The goal of the Kadler laboratory is to understand how cells in tendons and ligaments build an extracellular matrix (ECM) comprising parallel arrays of collagen fibrils. Our research is directly relevant to statistics released by the NHS that 14,000 tendon and 85,000 ligament injuries are reported each year, with repetitive strain injury (RSI) alone costing UK industry up to £20 billion pounds per annum in lost working days. We are using high-resolution electron microscopy to determine the structure of the cell-ECM interface in tendons and ligament, the developmental biology of tendon and ligaments, and stem cell approaches to engineer these tissues in vitro and to devise novel therapies for tendon and ligament healing.

Using serial section reconstruction we have identified novel plasma membrane protrusions, called fibripositors, in embryonic cells in tendon, ligament and other tissues where parallel collagen fibrils occur (Canty et al., 2004). Fibripositors contain collagen fibrils that extend from transport carriers within the cell to collagen fibril bundles in the ECM. Removal of fibripositors by depolymerisation of the actin cytoskeleton results in loss of fibril parallelism, suggesting that actin-mediated micromechanics are involved in generating tendon architecture (Canty et al., 2006). Future work is aimed at deciphering the mechanism of protein trafficking through fibripositors. Interestingly, we have shown that fibripositor-containing cells transiently appear in post-wounded tendons.

We have shown that cadherin-11 is a key component of cell-cell junctions between embryonic tendon cells. Cadherin-11 knockdown using siRNA results in loss of cell condensation and misalignment of collagen fibrils (Richardson et al., submitted). Future work is aimed at promoting cadherin-11 junctions in healing tendons and ligaments.

In collaboration with bioengineers we have developed a three-dimensional tendon cell culture system in which parallel collagen fibrils, cadherin-11-mediated cell junctions and fibripositor-containing cells are observed. This culture system is currently being extended to use tendon progenitor cells that have been derived from mesenchymal stem cells. This 3D culture system will be used to study the biogenesis of cell-cell junctions, fibripositors, and actin-mediated force generation during tendon and ligament formation.

The research is funded by The Wellcome Trust and the BBSRC (UK).