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Inhibiting mechanotransduction as a novel approach for oncology therapy

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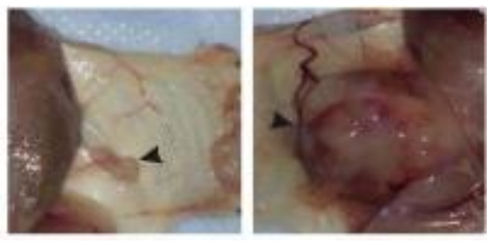
Introduction

- **Mechanotransduction** is a process of transmitting the mechanical cues to biochemical signals resulting in cellular function. function
- Increased tissue stiffness are implicated in most solid tumors leading to deregulated mechanotransduction and drive disease progression.
- Currently, there are **no compounds or drugs** available that block mechanotransduction.

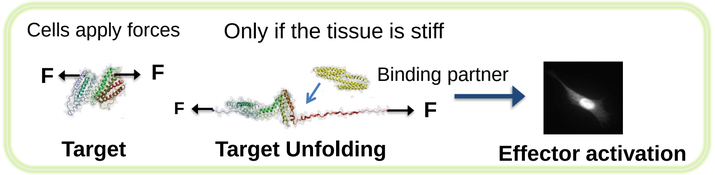
Normal tissue Stiff tissue



Tumour growth in breast cancer mouse model

Levental *et al., Cell* 2009

Background



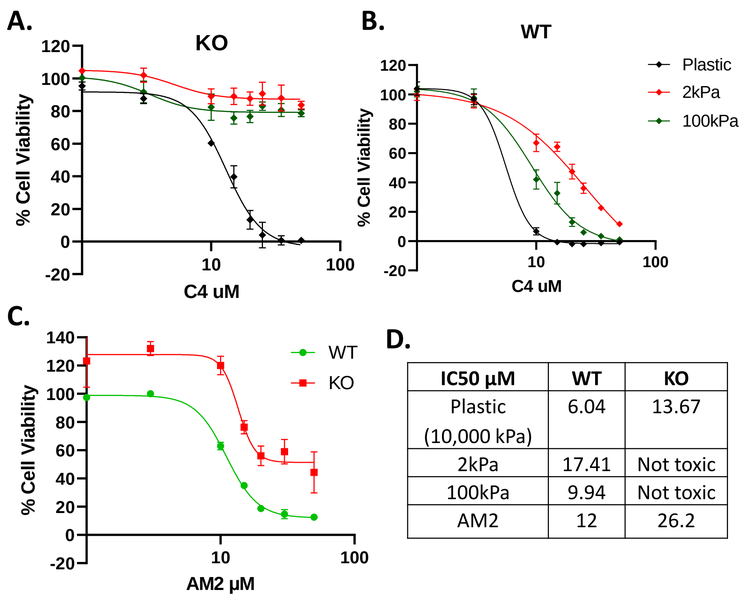
Elosegui-Artola *et al., Nat. Cell Biol*.2016

Target unfolding opens **cryptic binding site** and upon interaction with binding partner cascade of events occur in a process called mechanotransduction. This interaction results in nuclear localization of **mechanosensitive transcription factor** implicated in tumor progression of sevral cancer types.

Results

Cryo EM structure of target full length protein.

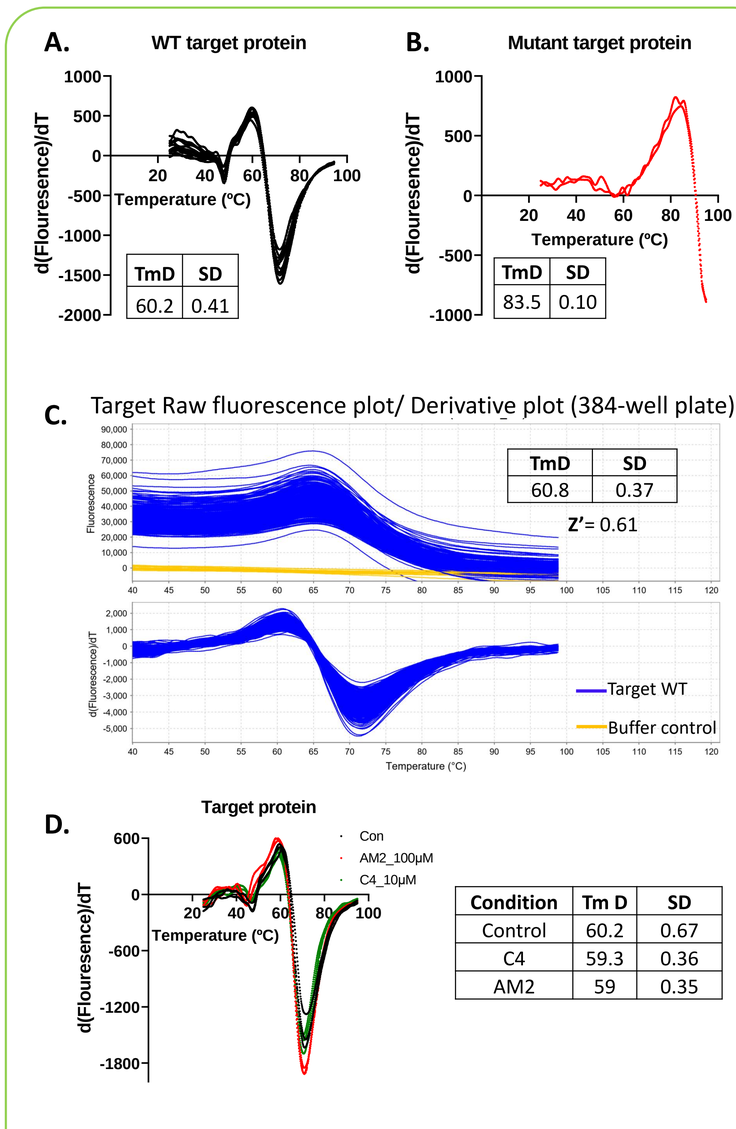
The target domain R3 is accessible for compound binding.



D.

IC50 µM	WT	KO
Plastic (10,000 kPa)	6.04	13.67
2kPa	17.41	Not toxic
100kPa	9.94	Not toxic
AM2	12	26.2

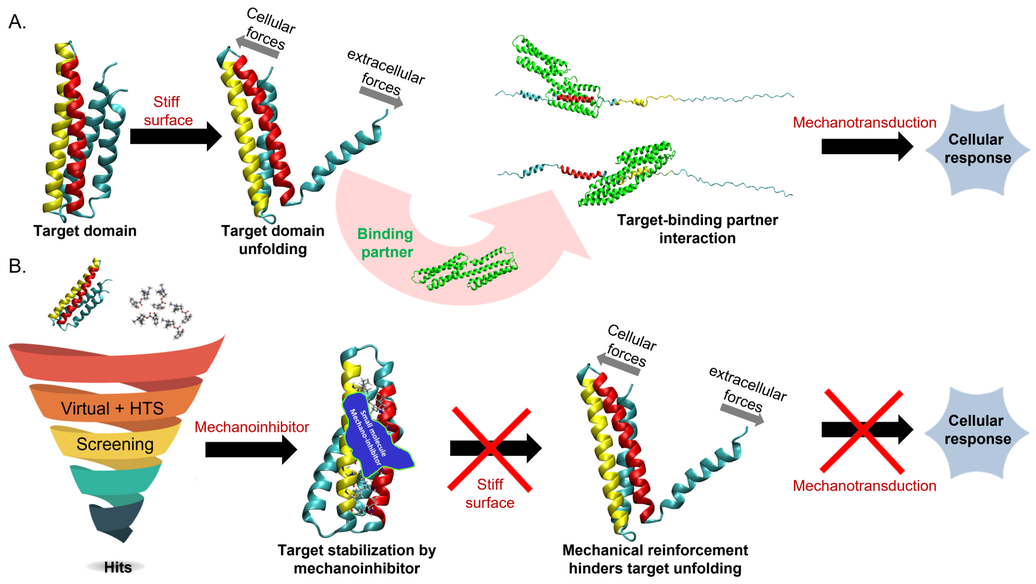
Cytotoxicity assay: C4 compound tested in target WT (**B.**) and KO (**A.**) cell line under soft and stiff conditions. AM2 compound tested in target WT and KO (**C.**) cell line in plastic surface. **D.** Table with IC50 values for indicated conditions



Condition	Tm D	SD
Control	60.2	0.67
C4	59.3	0.36
AM2	59	0.35

Thermal shift assay: Melting profile of WT protein (**A.**) and mechanically stable mutant protein (**B.**).
(**C.**) 384-well plate data for WT protein depicting raw fluorescence (up) and derivative (down).
D. Melting profile of WT protein with and without compounds.
***Inset table in each plot indicate mean Tm and std. deviation

Project Concept



Summary and outcome

Deliverables:

- **First-in-class** mechanoinhibitor
- **Tool compound** to study mechanobiology
- High potential for **therapeutic applications in oncology** and other pathologies

USP:

- **Novel concept** –mechanics in oncology
- Promising virtual screening hits- first **proof-of concept**
- Potentially compatible with other treatments
- Wide market in oncology

Challenges:

- Interfere only with pathological pressures
- No comparable drugs for reference
- Currently, limited in funds

References

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4. Elosegui-Artola, A. *et al.* Mechanical regulation of a molecular clutch defines force transmission and transduction in response to matrix rigidity. *Nat. Cell Biol* (2016).
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Future directions

- Interested in collaboration with partners for chemical library and to conduct HTS for identification of mechanoinhibitors.
- Seeking funding opportunitings for HTS and future development of identified hit to lead molecule.

ACCIÓ Tecniospring INDUSTRY
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