A thorough understanding of the mechanisms of human germ cell development is essential in the field of infertility, since this is a significant medical issue in developed countries. Currently, infertility affects approximately 8% of all married women. While the major etiologies of infertility are still unexplained, it is believed that defects in germ cell development, decrease in initial germ cell number endowment, or accelerated germ cell atresia is involved in the pathogenesis of the disease. Thus, understanding the mechanisms of human germ cell development will offer insights into the treatment of infertility.

Successful differentiation of functional gametes from embryonic stem cells (mESCs) has been reported in the mouse. The mechanisms of germ cell differentiation have been extensively investigated in the mouse in vivo using the readily available embryos at well timed gestational ages. In similar fashion, the mechanisms of germ cell differentiation derived from mESCs in vitro have been shown to be similar to those reported in vivo.

The information learned from the mouse system has been instrumental to the studies of germ cell development in human, given the lack of an in vivo model in humans. Using similar culture conditions, human germ cells have been successfully derived from human embryonic stem cells (hESCs). However, this process is still rather stochastic and poorly understood. Most studies have been descriptive without offering insights into the mechanisms of development. Thus, the precise mechanism of germ cell development in humans has not been well characterized.

The primary goals of our research are to investigate the cause of ovarian failure and the potential treatment using patient specific stem cells. The ultimate goal is to generate germ cells from patients’ own somatic cells by initially reprogramming these somatic cells into induced pluripotent stem cells (iPSCs). The results of the study will no doubt give insights into the biology and cause of ovarian failure. To answer our research question, we have successfully established a protocol in which we could consistently derive germ cells from established human ESC lines (H9, H1) and two iPS lines (BJ3, BJ4) that we generated. To this end, we have identified molecular pathways (Lin28-let-7-Blimp1) that control the development of germ cells. By manipulating these pathways, we demonstrated that we could enhance or suppress germ cell development. We have also developed novel ways of screening, over-expressing, and down regulating microRNAs (miRNAs) in hESCs to study the role of miRNAs in germ cell development. We have identified two families of miRNA that regulate germ cell development. Additionally, we have also identified pathways to drive germ cell development into either male or female germ cells, proving that achieving our goals is feasible in the near future with support. Currently, we are in the process of establishing iPSC lines from patients with ovarian failure. We routinely use BD antibodies and products to isolate germ cells for molecular
and microscopic analyses. Thus, the support from BD will be instrumental in our studies. I believe that my clinical and scientific experience is unique and it will allow me to integrate the information learned from both arenas into finding a cure for this debilitating disease.

The BD Biosciences Research Grant Program aims to reward and enable important research by providing vital funding for scientists pursuing innovative experiments to advance the scientific understanding of disease.

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