anterior infundibulum. In addition to sculpting the dorso-anterior infundibulum, the FGF3+/Sox3+ cells give rise to TUJ1+ neurons which migrate into the hypothalamus. My studies show that the Sox3+/Fgf3+ cells are themselves dependent upon FGF signalling. Finally, ex-vivo neurosphere assays indicate that the Fgf3/SOX3+ cells have stem cell-like character; they can self renew and differentiate into multiple lineages. In summary, my studies show that infundibular cells form from two distinct embryonic territories. Further, they reveal that a regionally restricted population of proliferating progenitors undergoes polarised differentiation to fashion the adult-like hypothalamus, and may be retained as a hypothalamic stem-like cell.

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Program/Abstract # 278
Roles of c-Myc and n-Myc in regulating proliferation in the *Xenopus* retina
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Program/Abstract # 279
Foxd3 is required to maintain glucose tolerance during pregnancy
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Diabetes mellitus affects an estimated 150 million people worldwide. This disease is characterized by hyperglycemia resulting from the inability of pancreatic beta cells to function normally. Treatments for diabetic patients are inadequate because they do not prevent complications associated with the disease; therefore, considerable efforts are focused on the derivation of beta cells from embryonic stem cells or understanding the molecular control of beta cell expansion *in vivo*. Mouse models are commonly used to study beta cell expansion, but beta cell proliferation in healthy adult mice is rare except when mice are metabolically challenged, such as during pregnancy. Changes in pregnant mutant and control mice can be studied to analyze mechanisms of beta cell expansion *in vivo*, providing information that will facilitate the manipulation of beta cell progenitors for cell therapies. The transcription factor Foxd3 is expressed in the pancreatic primordium beginning at 10.5 dpc and is localized predominantly to beta cells after birth. Mice carrying a deletion of *Foxd3* from the pancreatic epithelium appear normal during development and adult life, but mutants have impaired glucose tolerance during pregnancy. Preliminary data show that these mice have defects in beta cell proliferation. Because Foxd3 is required for survival, self-renewal and multipotent nature of multiple progenitor cell lineages, it may be a critical gene for molecular control of *in vivo* beta cell expansion. Understanding the molecular mechanisms of beta cell mass expansion *in vivo* may provide insight to developing treatments for diabetes.

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Program/Abstract # 280
Aph-1 is required to regulate Psn-mediated γ-secretase activity and cell survival in *Drosophila* wing development
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Aph-1 is a multi-pass transmembrane protein and an essential component of the Presenilin (Psn)-mediated γ-secretase complex. During protease assembly, Aph-1 stabilizes the newly synthesized Psn holoprotein to facilitate generation of the active form of Psn, which is a Psn-NTF/Psn-CTF heterodimer produced through a Presenilinase-initiated endoproteolytic cleavage of the Psn holoprotein. Although it is clear that loss of Aph-1 activity leads to failure of Psn heterodimer formation, little is understood about whether Aph-1 plays a role in regulating γ-secretase activity in addition to assisting Psn maturation. Using various modified Psn forms that do not require endoproteolysis or have a large deletion of the cytosolic loop, we show that in *Drosophila* Aph-1 is still required for γ-secretase activity independent of its role in promoting Psn endoproteolysis. In addition, our results indicate that Aph-1 is required to promote cell survival in the wing imaginal disc; aph-1 mutant cells are lost either through cell death or because of a defect in cell proliferation. This function of aph-1 is independent of its role in regulating γ-secretase activity but possibly involves down regulating the activity of uncleaved Psn holoprotein.

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Program/Abstract # 281
Alternative splicing and cell cycle regulation in vertebrate pigment cells
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Mitf is a gene encoding a transcription factor that is critical for the development of vertebrate melanocytes and that uses alternative splicing of two distinct subexons to generate proteins with different sequences. Among them is subexon 2B which contains a phosphorylatable serine that, based on in vitro results, regulates MITF protein activity and stability. Using a knock-in mouse in which the corresponding serine codon was changed to alanine, we noticed that exon 2B is excluded in over 90% of the MITF mRNA while normally it is excluded in only 10–15% of such mRNA. Hence, we are faced with two questions: how does the codon mutation lead to increased exon 2B exclusion, and what are the functional consequences in vivo? Addressing the first question, we tested a series of serine/arginine-rich (SR-) proteins, which are known to regulate splicing, for their effect on exon 2B splicing. We find that some of them promote inclusion of exon 2B while at least one promotes its exclusion. Filter-binding and RNA affinity chromatography show that the codon mutation influences RNA/SR protein interactions in a way consistent with the differential effect on splicing. Addressing the second question, we find that the splice alteration affects melanocyte proliferation through a shortening of S-phase that is due to a differential regulation of cell cycle regulators. We conclude that exon 2B splicing is an important parameter of melanocyte proliferation and are currently investigating whether exon 2B splicing is regulated spatio-temporally during development, and/or in a cell cycle phase-specific manner.

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