Fetal alcohol spectrum disorders (FASD) are conditions that can occur in a person whose mother drank alcohol during pregnancy. It is known as a “hidden disability”, which often goes undiagnosed until school age. Affected children are usually identified when they are referred for a learning disability or an attention deficit disorder. As individuals with FASD enter adulthood, they show increased vulnerability to secondary neuropsychiatric disorders. If clinicians can identify FASD earlier, intervention approaches can be taken to minimize adverse neurobehavioral outcomes and prevent complications later in life. The goal of this project is to identify structural and molecular signatures of alcohol-induced defects on the fetal brain that will assist prenatal recognition and detection of FASD. It is centered on the hypothesis that aberrant development of axonal connectivity may be part of the neural underpinning of the deficits associated to FASD.

While it is recognized that prenatal exposure to alcohol can affect many steps in neural development (ie. proliferation, migration and survival), it is unknown if and how alcohol affects the assembly of the brain circuits that shape our behaviors. The development of advance neuroimaging techniques has started to reveal structural brain abnormalities and white matter defects, mainly affecting the Corpus Callosum (CC) commissural tract, in FASD children and adults. However, to date it is not known whether pathological structural features and connectivity defects can be detected in the brain of fetuses exposed to alcohol. In addition, the mechanisms by which alcohol may affect prenatal wiring of neuronal circuits remain unknown. Interestingly, alcohol interferes with several epigenetic mechanisms, including microRNAs, which recently emerged as key regulators of axonal development. About half of the known FASD-deregulated miRNAs are expressed in the axonal compartment of neurons and therefore represent potential candidates to mediate connectivity defects in this condition.

The proposed work program will combine clinical imaging research and experimental approaches on animal models to investigate the effects and mechanisms of action of prenatal exposure to alcohol on the development of brain connectivity. The translation of preclinical observations to early human development requires the deployment of specific quantitative fetal in vivo and in utero neuroimaging techniques in order to detect subtle changes in structure and function of the developing human brain. The group of Gregor Kasprian (Medical University of Vienna, Austria) uses various advanced MR imaging approaches to study fetal brain development. They have pioneered the field of diffusion tensor imaging (DTI) and tractography and clinically implemented this technique to visualize the developing white matter macroanatomy of the human fetal brain in vivo and in utero. This imaging technique is currently the most promising approach to detect and characterize early brain alterations associated with FASD. The group of Fanny Mann (Developmental Biology Institute of Marseille, France) studies the fundamental mechanisms and molecules directing axonal growth and guidance in the mouse. They develop models of alcohol exposure at stages of wiring of young neurons, which will be instrumental to evaluate the effect of alcohol on axon navigation and targeting at cellular resolution, complementing the human data, and to study the biological function of FASD-deregulated miRNAs in these processes.

The results of this program will increase our understanding of the fetal brain abnormalities induced by maternal alcohol consumption and their underlying molecular mechanisms. They will contribute to the establishment of early imaging based markers for prenatal detection and diagnosis of FASD. This is expected to contribute to reduce disease burden and its significant socioeconomic costs for families and society.