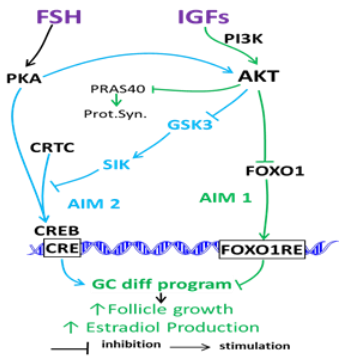
Research Projects In the Stocco Lab

Our current research focuses on the processes controlling ovarian function in mammals, mainly on hormone signaling and activation of genomic pathways regulating female fertility.

Groundbreaking observations from our laboratory demonstrated that insulin-like growth factor (IGF) 1 and its receptor (IGF1R) are essential for the stimulation of ovarian granulosa cells by follicle-stimulating hormone (FSH), a gonadotropin crucial for normal follicle development. At the molecular level, our *in vivo* and *in vitro* studies revealed that FSH and the IGF1R signaling pathway converge on the regulation of the serine/threonine kinase AKT and salt-inducible kinases. These novel findings show that IGFs signaling is obligatory for FSH stimulation of granulosa cell differentiation and represent a paradigm shift that significantly advances our understanding of the mechanisms by which FSH regulates ovarian function.

Recently we show that inhibition of salt inducible kinase (SIK) activity potentiated the stimulatory effect of FSH on markers of GC differentiation in mouse, rat, and human GCs and estradiol production in rat GCs. In humans, SIK inhibition strongly enhanced FSH actions in GCs of patients with normal or abnormal ovarian function. The knockdown of SIK2, but not SIK1 or SIK3, synergized with FSH on the induction of markers of GC differentiation. SIK inhibition boosted gonadotropin-induced GC differentiation *in vivo*, while the genomic knockout of SIK2 led to a significant increase in the number of ovulated oocytes. Conversely, SIK3 knockout females were infertile, FSH insensitive, and had abnormal folliculogenesis. These findings reveal novel roles for SIKs in the regulation of GC differentiation, female fertility and contribute to our understanding of the mechanisms regulated by FSH. Furthermore, these data suggest that specific pharmacological modulation of SIK2 activity could be of benefit to treat ovulatory defects in humans and to increase the propagation of endangered species and farm mammals.



Current NIH grant support is aimed to identify the molecular interactions between the signaling pathways activated by FSH and IGFs in the regulation of SIK activity. *The central hypothesis is that the coordinated activation of CREB and cofactors downstream of AKT and SIK are necessary to induce granulosa cell differentiation and female fertility (see scheme).*

My laboratory is also interested in understanding the regulation of granulosa cell function by oocyte-secreted factors in humans. The oocyte secretes growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP15), which act on the surrounding granulosa cells. However, the precise role of GDF9 and BMP15 in humans remains to be determined. The central *hypothesis is that cumulus cells integrate GDF9, BMP15, and FSH signals to coordinate oocyte maturation, primordial follicle recruitment, and gonadotropin-dependent growth of antral follicle (see scheme).*