New oncology target identification and validation platform combining artificial intelligence and preclinical pharmacology

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Introduction

Problematic

Despite major advances in cancer therapy in the last decades, treatment resistance can develop over time. Precision medicine allows for the successful implementation of targeted therapies and stratification of patients, but treatment resistance remains a major obstacle in patient management. The identification and validation of new targets associated with cancer resistance remains a major challenge. The great diversity of molecular mechanisms involved in treatment resistance phenomena, whether intrinsic (*de novo* or primary) or acquired (secondary), constitutes a real therapeutic challenge for patient care. A better understanding of resistance mechanisms would allow to explore new therapeutic strategies to circumvent these phenomena in different types of cancer.

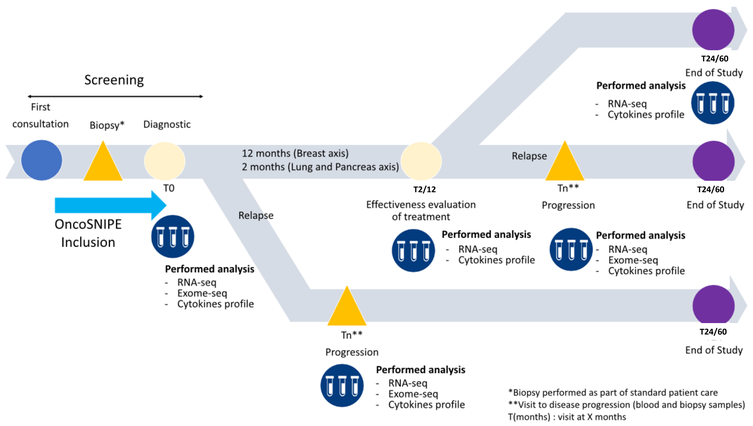
Clinical Trial

OncoSNIPE®, a powerful database

The OncoSNIPE® project was developed in this context as part of a multicenter and collaborative clinical study (**NCT04548960**) in more than 800 chemo-naive adult patients. The objective of this project was to **identify early and/or late markers of treatment resistance** in three different pathologies for which resistance problems are encountered: triple negative breast cancer (**TNBC**) or luminal B, locally advanced or metastatic non-small cell lung cancer (**NSCLC**) and pancreatic ductal adenocarcinoma (**PDAC**). The program included traditional clinical and whole exome sequencing (WES) monitoring of patient biopsies (Exom-seq and RNA-seq) at diagnosis and relapse, monitoring of blood markers (RNA-seq and Proteomics – Cytokine) at diagnosis, and the evaluation of best therapeutic responses and relapse.

OncoSNIPE®, a longitudinal clinical follow up with heteromodal data collection

OncoSNIPE® is a prospective, multi-centric, non-randomized study. Study inclusion period will be four years, each patient will be followed for 2 years for PDAC and NSCLC and for 5 years for TNBC and the overall study duration will be 8 years.



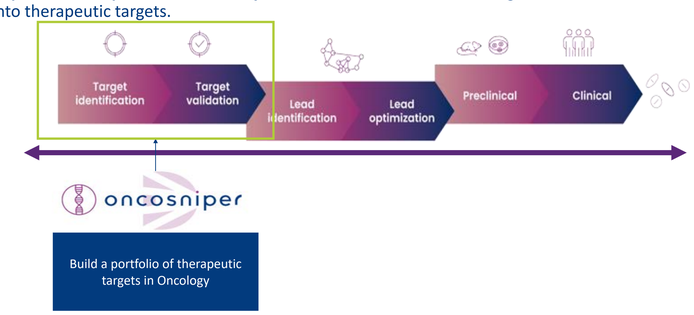
*Biopsy performed as part of standard patient care
**Visit to disease progression (blood and biopsy samples)
T(months) : visit at X months

OncoSNIPE® plans to enroll **800 patients, and their clinical, genomic and medical imaging data** is subject to longitudinal monitoring in three cancer indications representing sources of resistance and unresponsiveness – Lung Cancer (NSCLC), Breast Cancer (Triple Negative) and Pancreatic Cancer. This will include traditional clinical and genomic NGS monitoring of tumor (Exom-seq and RNA-seq) and blood markers (RNA-seq) at the time of diagnosis, as well as monitoring of best therapeutic responses and emergence of resistance. The obtained information will be contextualized using semantic enrichment through ConSoRe, a digital platform dedicated to cancer, and will be used to model resistance mechanisms, identify biomarkers, discover new therapeutic targets and generate the knowledge needed to create a precision medicine approach dedicated to patients resistant to cancer treatments.

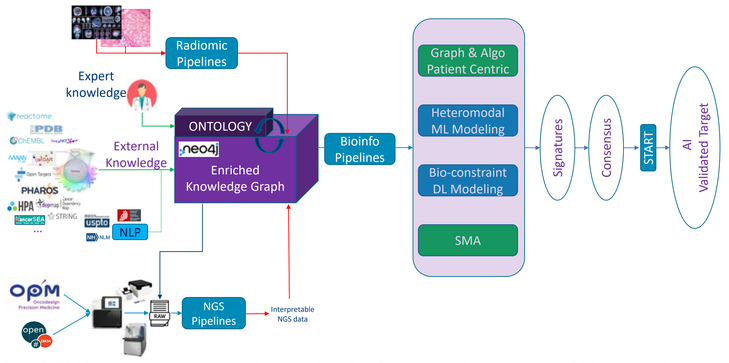
OncoSNIPER

OncoSNIPER, the target selection platform

The OncoSNIPER technology module is a pivotal manifestation of the key scientific competence of OPM's Study activity. This module was designed **to identify signatures that can stratify populations of patients' refractory to cancer treatments**. These signatures are then translated into therapeutic targets.



The Artificial Intelligence (AI) part of OncoSNIPER platform integrates public, private, and proprietary data sources (from projects such as IMODI, OncoSNIPE®, etc…) into a graph database and uses various AI technologies (machine learning, biologically constraint deep learning, computer vision, natural language processing, etc.) and dedicated scoring technologies. One of the algorithms of OncoSNIPER is able to dig into the knowledge of our Drug Discovery experts, enabling a hybrid AI approach that combines the advantages of approaches based purely on data and expert system-type approaches.



OncoSNIPER also benefits from Oncodesign Services' experimental capabilities, allowing us to generate ad hoc data and validate any results identified in silico at the preclinical stage. OPM thus identifies and selects targets based on an in silico scoring process and experimentation.

Target Validation

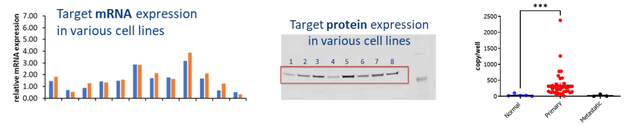
What's experimental target validation?

- Pharmaceuticals in development frequently encounter clinical stage setbacks due to insufficient efficacy and/or toxicity, both of which can be ascribed to incomplete preclinical validation of the intended target.
- Target validation is a multi-disciplinary process that involves the implementation of diverse methods to verify that drug-induced effects on the target can elicit therapeutic benefits within an acceptable safety profile.
- Thorough target validation at the initial stages improves the comprehension of the relationship between target modulation and disease efficacy, thereby increasing the likelihood of clinical triumph.

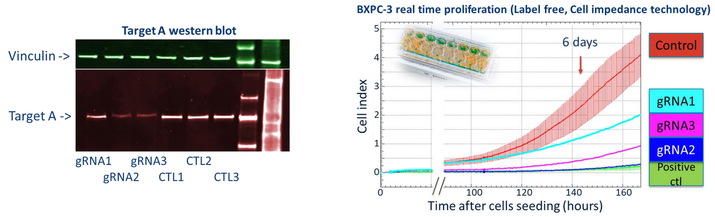
Experimentations

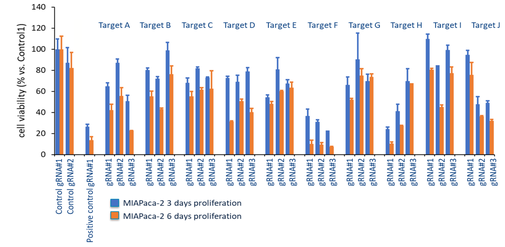
Examples of *in vitro* experiments aimed at characterizing the targets obtained through the OncoSNIPER platform.

Target expression determination:

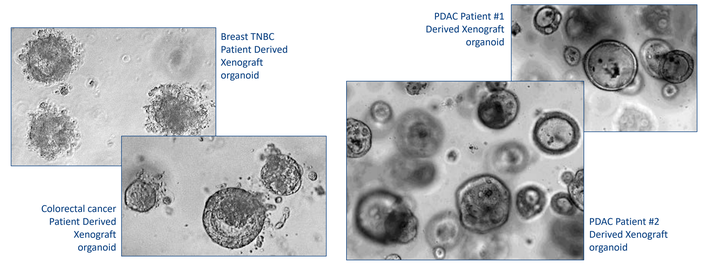


In vitro target validation example using CRISPR technology in PDAC cell line:





Advancing towards the next stage of *in vitro* validation, we implemented Patient-Derived Xenograft-derived Organoids (PDXOs). Herein, we present a demonstration of PDXOs derived from four distinct patient tumors cultivated in three-dimensional culture (3D – Matrix embedded).



Conclusion

We have devised a comprehensive Drug Discovery pipeline that facilitates the identification of novel therapeutic targets with high-quality data.
Subsequently, these targets undergo state-of-the-art *in vitro* assays to establish a correlation between target modulation and disease efficacy.
A diverse range of intrinsic or acquired molecular mechanisms contributing to treatment resistance are currently under scrutiny as potential candidates for both diagnostic and therapeutic development.

*Oncodesign restructured in 2022 into 2 entities : Oncodesign Precision Medicine (OPM) and Oncodesign Services