Cell proliferation, planar cell polarity and cell determination are fundamental processes for a proper development and morphogenesis of multi-cellular organisms. A well-known example of this coordination is asymmetric divisions, which ensure differential segregation of polarized cellular determinants during the mitosis of precursor cells. Deregulation of these mechanisms is associated with various developmental syndromes as well as pathologies including cancer. Although molecular mechanisms and regulatory gene networks underlying each process are well known, those that coordinate these processes remain largely unknown. This research project proposes to analyze this coordination in the Drosophila bristle cell lineage, which generates the peripheral nervous system organs. These organs are composed of four cells with distinct morphology and functions. All of these cells come from asymmetric divisions of a single precursor cell. As such, this first division generates two sub-lineages, one giving rise to the internal cells and the other one forming the external structures. Based on original observations, and using in vivo imaging, genetics, molecular and cell biology approaches, two axes of research will be developed based on two main questions:

1- How could cell cycle factors influence cell polarity and cell determination?
2- How could cell identity influence the activity of complexes that drive mitotic entry?

In the first axe, two essential factors, controlling cell proliferation, will be analyze: Cyclin A (CycA), a cyclin essential for the entry into mitosis, and Fizzy related (Fzr) an activator of the ubiquitin ligase complex; APC/C (APC/C). In the bristle cell lineage, we have observed that a pool of CycA is asymmetrically localized at the posterior pole of the precursor cells, and that cycA genetically interacts with frizzled, a gene involved in planar cell polarity. We hypothesize that CycA acts as a bridge linking cell proliferation with cell polarity. To study this possibility, we will investigate the physiological relevance of the CycA asymmetric cortical localization and their interaction with frizzled. We will also analyze the molecular mechanism leading to CycA localization, investigating whether a discrete domain of the CycA allows its location to the cortex and if this localization is dependent on Cdk1 activity. Concerning Fzr, we have observed, that its gain of function induces loss of sensory organs. One hypothesis is that a cell fate transformation changes external cells into internal cells.
Thus, we will analyze precisely this phenotype at cellular level and how Fzr could controlled cell identity.

The second axe is based on preliminary observations showing that the delay to entry into mitosis induced by cycA loss of function depends on cell identity. We propose to analyze whether Cdk1 activity is dependent on the cell identity and if so we will study the intriguing possibility that Cdk1 interacts with different cyclins depending to cell identity.

As such, our project will certainly clarify the mechanism underlying interaction between cell proliferation and cell determination, a relation that is often deregulated and at the origin of several human pathologies.