applications. We have recently identified a set of key bioactive factors derived from adult stem cells and are investigating the potential of such factors for cosmetic applications such as skin rejuvenation and hair growth. One of the key research findings using *in vitro* cell culture based models is that these factors posses' anti-wrinkling and anti-ageing properties. Current studies are focused on developing and testing suitable formulations in appropriate preclinical models. The objective here is to exploit natural bioactive agents secreted by the stem cells to develop products that promote or accelerate rejuvenation of the skin.

Stempeucel® - Next generation:
While the BM MSC product stempeucel® is undergoing phase II clinical trials (see below), the Stempeutics R & D team is focusing on developing umbilical cord Wharton's jelly-derived MSC (WJ MSC) as a next-generation product to augment our new product pipeline (Ref. 8-10). The umbilical cord can provide an inexhaustible source of stem cells for therapy and does not pose any ethical concerns. The cord matrix, also known as Wharton's jelly (WJ), contains cells which display properties similar, but not identical, to bone marrow or other tissue derived MSC. Current research focus (Ref. 11) is aimed at performing comparative studies between MSC obtained from WJ and other tissues in terms of their biological activity and therapeutic potential. A thorough understanding of MSC isolates from various tissues with respect to their disease curing potential would facilitate the development of highly efficacious disease specific products in the future. The WJ MSC product is being developed as an allogeneic, off-the-shelf, xeno and serum-free cell therapy product.

Stempeucel®: Technology and Product development

Manufacturing process:
A bone marrow donor program has been implemented at Manipal with approval from Manipal University. First, the informed consent of bone marrow donor is recorded on the Informed Consent Form (ICF) that has been approved by the Institutional Ethics Committee of Manipal University. Healthy volunteer donors are screened for eligibility for bone marrow aspiration. Selection of eligible donors involves screening for several parameters including physical fitness, infectious diseases, hereditary disorders, prescription medication intake etc. The bone marrow aspiration is done aseptically from the iliac crest of selected donors by a trained surgeon. The aspirate is then transported to a GMP manufacturing facility and processing begins immediately. Prior to initiation of the production process, the quality control department (QCD) tests all production related raw materials required for the various stages of manufacturing. All processing steps are carried out in a class A area with class B background. The bone marrow mononuclear cells (BM MNC) are isolated by ficoll density gradient centrifugation method from the buffy coat. The BM MNC are washed and seeded in tissue culture flasks containing complete growth medium and transferred into a 5% CO_2 incubator maintained at 37°C. Frequent medium change ensures that only the MSC are attached to the plastic surface because of their plastic adherence property. The MSC are characterized for master cell bank (MCB) production, and the MCB is cryopreserved at the vapor phase of liquid nitrogen (LN_2). Revived cells from the MCB are further passaged to produce working cell banks (WCB) and cryopreserved. For the large

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scale expansion, cells from the WCB are cultured in batches using Cell STACKs to produce the investigational medicinal product (IMP) or stempeucel®. The culture conditions, seeding densities of cells, screening parameters, harvesting and passaging procedures are perfected to obtain cells of the highest quality in terms of viability, phenotype, differentiation ability and other physiological criteria. The final product is cryopreserved in a xeno-free freezing mixture and stored in vapor phase of LN_2. The IMP is released for clinical trials after qualifying a battery of stringent QC criteria.

Description of facilities in India and Malaysia:

All the regulatory approvals for IMP manufacturing and clinical trials have been approved by the regulatory bodies in India and in Malaysia. In India, all approvals are controlled and approved by the office of the drug controller general of India (DCGI), central drugs standard control organization (CDSCO), under the cellular biology based therapeutics drug evaluation committee (CBBTDEC) for proposed commercial cell therapy products. In Malaysia, the national pharmaceutical control bureau (NPCB) regulates both manufacturing and clinical trial approvals for cell therapy products.

The recently opened facility in Bangalore (Fig. 2; Video) is located in Whitefield, has 8177 sq. ft. area and houses most of the basic R & D, product development and QC activities. The facility fulfills the requirements to meet GTP and GMP standards. The Bangalore facility has a dedicated R & D lab for stem cell culture, testing, assay development and a wet lab to conduct various cellular and molecular studies. It also has a cryopreservation room, a walk-in cold room, deep freezers and a clean room with grade B classification for performing product development related work.

Figure 2: Stempeutics facility in Bangalore

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The stempeucel® manufacturing facility in India is located at Manipal with a total area of 6400 sq. ft. and state-of-the-art design. The facility has received approval from the DCGI for clinical trial manufacturing. We are the first company in India to receive such an approval for manufacturing a stem cell based product for conducting clinical trials all across India. The production area has two manufacturing suites, sterile corridors, a cryopreservation room, change rooms and packaging and dispatch areas (Fig. 3). All cell culture and material processing are performed in Grade A with background of Grade B in the clean room. Throughout the production process of the IMP, complete aseptic procedures are followed as per international standards.

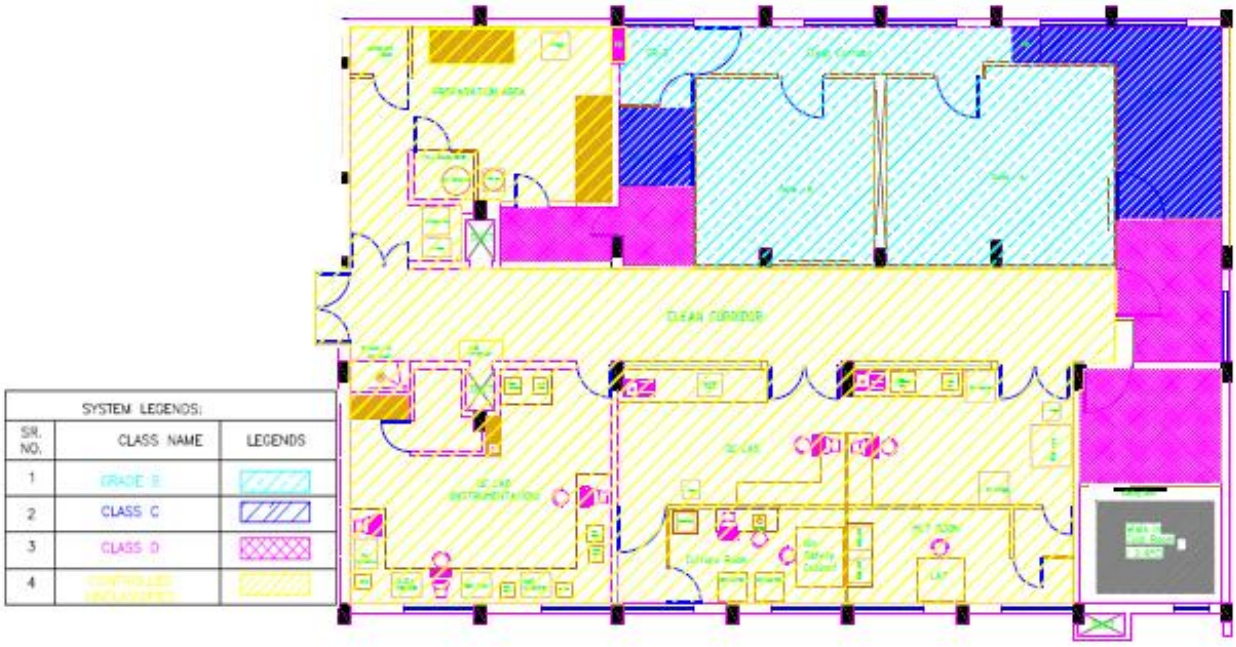

Figure 3: Floor plan of the GMP manufacturing facility at Manipal

In Malaysia, Stempeutics has received the Bionexus status and is the first company to obtain regulatory approvals for conducting clinical trials using allogeneic MSC. The manufacturing facility in Kuala Lumpur has received conformance from the NPCB for GMP compliance as per PIC/s standard. The total area of the Malaysia manufacturing facility is 4200 sq. ft. and has a production area, QC labs, a cryopreservation room, change rooms and R & D labs. (Fig. 4)

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Figure 4: The manufacturing facility at Kuala Lumpur, Malaysia

QA/QC and the regulatory process:

Stempeutics has established its own unique quality system encompassing the entire process from bone marrow aspiration to IMP production, for delivering consistently safe and efficacious products. The characterization of the MCB and WCB covers multiple parameters to establish the purity and identity of the BM MSC using a select group of positive and negative phenotypic markers, cell proliferation tests and assays to test potency, genetic stability, endotoxin and sterility. Infectious disease testing of the MCB, WCB and IMP is unique for stempeucel® and is performed to show that the cells are free from pathogens even after several passages. The process monitoring is performed with cells at various passages for identity, viability, phenotypic marker expression, and microbial contamination to prove the quality at every stage of processing. Based on the above criteria, a detailed set of specifications has been set for the IMP in order to qualify for clinical trial application. Every batch is subjected to the testing parameters, which has thus shown batch to batch consistency for the rigorous specification set by Stempeutics.

Preclinical studies on stempeucel® :

Stempeutics undertook a series of preclinical studies in rodent and non-rodent animals to establish the safety and toxicity profile of stempeucel® with both governmental institutions and with contract research organizations (CRO) in India. stempeucel® administration through various routes was shown to be safe. Administration of stempeucel® at doses equal to or higher than the intended therapeutic dose showed:

i. No acute or subchronic toxicity in rodents and non-rodents.
ii. No developmental disorder in new born animals.
iii. No genotoxicity in animals.

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iv. No tumor formation in immunocompromized mice.

We are excited by the successful completion of the preclinical studies demonstrating the safety of stempeucel®, which in turn has paved the way for regulatory filing to conduct phase I/II safety studies in human patients. In parallel, we are engaged in preclinical studies in animal models that mimic relevant human diseases to establish the efficacy of stempeucel®.

Clinical trials at Stempeutics:

Stempeutics received its first approval from the DCGI for two IND applications to conduct Phase I/II clinical trials using stempeucel® for acute myocardial infarction (AMI; NCT00883727) and critical limb ischemia (CLI; NCT00883870). These two trials were specifically designed to assess the safety of stempeucel® administration. Both trials were double blinded, randomized, placebo controlled studies of 20 patients each (10 patients randomized for the cell arm and 10 patients for placebo arm in each trial). The cells were injected intramuscularly in CLI patients and intravenously in AMI patients. The dose used in both trials was 2 million allogeneic bone marrow derived MSC per kg body weight. Stempeucel® was well tolerated by the patients enrolled in both trials as evidenced by physical examination, monitoring of vital signs and laboratory evaluations including renal and liver function tests. The immunological parameters were also found to be within normal limits and comparable to the values obtained in patients enrolled in the placebo group. The clinical trial data was evaluated by an independent data safety monitoring board (DSMB). The DSMB members unanimously concluded that stempeucel® is safe for human use.

Phase II Clinical trials:

Stempeutics is the first Indian company to have received approval for phase II clinical trials for multiple diseases in India and in Malaysia, from the respective regulatory authorities. The indications include osteoarthritis (OA) (Ref 12), Buerger's disease (a sub-group of CLI), liver cirrhosis (LC), diabetes mellitus (DM) type 2, cerebral stroke and chronic obstructive pulmonary disease (COPD). Currently, three phase II trials are in progress and patients are being enrolled for OA, Buerger's disease and LC conditions. The OA trial is simultaneously being conducted in Malaysia (NCT01448434) and in India (NCT01453738) with various doses of stempeucel® while the CLI (NCT01484574) and LC (NCT01591200) trials are being carried out in India. The objectives of all the phase II clinical trials include determining the safety and efficacy of stempeucel® administration via different routes with different doses. For example, stempeucel® is being administered via intra-articular injection in OA patients, intramuscularly in patients with Buerger's disease and in LC patients, the drug is being administered via the hepatic artery. All patients enrolled in these studies will be followed up for a period of two years. We at Stempeutics are confident that stempeucel® would be efficacious in these degenerative disorders and would help alleviate the sufferings of the patients. Clearly, the next logical step is to file for phase III clinical trials for diseases where stempeucel® is found to be most efficacious and safe, in order to take the drug for market approval.

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Commercialization Strategy

Since its inception in 2006, Stempeutics has concentrated on basic stem cell R & D to develop a diverse product portfolio to address some of the most important unmet medical needs of our time. The major focus of the company has been to take its allogeneic MSC product stempeucel® to the market for therapy of degenerative diseases that affect millions in India and the rest of the world. Stempeutics aims to introduce its first stempeucel® product into the Indian and Malaysian markets in 2015. In the autologous cell therapy arena, Stempeutics is developing Stempeutron™, for isolating adipose tissue derived SVF cells for soft tissue reconstruction. Stempeutics plans to launch Stempeutron™ in 2014 for the Asian market. In addition, Stempeutics is committed to develop its Stempeucare™ range of products for cosmetic applications such as skin rejuvenation and anti-ageing treatments. Thus, Stempeutics has positioned itself in a unique manner to collaborate or establish business partnerships with pharmaceutical, device and cosmetics manufacturers to bring these products to the global market in the near future.

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