Skeletal muscle makes up a major portion of the human body and is essential for life. Loss of skeletal muscle is a chronic problem in aging and an acute problem in muscular dystrophy and other diseases such as cancer. Muscle diseases occur not only in humans but also in other species such as dogs, cats, and mice. There has been tremendous progress in the diagnosis of muscular dystrophy. Although currently there are few available effective treatments for muscle loss in muscular dystrophy and aging, multiple approaches to reduce muscle degeneration and to promote muscle regeneration are being tested experimentally. Dr. Engvall’s laboratory is exploring the use of differentiation factors for muscle regeneration and the use of myogenic cells from non-muscle tissues for muscle cell replacement.

Stem cells and regeneration

Long life span requires continuous or intermittent regeneration of several tissues. The hematopoietic system and many epithelia regenerate continuously from stem cells/progenitor cells within the tissue, while other tissues, such as skeletal muscle or the central nervous system, regenerate intermittently or not at all. Our current focus is on regeneration of skeletal muscle and peripheral nerve.

Defective regeneration in muscular dystrophy and aging

Muscular dystrophy is a group of rare genetic diseases characterized by degeneration and ultimately loss of function of skeletal muscle. In these diseases, as
well as in normal aging, regeneration is not sufficient to compensate efficiently for
degeneration. The lack of regeneration may be lack of stem cells and/or lack of an
appropriate environment or of differentiation factors. Our goal is to identify cells and
differentiation factors that can be used to promote regeneration of skeletal muscle. In
collaboration with Drs. Millan and Stallcup, we aim to identify and characterize
mesenchymal stem cells that can be recruited and used as alternative sources of cells
for muscle regeneration. We are also investigating several proteins that play important
roles during muscle regeneration such as laminins and ADAMs (A Disintegrin
And Metalloprotease).

**Animal models of muscular dystrophy - diagnosis and therapy**

We have established several mouse models of human muscular dystrophy and
have identified distinct forms of muscular dystrophy in companion animals. The animal
models are used to characterize the cell and molecular biology of muscular dystrophy
and to evaluate means to correct gene defects via transgenic gene expression.

**Factors that regulate regeneration of muscle**

Laminins are a family of large basement membrane glycoproteins that have
both structural and informational functions. Laminin-2 (alpha-2,beta-1,gamma-1)
and laminin-4 (alpha-2,beta-2,gamma-1) are the major laminins in normal muscle.
Laminin alpha-2 is defective in one of the most severe forms of congenital muscular
dystrophy, testifying to its importance in skeletal muscle. Not only is degeneration
accelerated in laminin alpha-2-deficiency, but regeneration is also negatively affected.
ADAMs are transmembrane proteins with the capacity to participate in numerous development and differentiation processes. Their metalloprotease domain is involved in activation of growth factors and shedding of receptors, the disintegrin domain binds to certain integrins, and the cysteine-rich domain interacts with the heparin and heparin sulfate proteoglycans. In addition, the cytoplasmic domains may be involved in signaling. Several ADAMs are expressed in skeletal muscle, where they regulate various stages of muscle development and regeneration.

**Publications**

