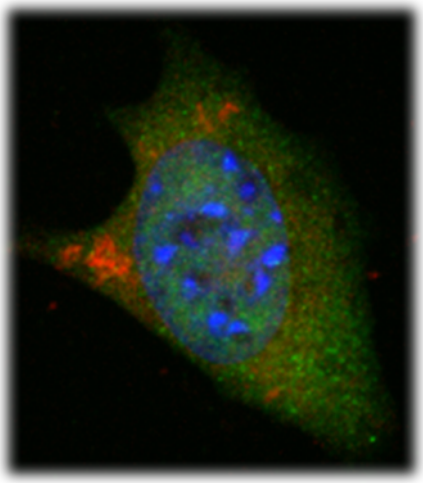
TALINH: Novel target and inhibitory compounds for the treatment of pancreatic cancer

The 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 is contributing in deregulating 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. Thus, inhibiting YAP activation in response to increased stiffness has a major potential to prevent tumor growth in a wide variety of tumors.



The market

Pancreatic cancer is the fourth leading cause of cancer-death in men and women combined in more developed countries. Its market has been valued at $ 1.7 billion in 2015 and expected to reach $ 4.2 billion in 2025.

The 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 (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; PCT/EP2017/056410)**.

Based on the VD1-talin interaction, we have designed a series of small peptidomimetic drugs (tetrapeptide with non-codified amino acids) that target the vinculin binding site of talin protein, that is unfolded only under tissue rigidity, and therefore block stiffness-mediated YAP activation. Results have shown cell growth inhibition in various pancreatic cancer cell lines but also in colon and prostate cancer cell lines **(PCT/EP2017/056410)**. Peptidomimetics are the preferred drug candidates in modulating protein-protein interactions, composed by large surfaces that cannot initially be targeted with a small molecule. We are currently optimizing our hit, by inhibiting the interaction of those cytoskeletal proteins with a more potent peptidomimetic, which will be protected by patent application as part of our IP strategy. According to the mechanism of action, it can also be applied to other solid tumors.

Product opportunity

To our knowledge, our product is a first-in-class product that specifically target 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 tumor growth.

We are thus proposing an entirely novel principle, which enhances its potential to work effectively in combination with existing treatments.

Scientific Project Leader

Dr. Pere Roca-Cusachs
(www.ibecbarcelona.eu/cellmolmech)

Stage of development

Family of compounds obtained in a first cycle of *in silico* study that inhibits unfolded talin only in tumoral tissue and shows *in vitro* antitumoral activity.

Hit optimization in a second cycle of *in silico* and *in vitro* analysis to develop a small peptidomimetic targeting talin.

PK/PD and toxicity studies to be performed in animals.

In vivo efficacy to be tested in pancreatic cancer mouse models.

Intellectual Property Status

PCT/EP2017/056410. Inhibitors of talin-vinculin binding for the treatment of cancer. Roca-Cusachs Soulere, P.; Elósegui-Artola, A. Institut de Bioenginyeria de Catalunya; Universitat de Barcelona.

Exploitation plan

Licensing or co-development.

Contact

TechTransfer@ibecbarcelona.eu