The main goal of our group is to investigate repair therapies based on engineered tissues (patches) to induce safe and efficacious angiogenesis and to rescue hibernating myocardium in a chronic ischemic myocardium. The three-dimensional (3D) bioreactor culture of heterogenous Stromal Vascular Fraction (SVF) cells aims to standardize the production of engineered patches (Fig. 1). SVF as a cell population is capable of releasing a broad secretome range comprising angiogenic and pro-survival factors. Further aims are to develop in vitro functional cardiac models to investigate processes of myocardial repair and regeneration.

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In this approach, we use human adipose tissue-derived SVF cells as a heterogeneous cell population with a high angiogenic potential thanks to the presence of numerous endothelial and mural progenitors (collaboration with A. Scherberich, Tissue Engineering Group, Department of Biomedicine, Unibas). We demonstrated that perfusion-based bioreactor culture supported the maintenance of endothelial and mural cells as compared to static culture, thereby accelerating whole construct vascularization and support of cell survival upon implantation in a subcutaneous nude rat model (Fig. 1–2). Moreover, medium conditioned during 3D perfusion-based culture of SVF was showed to partially rescue damaged cardiomyocyte function during monolayer culture under severe hypoxic condition (<1% of oxygen) (Mytsyk and Isu, 2018). An ongoing in vivo diseased study aims to investigate the repair potential of SVF-perfused patches in nude rat model of cardiac ischemia (in collaboration with the Department of Cardiac Surgery, USB).

Our angiogenic engineered tissues might also affect cardiac repair and regeneration by influencing cardiomyocyte maturation and functionality while increasing progenitor cell recruitment. Therefore, we aim to generate a 3D functional cardiac models as a tool to investigate the interactions of SVF cells’ secretome and cardiomyocytes. We hypothesize that the recapitulation of the proper physiological conditions, mimicking the native tissue environment, enhanced the cardiomyocyte maturation, 3D organization and functionality. Culture medium perfusion systems were employed to mimic the highly dense capillary network present in the myocardium to ensure the cardiomyocyte survival in vitro (Marsano, et al. 2010; Maidhof, et al. 2010; Cerino, et al. 2016). Mechanical stimulation (collaboration with the Politecnico of Milano, Italy and Politecnico of Torino, Italy) was employed to greatly promote rat neonatal cardiomyocytes or human induced pluripotent stem cell-derived cardiomyocyte maturation and contractility both at the micro- and macro-scale (Marsano, et al. 2016, Massai and Pisani, et al. 2020). Microfluidic culture systems harnessing mechanical stimulation was recently generated to recapitulate some of key steps of a scar formation (Occhetta, Isu, et al. 2019).

A novel 24-multi-well bioreactor (Patent number: EP19165964) was also developed to culture mm-scale engineered cardiac constructs in a highly controlled environment under multi-physical stimulations (isotonic and auxotonic loads combined with electrical stimulation).
Connection to Clinical Practice

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In vivo animal models to tackle vascularization issues at the macro- and micro-scale
Cardiovascular diseases and chronic myocardial ischemia cause progressive deterioration of cardiac function and lead to end-stage heart failure. However, the restore of blood flow both at the macro- and micro-level and the additional treatment with cardioprotective factors in the hypo-perfused myocardial areas could preserve cardiomyocyte survival and rescue their contraction, therefore improving the overall cardiac function.

Macro-circulation. Revascularization strategies aim to use autologous blood vessels (e.g. saphenous vein) as coronary artery bypass grafts (CABG). However, some patients might need an alternative to the autologous vessels due to recurrent operations or morbidity issues. Nowadays there still lacks a valid alternative to autologous grafts used for CABG. Our research group has developed a vascular graft made of acetobacteria-derived nano cellulose reinforced by a cobalt-chrome mesh. Previous results showed the cellulose vascular graft’s patency and its colonization by host vascular cells following a one-month implantation. The clinical research counterpart has established two long term studies to test the patency of the cellulose vascular grafts used as carotid artery replacement in sheep and as CABG in pigs.

Micro-circulation. 3D SVF cell-based patches as an adjuvant angiogenic and repair therapy could provide control over the targeted area, reducing undesired systemic effects, while enhancing implanted cell survival, compared to intramyocardial cellular injections. A nude rat model of chronic cardiac ischemia was recently established to test the angiogenic and repair potential of SVF cell-based patches.