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Blood vessels are conduits through which blood flows to carry oxygen and nutrients to all cells and tissues of the body. During embryonic development, blood vessels are formed in a highly regulated way in response to growth factors, extracellular matrix proteins, low oxygen, and through cell-cell contact. We are interested in the signaling pathways that regulate the response of endothelial cells, the cells that form capillaries and the lining of larger vessels, to these extracellular signals. One family of proteins called Sprouty (Spry) functions intra-cellularly to negatively regulate signals from receptor tyrosine kinases such as the fibroblast growth factor receptors. We are studying the Spry family of proteins to determine their role in normal and pathological blood vessel formation, and whether they are suitable targets for therapeutic intervention in tumor angiogenesis and other conditions of abnormal vascular function. Projects include analysis of the function of Spry proteins in vivo using conditional transgenic and gene targeted mice, and in vitro using human primary endothelial cells.

This laboratory also has a long standing interest in the regulation of skeletal development and repair by the fibroblast growth factor receptors. Genetic studies in mice and mutations in FGFRs in humans have revealed a very important role for these receptors in development of the skull and long bones. Mutations in human FGFR1 and FGFR2 result in craniofacial defects, whereas mutations in FGFR3 are manifest as short limbed dwarfism. We are now studying the role of Spry regulation of FGFR signaling in normal skeletal development, as well as a potential therapeutic target in skeletal repair. Because our current understanding of Spry function is as an inhibitor of downstream signaling of receptor tyrosine kinase pathways, and in particular the proto-oncogene Ras, loss of regulation of RTK pathways by Spry may be central to many pathological conditions including cancer. Transgenic and knock mouse models are used to determine the role of Spry in skeletal development and homeostasis.