

# **JFF and Wake Forest University: Recap Last 10 Years at the Wake Forest Institute for Regenerative Medicine (Director: Anthony Atala)**

Over the past 10 years the team at the Wake Forest Institute for Regenerative Medicine (Director: Anthony Atala) has focused on developing skeletal muscle cell therapy applications using tissue engineering and regenerative medicine approaches for clinical translation. The team of exceptionally dedicated experts from multiple disciplines, including cell biology, medicine, materials sciences, physiology, pharmacology, molecular genetics and engineering, have worked together to bring new therapies to patients suffering from muscle disorders. Toward this defined goal, the research team has taken four systematic and effective strategic approaches: 1) Develop methods of cell-based therapies, 2) harness microenvironment in vivo for the survival and maintenance of implanted muscle cells and tissue, 3) develop systems that accelerate muscle tissue maturation and function, and 4) develop a reliable and powerful stem cell system for regenerating normal muscle tissue for clinical use.

The initial studies focused on establishing methods for culture and expansion of the skeletal muscle progenitor cells (cells that are committed to become mature muscle cells) using mammalian species including the human. The team has successfully established muscle cell expansion systems which allowed for the creation of functional muscle tissues in vivo using several model systems.

To test the effectiveness of muscle tissue replacement therapy, it was necessary to create muscle defect models. Successful working models were created in several species, followed by treating tissue defects with new muscle in the form of injection and surgical implant. The team has demonstrated functional recovery of the tissue defects, which indicates the clinical feasibility of this approach.

Ongoing development efforts are focused toward translating this technology to patients. These include refining cell expansion systems that are compliant with regulatory agencies (i.e., FDA), generating standard operating procedures (SOP) that can be used widely and developing cell-based systems that can be applied to all age groups of patients with muscular disorders. The team is currently working actively with an FDA consultant to obtain approval for a clinical trial. In addition, the cell and tissue processing facility for clinical trial has been

designed and planned for completion in 2008.

One of the continued challenges in transplantation is the inadequate blood supply to implanted tissues. The team has recognized the need to control the microenvironment where new tissue could adapt and receive sufficient amounts of blood for muscle survival. To overcome this limitation, the team has sought methods to enhance blood supply to muscle tissue through stimulating the tissue environment with biologic factors (VEGF, vascular endothelial growth factor) that promote new vessel formation. Several growth factor delivery methods (protein and gene delivery) were developed and confirmed of the effectiveness in the body. Ongoing research focus is directed toward developing an implant system that provides sufficient amount of nutrients and oxygen to cells for tissue survival and maturation in the body.

Another arm of the team's research efforts has focused on developing a system that would result in rapid functional tissue restoration *in vivo*. The research team has successfully developed a muscle bioreactor system that preconditions muscle and accelerates tissue maturation and function *in vitro*. The computerized bioreactor system is designed to exercise muscle for functional enhancement. The levels of muscle tissue maturation and contractile function were distinctively enhanced when the bioreactor system was applied. Further investigation is currently being performed to refine the system for application *in vivo*.

The existing defective muscle cells are destined to become dysfunctional with time. The research team has recognized the need to overcome this challenge for successful clinical translation. The goal was to develop a reliable and potent stem cell system for regenerating normal muscle tissue for clinical use. Amniotic fluid and placenta were identified as reliable sources of stem cells that can be used for muscle tissue regeneration.

Stem cells, isolated from amniotic fluid and placenta, behave similarly to embryonic stem cells, and these cells are able to become multiple cell types, including muscle, when they are guided appropriately. The stem cells can be easily obtained through a routine amniocentesis procedure or from the placenta after the baby is born. The team continues to investigate a means to utilize these stem cells for muscle tissue regeneration applications.

During the past decade, the team has made an enormous leap toward the development of skeletal muscle cell therapies for clinical

applications. The comprehensive and systematic approaches employed in this program are designed to converge into the ultimate goal of delivering new therapies to patients with muscular disorders.

The technological progress made in each of the four tracks could be used as a stand-alone or as an integrated system for specific utility. A decade of continued technological developments would not have been possible without the generous and consistent support of the Joshua Frase Foundation. The Wake Forest Institute for Regenerative Medicine is fortunate to have the Joshua Frase Foundation as its partner in a mission to treat patients with muscular disorders and eventually improve the quality of their lives.