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Human Definitive Hematopoietic Specification from Pluripotent Stem Cells Is Regulated by Mesodermal Expression of CDX4

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All adult blood cells arise from hematopoietic stem cells (HSCs), which are multipotent stem cells found within the bone marrow. The generation of HSCs from human pluripotent stem cells (hPSCs) is a major goal for regenerative medicine, and can lead to transplantation of HSCs for the treatment of patients with immunodeficiency or cancers such as leukemia or lymphoma. Successful HSC transplantations would address issues with donors, and also allow for the correction of genetic illnesses that are untreatable with current stem cell technology. The Sturgeon lab aims to produce HSCs from hPSCs by replicating *in vitro* the signals that control embryonic HSC development.

Two programs have been identified as being involved in the development of blood cell progenitors: the primitive and the definitive program. The earlier primitive program does not yield HSCs, but transiently gives rise to a restricted subset of blood cell lineages. Shortly after, the definitive program produces bona fide HSCs, as well as all lineages found in the adult. Within our hPSC differentiation system, we have identified WNT signaling as a critical determinant of the definitive program, and have further found strong CDX gene expression within definitive hematopoietic mesoderm. Specifically, exogenous CDX4 expression resulted in repression of primitive hematopoietic potential, but increased definitive potential. Meanwhile, knockout CDX4 hPSCs had intact primitive potential but a significant decrease in multi-lineage definitive hematopoietic potential. Taken together, these findings indicate that CDX4 is a critical transcription factor in the regulation of human definitive hematopoietic specification, and provides a mechanistic basis for WNT-mediated definitive hematopoietic progenitor specification from hPSCs.