Pharmacologic strategies to inhibit progression of arrhythmogenic right ventricular cardiomyopathy

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Both biologist and medical genetist, Alessandra Rampazzo has worked in the field of molecular genetics of inherited cardiomyopathies since 1992. Dr. Rampazzo and her research group succeeded in the identification of 6 novel genes involved in arrhythmogenic right ventricular cardiomyopathy (ARVC); two of them, encoding for desmoplakin and desmoglein-2, are among the three genes most frequently mutated in ARVC patients. These findings allowed the employment of mutation screening for carrier detection among family members of affected subjects and played an essential role in sudden death prevention and genetic counselling.
In the last years, she moved from molecular genetic studies to functional studies to unveil molecular mechanisms involved in the pathogenesis of ARVC through generation of animal models.

Research project
Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a dominant, degenerative cardiomyopathy, frequently involved in sudden death of asymptomatic athletes and teenagers. The pathological hallmark of ARVC is fibrofatty replacement of myocardium, which leads to ventricular arrhythmias; no therapy is available to prevent these progressive, potentially lethal histological changes.
Currently, the main goal of therapy is the prevention of sudden death. To this end, implant of a cardioverter-defibrillator is the most effective strategy, which should however be reserved to selected patients after accurate risk stratification, in view of the high complication rate, costs and significant psychological impact of such therapy, especially in young individuals.
Recently, Fabio Rossi's group at the University of British Columbia (Vancouver) has reported the identification of cardiac fibroadipogenic progenitors (cFAPs), and showed their involvement in the development of cardiac fibro-fatty infiltration in an ARVC murine model we recently created and characterized (Soliman et al., 2020). In an attempt to block differentiation of cFAPs into fibrogenic cells after cardiac damage, the tyrosine kinase inhibitor Nilotinib was administered in a murine model of left anterior descending artery (LAD) ligation. The treatment not only diminished cardiac fibrosis but significantly improved cardiac function and performance. Although this finding holds therapeutic potential, it is important to mention that Nilotinib dramatically and rapidly increased mortality rates in mice when the treatment was started before acute cardiac damage.
Altogether, the results recently obtained by these two research groups indicate that subclinical cardiomyocyte damage chronically activates cFAPs, which slowly expand and differentiate in matrix producing cells and adipocytes. Therefore, we propose that cFAPs are a promising therapeutic target to inhibit ARVC progression.
In this research project we will test the ability of pharmaceutical compounds to inhibit ARVC progression in three ARVC murine models already available to the study.
In a two-year project, we will gain insight in the treatment of this devastating disease and come up with therapeutic options ready for clinical studies.