Description for the general public

Human heart is one of the most specialized organs in our body. It needs to work through all our lifetime without any mistake. If damaged, there is almost no possibility to fix it (until now). Cardiomyocytes are the contracting muscle cells in the heart and they are focalizing all the therapeutic and scientific attention. They cannot divide and grow, so if dead, the muscle is losing its function, which finally might lead to death. However, although at the backstage, the cardiac fibroblasts are the most common cell population in the heart (over 60% of total cell number). They are not specialized so much and they cannot contract. Why are they so common, then? It appears that these fibroblasts release many factors, including those, which bound all cells together to form a heart tissue (we call these proteins collagens). Moreover, many other functions of fibroblasts are being investigated recently. As heart possesses 2 major parts: ventricles and atria that differ in function and characteristics, there are 2 different populations of fibroblasts (and cardiomyocytes) existing as well.

We are convinced that the fibroblasts are so influential that they can force cardiomyocytes to change their fate (from one cardiomyocyte type to the other). This is what we want to prove in this Project. If so, this would mean that not cardiomyocytes, but fibroblasts instead, are the most important factor that organize the structure and function of the heart cells. This would have a tremendous implications. For now, after heart injury (infarct etc.) we are focused on cardiomyocytes and try to force them to proliferate, however they are not responding to our effort so much (that is why cardiovascular diseases are the major cause of death worldwide). If this Project will prove our hypothesis correct, it will mean that we should target and stimulate fibroblasts instead, which can then organize the tissue and drive it back to the initial state. This would be a really major breakthrough for existing therapies.

To prove our hypothesis, we will create human heart tissue *in vitro*. It is a piece of muscle of noticeable size (around 1cm long) that consists of all major factors of the heart tissue. It has remarkable features that are mimicking advanced functions of the human heart including: stimulation to pharmacological factors, tissue elasticity and physiological relations (i.e. increase in beating force when the muscle is stretched – Frank-Starling mechanism). To form these tissues, we will use different cell populations and after two weeks evaluate if cardiomyocytes have changed their fate to atrial. We will perform simple gene expression analyses, as well as full RNA and secretome analyses to discover what is causing these differences and therefore, to learn the mechanism that underlies this ‘converting’ potential of the fibroblasts. At the end of the Project we would like to propose a substance that will be responsible for regulation of this action.