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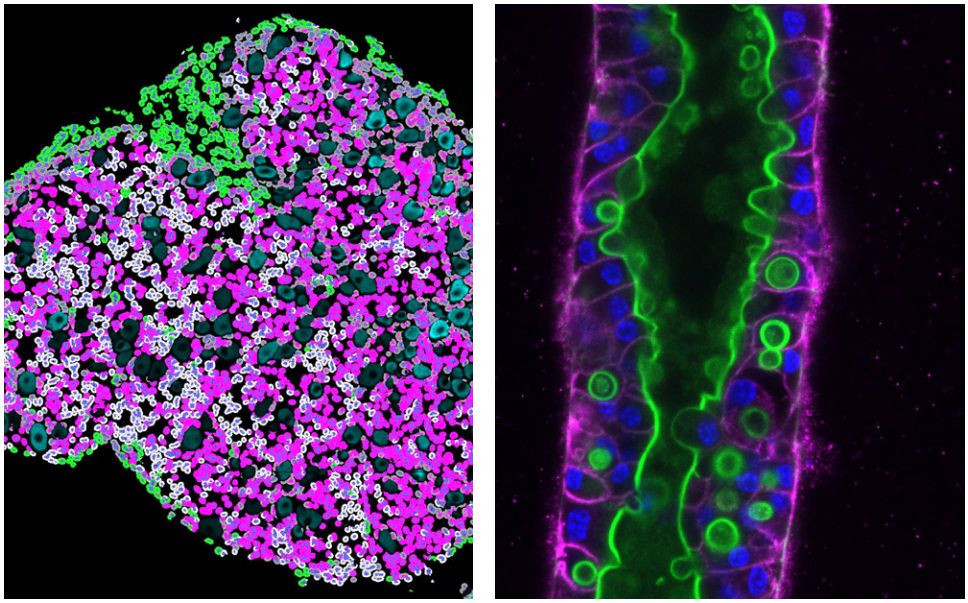
The McClatchey laboratory focuses on understanding how cells organize their outer surface – an important cellular compartment created by the interface between the cell membrane and underlying cortical cytoskeleton. This compartment governs the shape, identity and behavior of individual cells, as well as how they interact biochemically and mechanically with the extracellular environment. Normal cells modulate the features of the membrane:cytoskeleton interface to carry out key developmental processes and build functioning tissues. On the other hand, cancer cells exploit this compartment to interact inappropriately with other cells and with their environment during tumor initiation, invasion and metastasis. Our research stems from a longstanding quest to understand the molecular basis of a familial cancer syndrome caused by mutation of the *neurofibromatosis type 2 (NF2)* tumor suppressor gene. The *NF2*-encoded protein, Merlin, and closely related ERM proteins (Ezrin, Radixin and Moesin) are central architects of the cell cortex that have important roles in development and in many human cancers.

Understanding morphogenesis and tumorigenesis

The vast array of forms and functions exhibited by different cell types is enabled by the intrinsic organization of specialized domains within the cell cortex such as the leading edge of migratory cells, immunological synapse and microvillus-studded apical surfaces of epithelial cells. The spatial organization of individual cells, in turn, governs their organization into three dimensional structures that carry out organ-specific functions, such as the tubular networks of the lung, kidney, breast and liver and the heterotypic axoglial junction of peripheral nerves. The spatial organization of cortical domains in individual cells and tissues provides an essential layer of regulation to both biochemical and adhesive receptors on the cell surface. Alterations in cellular architecture are the earliest evidence of a developing tumor and signatures of tumor invasion and metastasis.

The assembly of cortical domains requires the coordination of processes occurring at the plasma membrane and underlying cytoskeleton. The overarching goal of my laboratory is to understand how the dynamic organization of this cellular compartment contributes to morphogenesis and tumorigenesis. We have focused particular attention on the neurofibromatosis type 2 (NF2) tumor suppressor, Merlin, and closely related ERM proteins (Ezrin, Radixin and Moesin) - membrane:cytoskeleton linking proteins that simultaneously influence membrane complexes and the cortical actomyosin cytoskeleton. The activities of Merlin/ERM proteins are critical for the morphogenesis of many tissues and have been implicated in many cancers.

Ongoing projects utilize mouse models, bioengineered 3D models and quantitative imaging to study the roles of Merlin/ERM proteins in the morphogenesis



Left: Digital image analysis highlights intra-tumoral heterogeneity of autocrine ligand production in a dorsal root ganglia from a six-month old Postn-Cre/Nf2flox/flox mouse. The Highplex FL algorithm in HALO imaging software was used to achieve single cell segmentation and detect neuregulin-1 positive (magenta), phospho-S6 positive (green), or neuregulin-1/phospho-S6 positive (gray) cells (in collaboration with the laboratory of Dr. Shannon Stott).

Image credit: Christine-Chiasson MacKenzie, PhD

Right: Confocal image of a three dimensional cell culture model of biliary tube formation labelled for E-cadherin (green) and actin (magenta). *Image credit: Evan O'Loughlin, PhD*

of intrahepatic bile ducts in the liver and Schwann cell:axon relationships in peripheral nerves, and in the development of biliary and schwann cell tumors. Our studies have uncovered novel design principles that govern tissue morphogenesis and are hijacked by tumor-causing alterations, identified mechanisms by which aberrant cortical organization can drive intrinsic tumor heterogeneity, and yielded unexpected therapeutic targets and avenues of translation for cancer therapy.

It is increasingly clear that cancer fundamentally reflects the aberrant re-enactment of developmental processes. We believe that the continued partnering of discovery-based science and translational studies will lead to novel therapeutic avenues while continuing to advance our understanding of the basic cellular activities that contribute to many human cancers.

Selected Publications:

Chiasson-MacKenzie C, Liu CH, Vitte J, Giovannini M and **McClatchey AI**. Cellular mechanisms of heterogeneity in NF2-mutant schwannoma. *bioRxiv* MS ID#: BIORXIV/2020/424999 [Preprint], 2020.

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Benhamouche-Trouillet S*, O'Loughlin E*, Liu CH, Polacheck W, Fitamant J, McKee M, El-Bardeesy N, Chen CS, **McClatchey AI**. Proliferation-independent role of NF2 (merlin) in limiting biliary morphogenesis. *Development* 145(9), 2018 April 30.

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Hebert AM, Duboff B, Casaletto JB, Gladden, AB, **McClatchey AI**. Merlin/ ERM proteins establish cortical asymmetry and centrosome position. *Genes Dev*. 26(24): 2709-23, 2012 Dec 15.

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