MechanoforOncology: Novel target and compounds for the treatment of pancreatic cancer

Challenge

Successful pharmacotherapy of solid tumors remains an unfulfilled medical goal, with pancreatic cancer being a prime example. It has been disclosed that, when cells are submitted to high values of force, such as the forces found on solid tumors environments, cytoskeleton changes promote YAP (Yes-associated protein) protein translocation into the cell nucleus. YAP is a potent oncogene, amplified in various human cancers, and contributes to deregulate the cell proliferation, death, and migration, which turns the cell into a tumor cell.

Both **increased rigidity and YAP activation** are prevalent features in most solid **tumors**. Further, reducing tissue stiffness or YAP expression have been demonstrated to inhibit tumor growth in prostate, breast, and other cancers. Stiffness-mediated YAP activation has been recently demonstrated. Thus**, inhibiting YAP activation** in response to increased stiffness has a major potential to **prevent tumor growth** in a wide variety of tumors.

Market

Pancreatic cancer is the fourth leading cause of cancer-death in men and women combined in more developed countries. The global pancreatic cancer therapeutics market is estimated to be **USD 2.59 billion in 2021** and growing with **a CAGR of 7.54%** from 2021 to 2026.

Asset

We have shown that the **interaction** between **talin and vinculin** in cells triggers the activation of the YAP oncogene in response to an increase in the rigidity of their surrounding tissue. This interaction only occurs in **abnormally stiff tissues** due to the mechanical unfolding of the vinculin binding domain of talin.

We identified a fragment of vinculin (VD1) which acts as dominant negative, blocking binding of endogenous vinculin to talin and preventing YAP activation (Elosegui-Artola et al., Nat. Cell Biol. 18, 540-548, 2016). This suggests that blocking talin-vinculin interaction has a major therapeutic in several solid cancer by reducing the cancer cell proliferation.

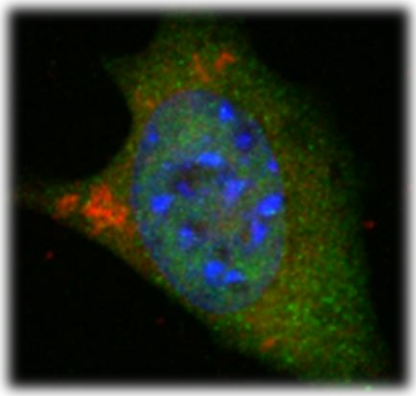
Preliminary results from target-based virtual-screening is promising with one of the **hit molecule showing decrease in cell proliferation** in Talin WT cells but not in Talin KO. According to the mechanism of action, it can also be applied to many solid tumors.

Asset Value

- First-in-class product that specifically targets mechanotransduction for cancer therapy. By selectively inhibiting the interaction of talin and vinculin occurring only in pathological and abnormally stiff tissues, we specifically block a malignant molecular event without affecting surrounding tissue.
- Mechanism of action independent of mutations or molecular signature driving tumor growth. We are thus proposing an entirely novel principle, which enhances its potential to work effectively in combination with existing treatments.

IBEC
Institute for Bioengineering of Catalonia

EXCELENCIA SEVERO OCHOA



Uses

- Mechanoinhibitor
- Therapeutic application in oncology and fibrosis

Team

Pere Roca-Cusachs - Scientific Leader
Ignacio Viciano - Scientist
Mamatha Nijaguna - Scientist
Asli Raman - Tech Transfer Manager

Stage of Development

- Family of compounds from a first *in-silico* study, that inhibits talin unfolding
- Hit optimisation in a second cycle of *in-silico* and *in vitro* analysis improving solubility and potency
- Target-directed assays developed to test hit binding to the target and estimate K_d
- High-throughput screening (HTS) assay designed to maximise hit identification

Future activities

- Antitumor activity in different cancer cell lines needs to be evaluated
- PK/PD and toxicity studies to be performed in animals
- *In vivo* efficacy to be tested in pancreatic cancer mouse models

Regulatory Path

Rx

Intellectual Property Status

IP strategy under development

Exploitation plan

Technical co-development

Contact

techtransfer@ibecbarcelona.eu