



Pluripotency and Directed Differentiation of Human Pluripotent Stem Cells

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Location: 1000 MNTL at Illinois (KL 361 at UC Merced)

Abstract:

Our long-term goal is to define new conditions and molecular programs that govern fate decisions of human pluripotent stem cells such as human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs). The knowledge is essential if we are ultimately to use these cells for therapy. To dissect the mechanism underlying hESC/hiPSC fate determination, we screened a collection of pharmacological inhibitors (~50) against kinases and other signaling molecules, enabling us to identify mTOR as a critical pluripotency-maintaining molecule in hESCs and uncover an mTOR-dependent signaling mechanism that suppresses mesoderm and endoderm differentiation. The screening efforts led us to also identify an E-cadherin-based highly integrated biochemical and mechanical signaling network essential for intercellular adhesion, stability of the transcriptional circuitry for pluripotency and long-term survival of hESCs/hiPSCs. In addition, we discovered compound C, a kinase inhibitor, as a potent regulator of hESC/hiPSC fate. Compound C suppresses mesoderm, endoderm and trophoectoderm differentiation and induces rapid and high-efficiency neural conversion in both hESCs and hiPSCs (up to 90%). Compound C targets at least seven TGF-beta superfamily receptors and thereby blocks both the Activin and BMP signaling pathways, which accounts for compound C's ability to induce high-efficiency neural conversion. This small-scale screening provided proof-of-concept for applying large-scale library screening to the study of hESCs/hiPSCs. Accordingly, we conducted large-scale screening of small molecules and shRNAs and identified a number of novel regulator components of hESC/hiPSC pluripotency and directed differentiation. In the next few years we will extend these findings to provide new mechanistic insights into pluripotency and early lineage specifications in hESCs/hiPSCs. The results of these studies will markedly improve our knowledge of the molecular mechanisms underlying fate determination and may contribute to effective strategies for tissue repair and regeneration.

Seminar Presented by:

 Center for Cellular Mechanics University of Illinois at Urbana-Champaign	 IGERT Integrative Graduate Education and Research Traineeship Cellular and Molecular Mechanics and BioNanotechnology	 
	 M-CNTC NCI Alliance for Nanotechnology in Cancer Midwest Cancer Nanotechnology Training Center	 