ECM-based 3D model of alveolar rhabdomyosarcoma

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Alveolar Rhabdomyosarcoma (ARMS) is the most aggressive subtype of the rhabdomyosarcomas, affecting children from 5 to 19 years old, an incidence at approximately 1 case per 1 million, and a 5-years survival rate below 40%. ARMS is defined as an aberrant stage of muscle development, arising from skeletal muscle cells exhibiting impaired differentiation and uncontrolled proliferation. Due to its low incidence, the knowledge regarding the ARMS development and progression, in relation to its tumor microenvironment (TME), is still incomplete.

The extracellular matrix (ECM) is a non-cellular component of a tissue playing an important role not only confined to provide physical support to cells, but also regulating several cellular responses.

The aim of this work is to develop an *in vitro* 3D model of ARMS, based on ARMS-derived ECM, that recapitulates the complexity of the *in vivo* ARMS TME.

First, we obtained ARMS ECM by decellularization of xenograft-derived ARMS maintaining the structure and the content of laminin, collagen, and fibronectin, with a residual DNA content < 5%. In a second ongoing phase of the project, we are now using the decellularized ECM, representative of the cell-ECM interactions in ARMS TME, as scaffold for 3D culture of tumor cells, to generate an organotypic model of the malignancy. Recellularization is conducted using a perfusion-based bioreactor that allows homogeneous culture by reducing the mass transport phenomena. Cell motility and ECM remodeling will be investigated assessing integrins and metalloproteases expression together with the CXCR4/SDF1 and c-Met/HGF pathways involved in tumor invasiveness. This 3D model will be further implemented with stromal cells (e.g. endothelial cells) to study, in a controlled fashion, the role of TME components during ARMS progression. A promising application of this system, that closely mimics the *in vivo* complexity of ARMS TME, could be the investigation of innovative drugs targeting also cancer-supporting cells.