## 1. Aim of the project/research hypothesis

Approximately 50% patients with cardiovascular disease die suddenly of arrhythmias. The most common cause of sudden cardiac death (SCD) is an acute coronary event and related ventricular arrhythmias. Incidence of SCD increases with age, following development of cardiovascular disease. SCD is twice as common in men than in women. This results from the fact that advanced age and male sex predispose to coronary artery disease, while the risk of SCD is comparable in subjects of both sexes with comparable condition of coronary arteries. However, electrophysiology tests less often induce arrhythmias in women and arrhythmias occur more commonly in women without structural myocardial changes and with higher left ventricular ejection fraction. This may suggest different mechanisms of arrhythmias in both sexes.

Both in women and men the most common cause of SCD is acute coronary event and related arrhythmias. Mechanism of arrhythmias in myocardial infarction (MI) is complex and not completely understood. Main presumable factors involved in generation of arrhythmias and SCD in MI include: abnormalities of intracellular $Ca^{2+}$ handling and heterogeneous action potential duration in myocardial cells. Arrhythmias are favored by slow conduction that can result from underlying myocardial fibrosis and reduced number of intercellular connections (connexons). No data are available on age- and sex-dependent differences in mechanisms of arrhythmias in acute MI. Thus the **aim of the project is to verify a hypothesis that incidence of cardiac arrhythmias and mechanism of these arrhythmias are age- and sex-dependent.**

This hypothesis is based on several facts documented in the literature: (1) there are significant electrophysiological differences between female and male hearts resulting from different expression of ion channels and their different regulation by hormonal factors; (2) function of proteins involved in the intracellular $Ca^{2+}$ handling is sex-dependent and changes with ageing; (3) ageing is accompanied by remodeling of the extracellular matrix, involving excessive fibrosis and as our preliminary data indicate, this process is more pronounced in male rats.

## 2. Methods

To verify this hypothesis, large MI will be induced in 3 age groups of Wistar-Kyoto rats (aged 3 months, 18 months and 28 months) of both sexes by ligation of the left anterior descending artery. Age- and sex-matched sham operated rats will constitute control. Infarct size will be evaluated by echocardiography. ECG will be recorded using telemetry over 6 hours after induction of the MI. The following parameters will be analyzed: heart rate, QT interval, number of premature extrasystolic beats, number of total duration of episodes of ventricular tachycardia and fibrillation. To identify mechanisms of arrhythmias, the following parameters will be studied: (1) electrophysiology changes (recording of epicardial potentials in vivo); (2) changes of intracellular $Ca^{2+}$ handling in isolated cardiomyocytes using a fluorescence probe FURA-2; (3) degree of myocardial fibrosis (amount and composition of extracellular matrix); (4) efficiency of intercellular conduction (connexin expression and phosphorylation).

To get better insight into mechanism of arrhythmias, in vitro experiments will be conducted in which rats from the above mentioned age and sex groups will undergo Langendorff perfusion with the addition of inducers of early and delayed afterdepolarizations (catecholamines and hydrogen peroxide, respectively) to correlate a specific arrhythmia inducer with nature of resulting arrhythmias.

## 3. Effect of expected results on development of science, civilization and society

We hope that results of such project will provide data on cardiac susceptibility to arrhythmias in acute myocardial infarction. But mainly they will provide insight into poorly understood mechanisms of age- and sex-dependent differences in arrhythmogenesis under these conditions. These results can eventually result in preparation of personalized therapies adjusted to sex and age of each patient.

The problem of equal treatment and lack of discrimination of any social group is currently especially important. It also applies to diagnosis and treatment, but in this context it means quite opposite thing, i.e. right to receive individualized therapy, adjusted to specific needs of each subject, which may be different from those of other subjects.