MechanoforOncology - Novel Target and Inhibitory Compounds for the Treatment of Pancreatic Cancer

Challenge

Successful pharmacotherapy of solid tumours 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 tumours 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 tumour cell.

Both increased rigidity and YAP activation are prevalent features in most solid tumours. Further, **reducing tissue stiffness or YAP expression have been demonstrated to inhibit tumour 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 tumour growth in a wide variety of tumours**.

Market

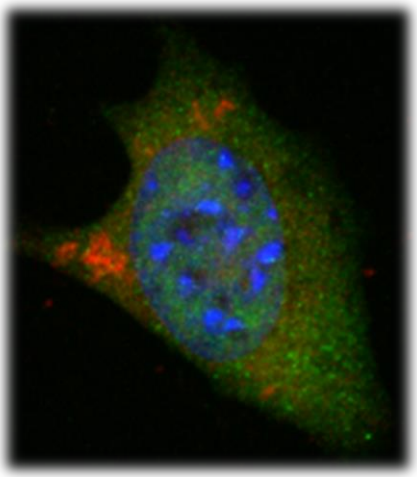
Pancreatic cancer is one of the more common types of cancers and it is the seventh leading cause of cancer deaths worldwide. The global pancreatic cancer therapeutics market is estimated to grow to USD 4.1 billion in 2029 with a CAGR of 8.2%.

Asset

We have shown that the interaction between the cytoskeletal proteins 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 is triggered by mechanical force exerted by cells, and it only occurs in abnormally stiff tissues due to the mechanical unfolding of the vinculin binding domain of talin. We identified a fragment of vinculin 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 potential as a therapeutic approach in several solid cancer types. The strategy is identification of small molecules that stabilise talin mechanically thereby preventing its unfolding. This will result in blocking the interaction with vinculin and therefore reduces stiffness-induced YAP nuclear localization. As a consequence, there will be reduction in cancer cell proliferation. **Preliminary results from target-based virtual-screening are 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 tumours.

Asset Value

To our knowledge, our product is a 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**. This is a mechanism of action independent of the specific mutations or molecular signature driving tumour growth. We are thus proposing an entirely novel principle, which enhances its potential to work effectively in combination with existing treatments.



Uses

Mechanoinhibitor
Therapeutic application in oncology

Scientific Project Leader

Dr. Pere Roca-Cusachs

Stage of Development

Past and Current Activities

- Family of compounds obtained in a first cycle of in silico study that inhibits unfolded talin only in WT background but not in KO condition
- Hit optimisation in a second cycle of in silico and in vitro analysis to develop molecule with improved solubility and potency
- Development of target-directed assays to test the hit binding to the target and estimate Kd
- Assay developed to perform high-throughput screening (HTS) to maximize hit identification

Future Activities

- Antitumour 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

Intellectual Property Status

IP strategy under development

Exploitation Plan

Licensing
Co-development

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