TITLE: PAPER-BASED CELL CULTURE: PAVING THE PATHWAY FOR 3D LIVER TISSUE MODEL DEVELOPMENT ON A PAPER CHIP

ABSTRACT:

Maintenance of functional hepatic phenotype has been challenging for the reconstruction of 3D liver tissue models. An enormous amount of efforts have been directed towards developing a suitable platform that could suffice this challenge. In this milieu, commercially available paper matrices have become an attractive biomaterial platform for various cell-based applications, including tissue engineering and *in vitro* tissue model development. However, its applicability in the sphere of hepatic models is still in its infancy and requires a comprehensive standardization of a plethora of factors that could contribute to the success of the developed liver models.

With this perspective, the present thesis delineates the fabrication of paper-based devices for culturing hepatic cells and developing related bioassays. The devices were prepared by conventional lab-based LaserJet printing technology and biofunctionalized with (3-aminopropyl)triethoxysilane (APTES) and caprine liver-derived extracellular matrix (CLECM). We opted for an unconventional floating cell culture strategy, which ensured easy cell seeding, maintenance of cultures, and post-culture analytical analysis. The developed paper substrates effectively supported the culture of hepatic cells. However, the cells exhibited significant variation in their proliferative and functional phenotype, attributing to different biochemical substrate properties, paper specification, and design parameters. The paper devices were further explored multifaceted applications, including routine cell culture, in-cell ELISA, drug screening, coculture, and transwell migration assays.

To further extend the applicability of biofunctionalized paper matrices, they were evaluated for their systemic toxicity and delivering cells *in vivo*. Upon implantation into the mice model, the developed paper matrices supported infiltration of the host cells and vasculature without any evidence of significant systemic toxicity. Moreover, cell-seeded paper matrices, when delivered to chick embryo chorioallantoic membrane and mouse models, showed an enhanced vascular network around the substrate, thereby confirming its potential for cell delivery and maintain cell viability *in vivo*.

Considering the multitude of advantages of the paper substrates and devices, including biocompatibility, flexibility, multiplexibility, and cost-effectiveness, it is ideal for liver-on-a-paper chip model development and *in vivo* cell delivery application, especially under resource-limited settings.

Keywords

Liver, 3D culture, Paper matrix, Decellularized liver ECM, Liver-on-a-paper chip model, Cell delivery