# PROTEIN KINASES IN CANCER RESEARCH
# JOSE MIGUEL LIZCANO

## RESEARCH

**RESEARCH INTERESTS**

Nearly all aspects of cell life are controlled by the reversible phosphorylation of proteins. Therefore, our understanding of the molecular control of cell physiology requires the dentification of the substrates targeted by specific protein kinases. Many studies have identified alterations in genes that encode kinases, which cause diseases such cancer or neurodegenerative diseases. Our research is focused on dissecting new cellular signaling pathways that control cancer cell proliferation and differentiation. We study the new protein kinases ERK5 (a MAP kinase) and the tumor suppressor LKB1, but we are also interested in the Akt-mTORC1 pathway.

**MAIN RESEARCH LINES**

Lizcano's Lab is interested in dissecting new cellular signaling pathways that control cancer cell proliferation and differentiation. We study the new protein kinases ERK5 (a MAP kinase) and the tumor suppressor LKB1, but we are also interested in the Akt-mTORC1 pathway. We use two different perspectives to approach fundamental problems:

a) Basic Research. Dissection of the mechanisms by which LKB1, Akt and ERK5 kinases exert a control on the proliferation and survival of tumor cells. We have contributed to propose new molecular mechanism for regulation of protein kinase Akt; discovered that tumor suppressor kinase LKB1 functions as a master kinase; or more recently, we have established a new mechanism by which ERK5 translocates to the nucleus and regulates the proliferation of tumor cells regardless of its enzymatic activity.

b) Research directed to pharmacological intervention in cancer. We are involved in potentiating translational aspects of our resources. We established collaboration with the company NeoPharm Obesity forthe screening of new anti-obesity drugs. Since 2011, we actively collaborate with Ability Pharmaceuticals SL in the preclinical/clinical development of the new antitumor drug ABTL0812, which it just finished Clinical Trial Phase I/Ib, first-in-humans (NCT02201823) in cancer patients with solid tumors.We have discovered a new cellular signaling pathway by which ABTL0812 exerts its antitumor action: ABTL0812 activates PPARa/g-mediated transcription of TRIB3 pseudokinase, which in turn binds and inhibits Akt resulting in mTORC1 inhibition, growth arrest and autophagy-mediated cancer cell death. Finally we actively collaborate with other academic laboratories characterizing new ERK5 inhibitors that show anti-tumor activity.

## LAB FEATURED PUBLICATIONS


Muñoz-Guardiola et al. *The anti-cancer drug ABTL0812 induces ER stress-mediated cytotoxic autophagy by increasing dihydroceramide levels in cancer cells.*
Autophagy 2020. doi: 10.1080/15548627.2020.1761651

Ferguson et al. *Discovery of a selective inhibitor of doublecortin like kinase 1.*
Nature Chemical Biology 2020. 16:635-643. doi: 10.1038/s41589-020-0506-0

Hermanova et al. *Genetic manipulation of LKB1 elicits lethal metastatic prostate cancer.*
J Experimental Medicine. 2020. 217: e20191787. doi: 10.1084/jem.20191787.

Erazo et al. *SUMOylation Is Required for ERK5 Nuclear Translocation and ERK5-Mediated Cancer Cell Proliferation.*
J Inter Mol Sci. 2020. 21(6). pii: E2203. doi: 10.3390/ijms21062203.

Felip et al. 2019. *Therapeutic potential of the new TRIB3-mediated cell autophagy anticancer drug ABTL0812 in endometrial cancer.*
Gynecol Oncol. 2019. 153: 425-435. doi: 10.1016/j.ygyno.2019.03.002.

Erazo et al. *The New Antitumor Drug ABTL0812 Inhibits the Akt/mTORC1 Axis by Upregulating Tribbles-3 Pseudokinase.*
Clinical Cancer Research 2016. 22: 2508-16. doi: 10.1158/1078-0432.CCR-15-1808

Gomez et al. *ERK5 and Cell Proliferation: Nuclear Localization Is What Matters.*
Frontiers Cell Development Biology 2016. 4:105. doi: 10.3389/fcell.2016.00105

Erazo et al. *Canonical and kinase activity-independent mechanisms for extracellular signal-regulated kinase 5 (ERK5) nuclear translocation require dissociation of Hsp90 from the ERK5-Cdc37 complex.*
Molecular & Cellular Biology 2013. 33:1671-86. doi: 10.1128/MCB.01246-12

Lizcano et al. *LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1*
EMBO Journal 2004. 23: 833-43. Doi: 10.1038/sj.emboj.7600110

Biondi et al. *High resolution crystal structure of the human PDK1 catalytic domain defines the regulatory phosphopeptide docking site.*
EMBO Journal 2002. 21: 4219-28. doi: 10.1093/emboj/cdf437

Lizano & Alessi. *The insulin signalling pathway.*
Current Biology 2002. 12:R236-8. doi: 10.1016/s0960-9822(02)00777-7.