Advancing precision oncology: Integrating AVI-PDX and patient-derived organoid technologies for enhanced preclinical modeling in immuno-oncology

ABSTRACT N°
4701

Author Block:
Clélia Costechareyre, **Romain Teinturier**, Mayrone Mongellaz, Marjorie Lacourrège, LoraineJarrosson, Céline Delloye-Bourgeois, Valérie Castellani
ERBC Lyon - OncoFactory, Bioparc Bâtiment Adenine, 60c avenue Rockefeller 69008 Lyon, France

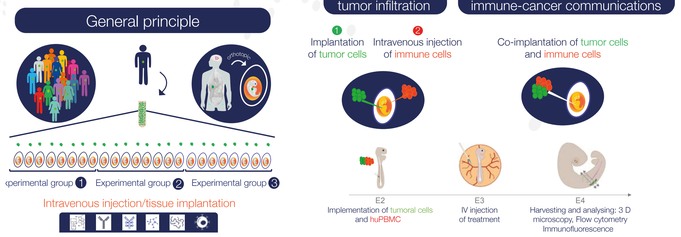
Contact: contact@oncofactory.com - romain.teinturier@oncofactory.com

Abstract

The AVI-PDX technology enable to create miniature replicas of patient samples within an in vivo organism, the avian embryo. We have developed new generation of models, humanized with immune cells, that extend the applications of the AVI-PDX technology to modified immune cell-based therapies and checkpoint inhibitors in monotherapy and in combination with standards of care. Over the past years, extensive effort has been made to develop patient-derived organoids, bringing valuable diversity of molecularly characterized biological resources for oncology studies. Despite their great interest, organoids hardly allow to integrate the stroma and immune microenvironment components, which limits their use, in particular concerning immune-modulators. To overcome these limitations, we combined AVI-PDX and patient-derived organoid technologies to create an avian patient-derived organoid model, the AVI-PDO. We report here the generation of colorectal AVI-PDO. Organoids from a CRC patient tumor were grown in culture, then dissociated and micro-implanted in batches of avian embryos, within one of the territories classically used in the AVI-PDX models. We conducted a time-course analysis of the behaviors of organoids-derived cells, harvesting the embryos within 3 to 6 days post-implantation. Embryos were cleared and imaged by light sheet microscopy. Remarkably, we observed that organoid-derived dissociated tumor cells were initially scattered, then regrouping together to finally reconstitute 3D organoid-like structures. To more closely characterize these 3D structures, we performed immunolabeling of various markers on tissue cryosections. We observed that tumor cells organized in spheres with central lumen, expressing polarity markers. Moreover, we found significant number of Ki67-positive cells, thus indicating they undergo active proliferation. Thus, thus this study reveals that our paradigm allows to re-create organoids within the avian embryo tissues, thus paving the way to the generation of humanized organoid-derived models and studies of immune-based therapies in whole organism model providing systemic signaling and tissue microenvironment.

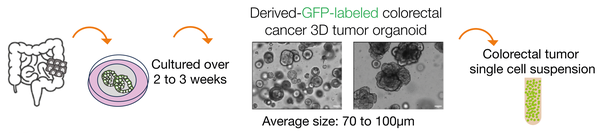
Method and Models

The AVI-PDX™ platform

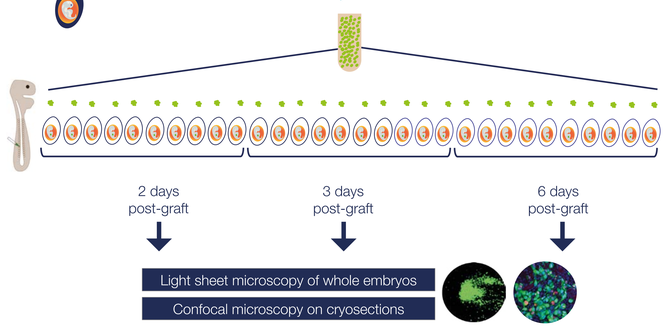


1 Experimental paradigm

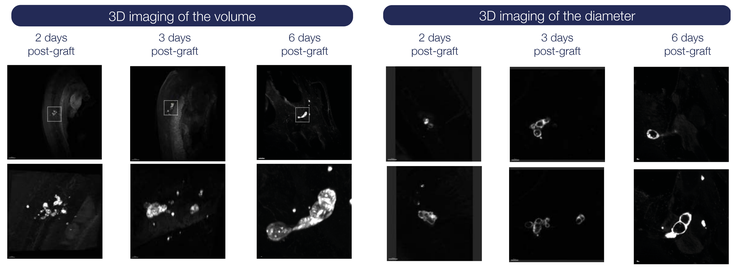
STEP 1 Generation of single cell from tumor organoids



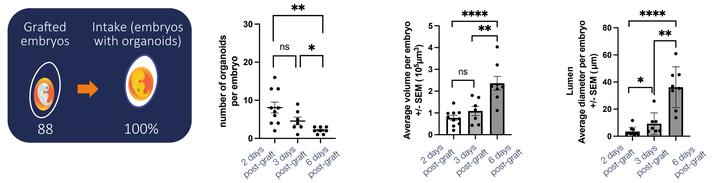
STEP 2 Implantation of tumoroid cells in the avian embryo tissues & analyses



2 3D Imaging of whole grafted embryos at day 2, 3 and 6 post-graft

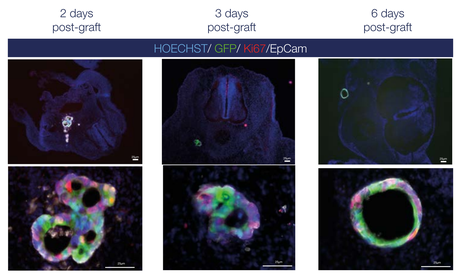


✓ Grafted CRC tumoroid cells reform organized3D structures with central lumen (Avian-Patient derived organoids "AVI-PDOs")

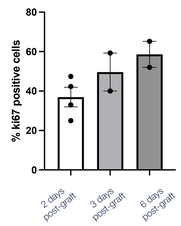


✓ 3D structures evolve over time: reduction of number/embryo, increase of volume & diameter /embryo

Immunolabeling on embryo sections

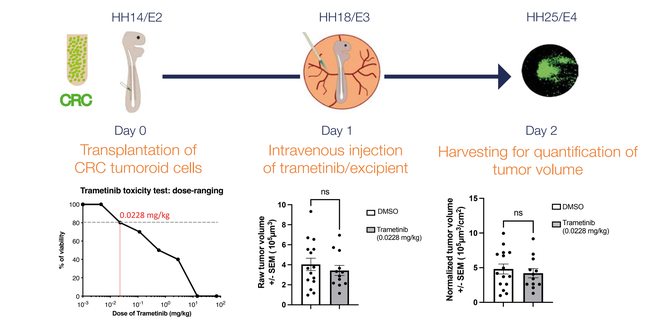


Cell proliferation



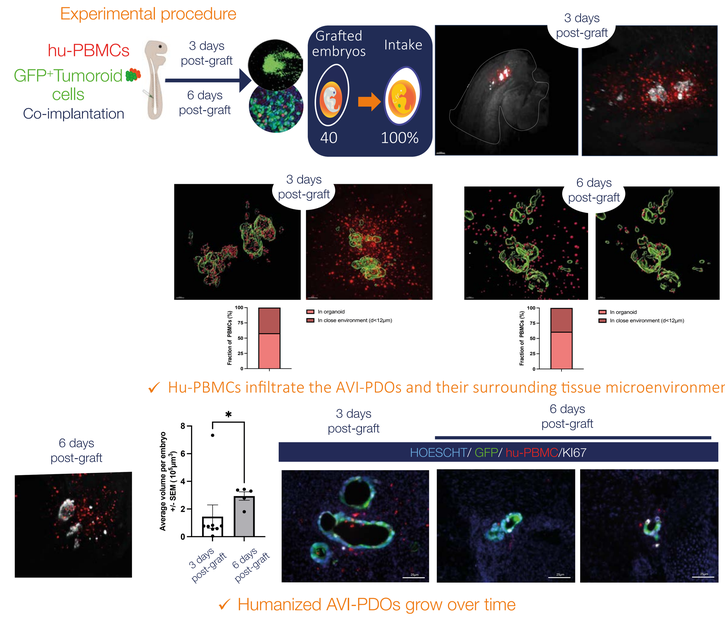
✓ AVI-PDOs express EpCAM marker and proliferate over time

3 Administrating therapy in the AVI-PDO model



✓ 24 hours Trametinib administration induces a slight non significant reduction of AVI-PDO volume

4 Humanizing the AVI-PDO



✓ Hu-PBMCs infiltrate the AVI-PDOs and their surrounding tissue microenvironment

✓ Humanized AVI-PDOs grow over time

Conclusion

We developed an avian embryo model that allows
- Integrating CRC patient-derived organoids into tissue and whole organism context
- Recapitulating an immune microenvironment

The setting of the AVI-PDO paves the way to studies of candidate therapies in oncology and immuno-oncology