Abstract ID #6907

Micro-implantation of patient tumor samples into the avian embryo, a fast and reliable alternative *in vivo* technology for preclinical studies on melanoma and follicular lymphoma

ERBC

oncofactory
Patient-derived xenograft avian models

«We provide pre-clinical services in oncology and immuno-oncology by creating avian tumor replicas»

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

Authors:

Clélia Costechareyre[1], Loraine Jarrosson[1], Marjorie Lacourrège[1], Romain Teinturier[1], Manon Zala[2], Julie Caramel[3], Stéphane Dalle[3,4], Pierre Sujobert[2,4], Frédéric Berget[1], Valérie Castellani[1], Céline Delloye-Bourgeois[1]

1-OncoFactory SASU, Bioparc Bâtiment Adenine, 60c avenue Rockefeller 69008 Lyon, France - 2-Centre International de Recherche en Infectiologie (CIRI, INSERM U1111, CNRS UMR 5308, École Normale supérieure de Lyon), Lymphoma ImmunoBiology team, Faculté de Médecine Lyon sud, Université Claude Bernard Lyon 1, 69007 Lyon, France
3-Université de Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Centre Léon Bérard, Cancer Research Center of Lyon, Lyon, France - 4.Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France

Abstract

Despite recent efforts to develop reliable and predictive patient-derived cancer models, drug attrition rates in oncology remain high. Moreover, conventional models such as patient-derived xenograft (PDX) mouse models face major cost and time limitations, not supporting real-time clinical decision making. To overcome such limitation, ONCOFACTORY developed a proprietary PDX platform enabling the engraftment of small size tumor biopsy samples within targeted tissue of the avian embryo at early stage of development, to conduct preclinical proof of efficacy studies and provide PDX clinical trial solution helping with patient's selection prior to clinical phase II/III.

On one hand, we performed prospective co-clinical trial aiming to evaluate the utility of the AVI-PDX™ model in predicting the response to standard therapy, consisting of BRAF and MEK inhibitors, for patient with metastatic melanoma harboring BRAF mutations. For that, skin biopsy samples were implanted into specific tissue driving tumor formation under skin into the avian embryo. On the other hand, we conducted retrospective cohort study with 20 follicular lymphoma (FL) patient samples characterized by either "partial" or "complete" response to establish FL AVI-PDX™, and examine sensitivity to the standard immuno-chemotherapy RCHOP regimen. FL biopsies were implanted within the aorta-gonado-mesonephros (AGM) to create avian patient tumor replicas. Twenty-four hours post-implantation, avian melanoma and FL replicas were respectively exposed to BRAFi/MEKi or RCHOP and their vehicles, over 24h. Then, embryos were harvested, and drug sensitivity was examined by measuring tumor volume using light sheet microscopy. Alongside, in independent series of avian embryos implanted with FL samples, tumors were harvested for single-cell transcriptomic analyses to explore mechanism of response to RCHOP.

For melanoma, we provide the proof of concept that the AVI-PDX™ reliably predicts sensitivity or resistance to BRAF and MEK inhibitors within days, matching patients clinical outcome observed in clinic. For follicular lymphoma, we showed that tumor volume analyses into FL-AVI-PDX™ efficiently capture clinical response to RCHOP in a heterogenous cohort of patients, enabling to discriminate partial and complete responders within short-time frame. Next, we identified a robust genetic signature reflecting exposure of tumoral cells to RCHOP and showed that drug-mediated targeting of one of these genes with a chemotherapy resulted in strong potentiation of RCHOP.

Thus, we provide evidence of the high predictive power of the AVI-PDX™ models allowing fast and reproducible generation of tumors replicas from small size patient tumor samples. The AVI-PDX™ platform can be used to predict the result of human clinical trial, further positioning it as a valuable tool for the design of personalized medicine assays.

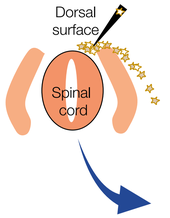
AVI-PDX platform for prediction of clinical response to BRAF and MEK inhibitors in patients with advanced metastatic melanoma

1 Rational and objectives

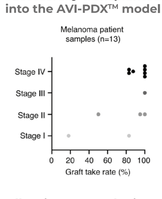
While some patients with metastatic melanoma harboring BRAF mutations experience significant tumor shrinkage and prolonged disease control with BRAF and MEK inhibitors, not all patients respond equally well to these treatments. Moreover, preclinical models face challenges in accurately representing the complexity of human melanoma and predicting clinical responses to treatment. Addressing these limitations will be crucial for advancing the development of more effective therapies. ONCOFACTORY has developed an avian-PDX model of melanoma, requiring low amounts of tumor samples and displaying a short-timeframe of development for assessing treatment efficacy in melanoma.

2 Setting up a clinically-relevant model of metastatic melanoma in the AVI-PDX™ platform

Implanting melanoma cancer cells in the migration path of melanocyte precursors



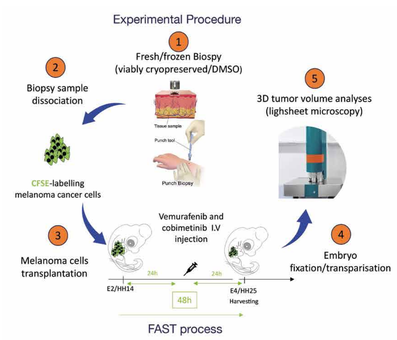
Thirteen stage I to IV melanoma biopsies were successfully transplanted into the AVI-PDX™ model

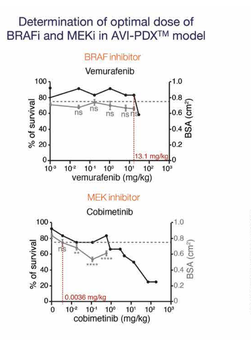


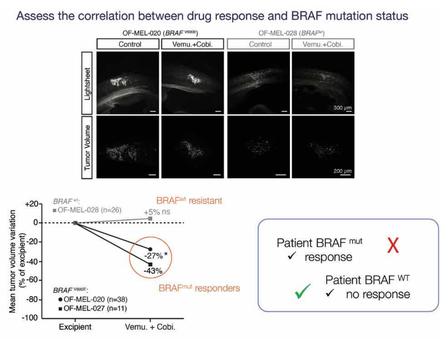
Transplanted melanoma cancer cells migrate to colonize the dermis/hypodermis and form a detectable tumor that can be measured with light sheet microscopy

3 Proof of concept for predicting response to BRAF and MEK inhibitors in AVI-PDX™ model

While some patients with metastatic melanoma harboring BRAF mutations experience significant tumor shrinkage and prolonged disease control with BRAF and MEK inhibitors, not all patients respond equally well to these treatments. Moreover, preclinical models face challenges in accurately representing the complexity of human melanoma and predicting clinical responses to treatment. Addressing these limitations will be crucial for advancing the development of more effective therapies. ONCOFACTORY has developed an avian-PDX model of melanoma, requiring low amounts of tumor samples and displaying a short-timeframe of development for assessing treatment efficacy in melanoma.



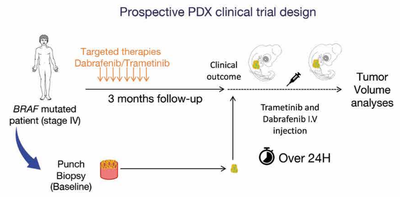


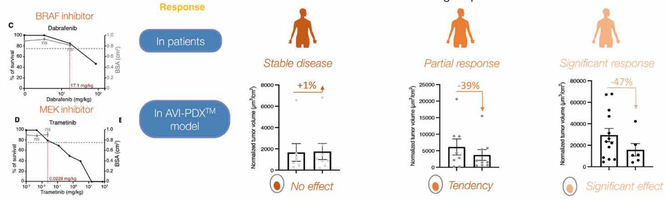


Patient BRAF mut ✓ response — X

Patient BRAF WT ✓ no response — ✓

4 Prospective study: comparing patient response in the clinics and in the AVI-PDX™





Link to the publication : https://www.embopress.org/doi/full/10.15252/emmm.202216629

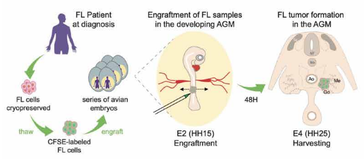
Implementing Functional Precision Oncology for Follicular Lymphoma utilizing the AVI-PDX platform

1 Rational and objectives

Follicular lymphoma (FL) is one of the most common subtypes of non-Hodgkin's lymphoma and is characterized by a heterogeneous clinical course and variable response to treatment. Over the past decades, rituximab, a monoclonal antibody targeting the CD20 antigen expressed on B-cell lymphomas, has revolutionized the treatment of FL when used in combination with chemotherapy (RCHOP regimen), with a response rate > 90% in advanced stage patients. However, a subset of patients still experience disease progression or relapse following initial treatment, associated with the emergence of resistance mechanisms. Existing preclinical models of FL have inherent limitations, such as a lack of representation of the tumor microenvironment as well as limited genetic diversity and heterogeneity, which limit their ability to accurately predict treatment response and translate findings into clinical practice. This highlights the need for more sophisticated and clinically relevant model systems that faithfully recapitulate tumor heterogeneity and enable the translation of therapeutic strategies into clinical practice. Therefore, ONCOFACTORY has newly developed an avian patient-derived xenograft model of follicular lymphoma that is specifically tailored to assess drug response in FL and implements comprehensive approach to gain deeper insight into the molecular mechanism underlying drug action. Here, we conducted a retrospective clinical study to evaluate whether the AVI-PDX™ platform can predict RCHOP outcome in FL patients and identify new therapeutic strategy for FL patients with early RCHOP resistance.

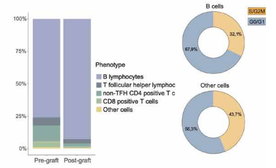
2 Establishment and characterization of the FL-AVI-PDX model

Implantation of primary FL cells into the AGM where hematopoietic precursors emerge



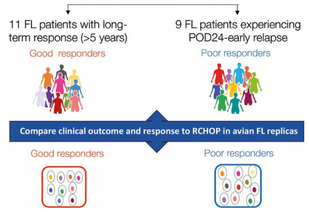
All primary FL samples tested (N=20) successfully grew in 98% of avian embryos

Analyses of FL cell composition before and after engraftment (FACS)

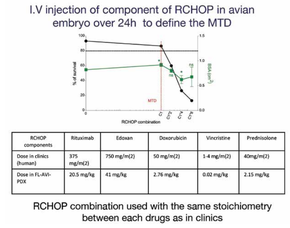


Cycling B cell lymphoma expand in the avian tissue, which retain non-tumor cells from the TME

3 Retrospective PDX clinical trial design



4 RCHOP exposure in FL-AVI-PDX

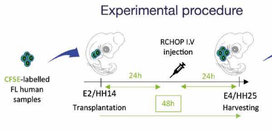


RCHOP components	Rituximab	Edoxan	Doxorubicin	Vincristine	Prednisolone
Dose in clinics (human)	375 mg/m(2)	750 mg/m(2)	50 mg/m(2)	1.4 mg/m(2)	40mg/m(2)
Dose in FL-AVI-PDX	20.5 mg/kg	41 mg/kg	2.76 mg/kg	0.02 mg/kg	2.15 mg/kg

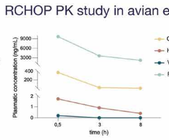
RCHOP combination used with the same stoichiometry between each drugs as in clinics

5 FL-AVI-PDX model captures inter-patient heterogeneity in response to clinically relevant dose of RCHOP therapy

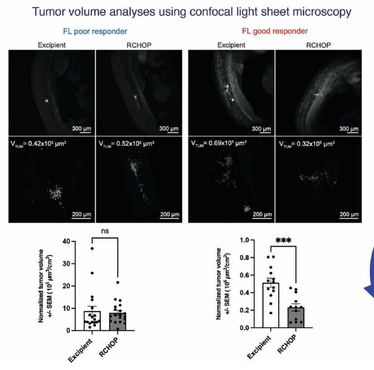
Experimental procedure

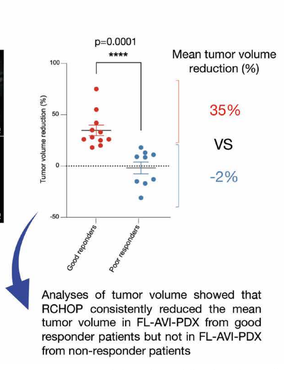


RCHOP PK study in avian embryo



Tumor volume analyses using confocal light sheet microscopy





Mean tumor volume reduction (%)

35%

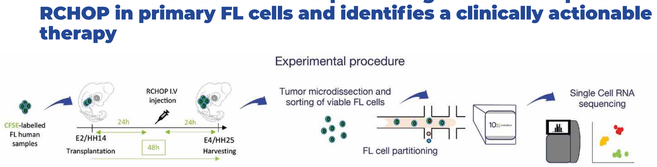
VS

-2%

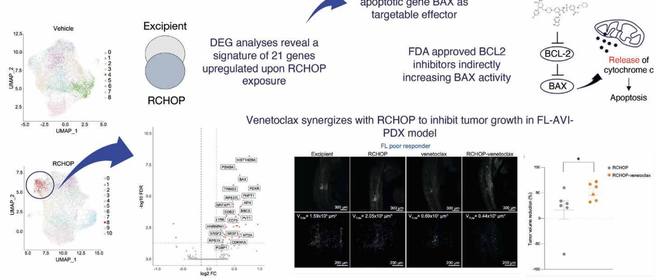
Analyses of tumor volume showed that RCHOP consistently reduced the mean tumor volume in FL-AVI-PDX from good responder patients but not in FL-AVI-PDX from non-responder patients

6 Implementation of single-cell RNA sequencing in the FL-AVI-PDX model reveals a transcriptomic signature of response to RCHOP in primary FL cells and identifies a clinically actionable therapy

Experimental procedure



9 FL patients treated with RCHOP or the excipient

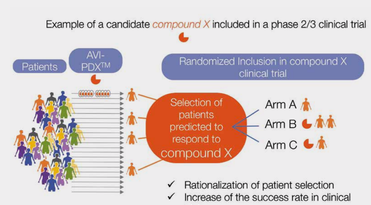


Link to the publication : https://www.nature.com/articles/s41375-024-02150-9

Conclusion

The AVI-PDX™ model developed by ONCOFACTORY presents a compelling opportunity for advancing clinical decision-making in the management of melanomas and follicular lymphomas (FL). By successfully grafting patient-derived samples from these malignancies into avian embryos, ONCOFACTORY has established a versatile platform for evaluating and predicting responses to both standard-of-care therapies and novel treatments. The robustness of this model in replicating patient responses across diverse cancer types, including melanomas and FL, underscores its potential to inform clinical practice. For patients with melanoma, where treatment decisions can be particularly challenging due to the development of resistance to standard therapies, the AVI-PDX model offers a valuable tool for assessing treatment responses and guiding personalized medicine approaches. Similarly, in the context of FL, where a subset of patients experiences disease progression despite standard immunochemotherapy regimens, the AVI-PDX model holds promise for identifying poor responders and guiding treatment selection. Through the evaluation of primary FL cells in avian embryos, ONCOFACTORY has demonstrated the model's ability to capture interpatient heterogeneity, predict therapeutic responses and implement large-scale molecular analyses to identify new treatments. This capability is crucial for optimizing treatment decisions and improving patient prognosis.

Furthermore, the AVI-PDX model's ability to assess responses to both standard-of-care therapies and novel treatments enhances its utility in guiding treatment decisions across various cancer types. Of particular significance is the model's potential to stratify treatment responses based on individual tumor characteristics, thus enabling the de-risking of patient inclusion or enrollment in early-phase clinical trials. By accurately predicting responses to therapies, the AVI-PDX model allows for the identification of patients who are most likely to benefit from specific treatments, thereby optimizing patient selection and improving clinical trial outcomes.



- ✓ Rationalization of patient selection
- ✓ Increase of the success rate in clinical trials
- ✓ Conduct biomarker discovery program