Role of integrin cell-surface receptors in neurulation and neural tube defects

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Neural tube defects (NTDs; e.g. spina bifida) are severe birth defects resulting from failure of embryonic neural tube closure. Folic acid (FA) can prevent a proportion of NTDs but its mechanism of action is unknown. Improved understanding of how NTDs arise, and how FA functions, could lead to improved prevention of these disabling conditions in humans. The PhD project will use a new mouse model of spina bifida recently developed in our lab in which integrin-b1 (Itgb1), a cell surface receptor for the extracellular matrix (Figure 1), is conditionally deleted during neural tube closure. Spina bifida develops in ~ 80% of mutant fetuses (Figure 2), and the *Itgb1* mutant mice will be used to study the embryonic mechanisms leading to spina bifida, and to determine the response to FA. This will involve investigating cell cycle control, apoptosis and the actin cytoskeleton (all known to be regulated by Itgb1) in mutant tissues, developing new assays for biomechanical disturbance of embryonic morphogenesis which may underlie the NTDs, and testing whether maternal folate deficiency or FA supplementation alters the frequency of NTDs in the mutant mice. The student will receive training in several techniques of developmental biology, including whole embryo culture, with a special focus on neurulation.

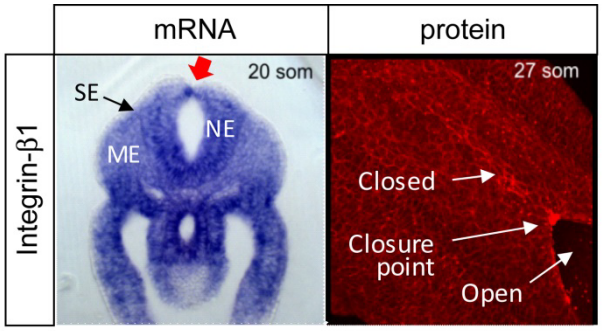

Figure 1. Integrin-β1 expression shown by in situ hybridisation on cryosection (left) and whole mount immunohistochemistry: top view of the closing spinal region (right). ME, mesoderm; NE, neural plate; SE, surface ectoderm. Integrin-β1 is expressed in all tissues, and strongly at the closure point (red arrow). Embryos: 20 & 27 somite stages

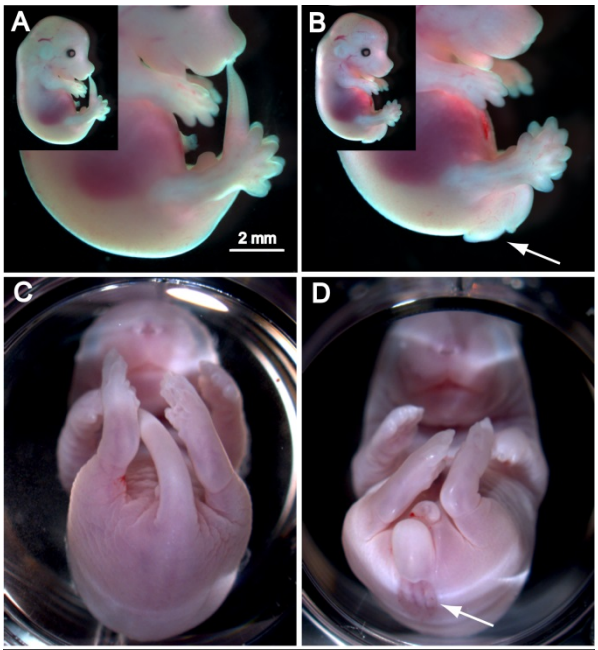

Figure 2. Fetuses at E14.5 (A,B) and E18.5 (C,D) of wild-type (non-Cre; Itgb1-fl/+)(A,C) and mutant (Cre; Itgb1-fl/fl)(B,D) genotype. Note: spina bifida & tail defects in mutant fetuses (arrows).