

Calcium signaling in BRAF mutant melanoma

Agnes Enyedi

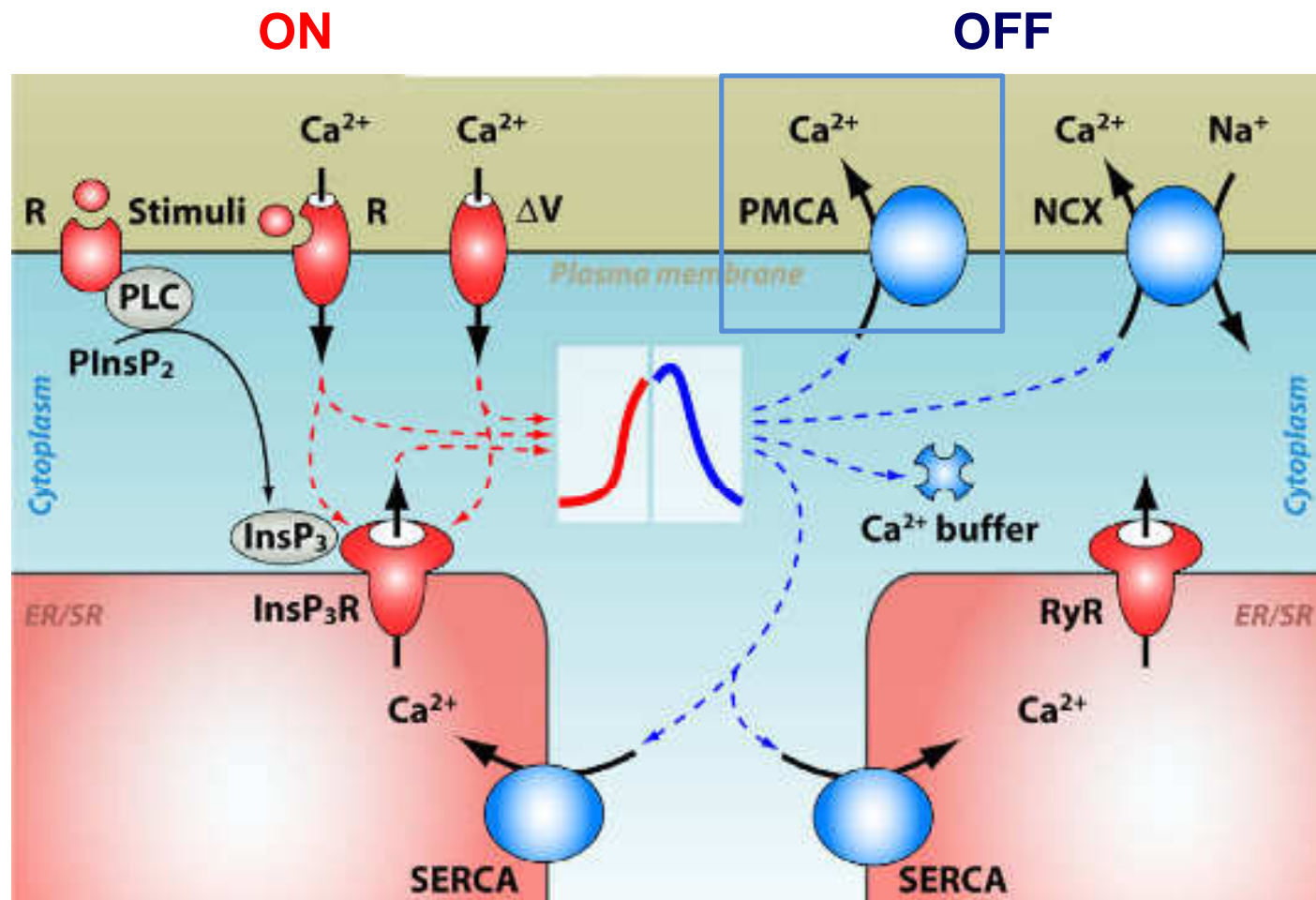
Molecular Oncology Research Group

HAS - Semmelweis University

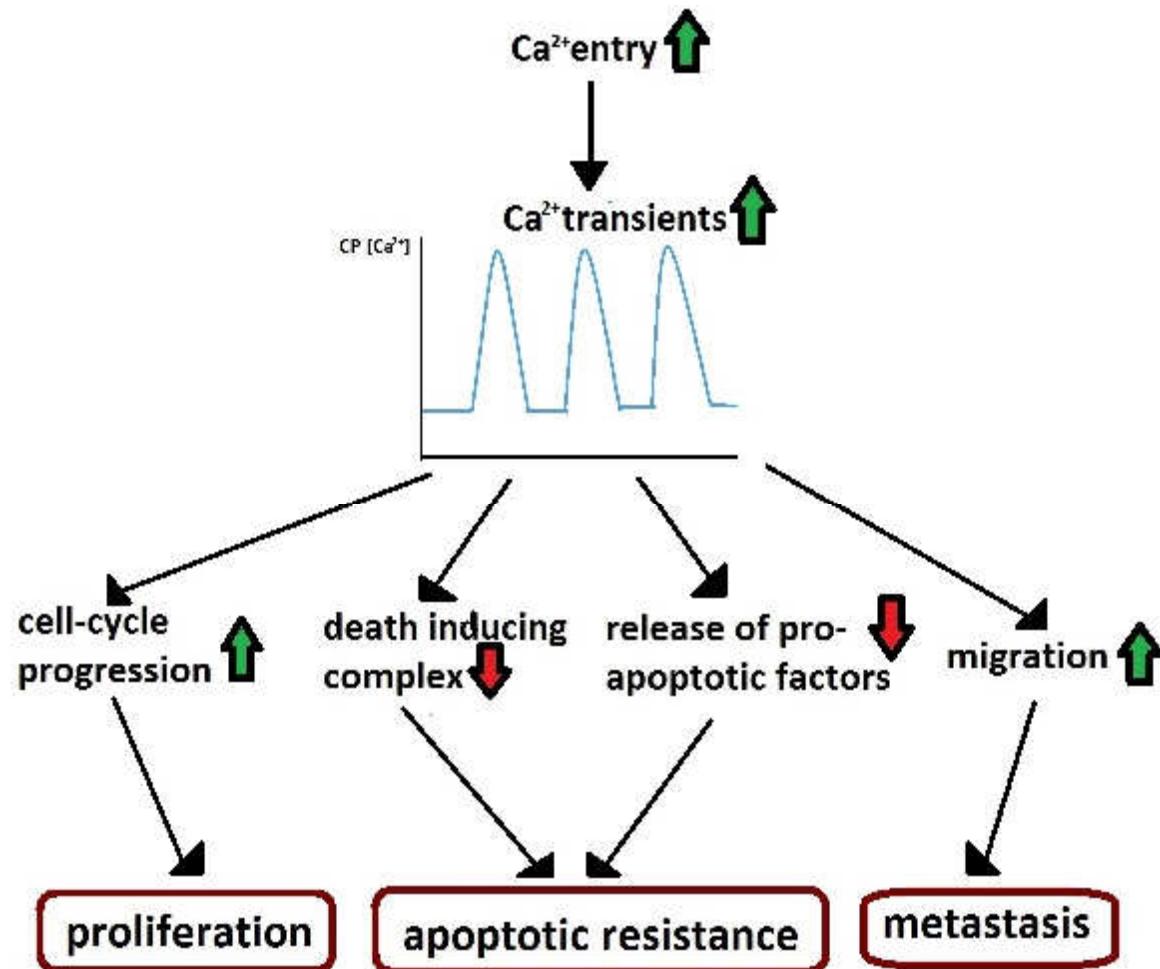
Budapest, Hungary

The role of a Ca^{2+} transport ATPase (PMCA) in the motility and metastatic activity of BRAF mutant melanoma cells.

Ca²⁺ channels initiate while Ca²⁺ pumps terminate the Ca²⁺ signal

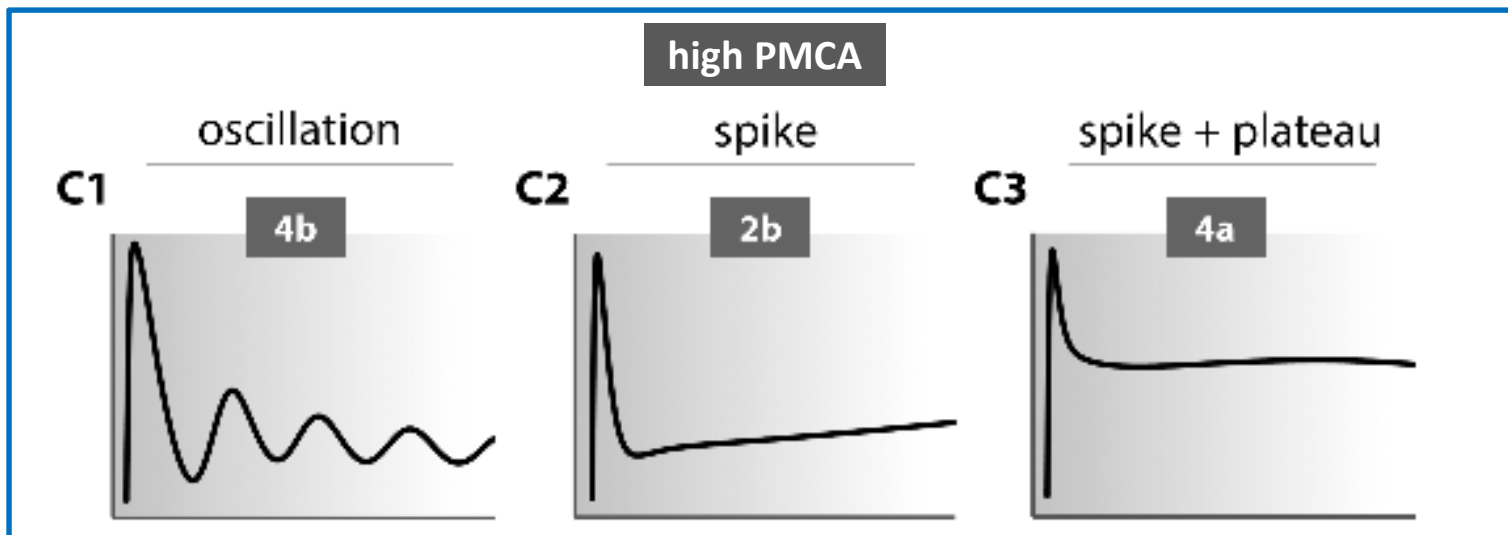
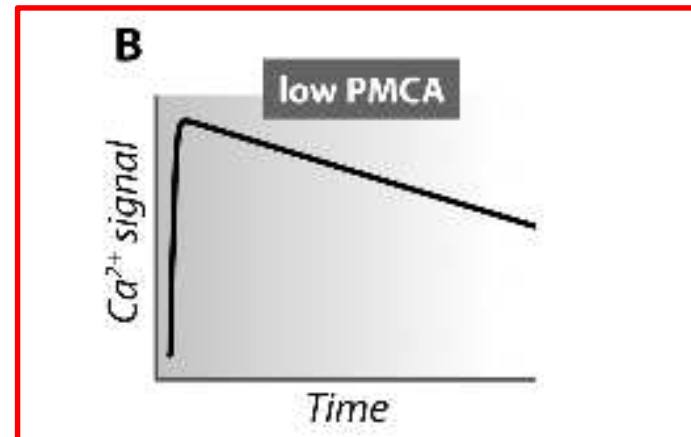


Altered Ca^{2+} signaling in cancer



Ca²⁺ signal patterns formed by different PMCA variants

Plasma membrane Ca²⁺ATPase
PMCA 1-4, ATP2B 1-4
+ alternative splice (*a, b, c...*)
>20 PMCA variants



Plasma membrane Ca^{2+} pump (PMCA) in cancer

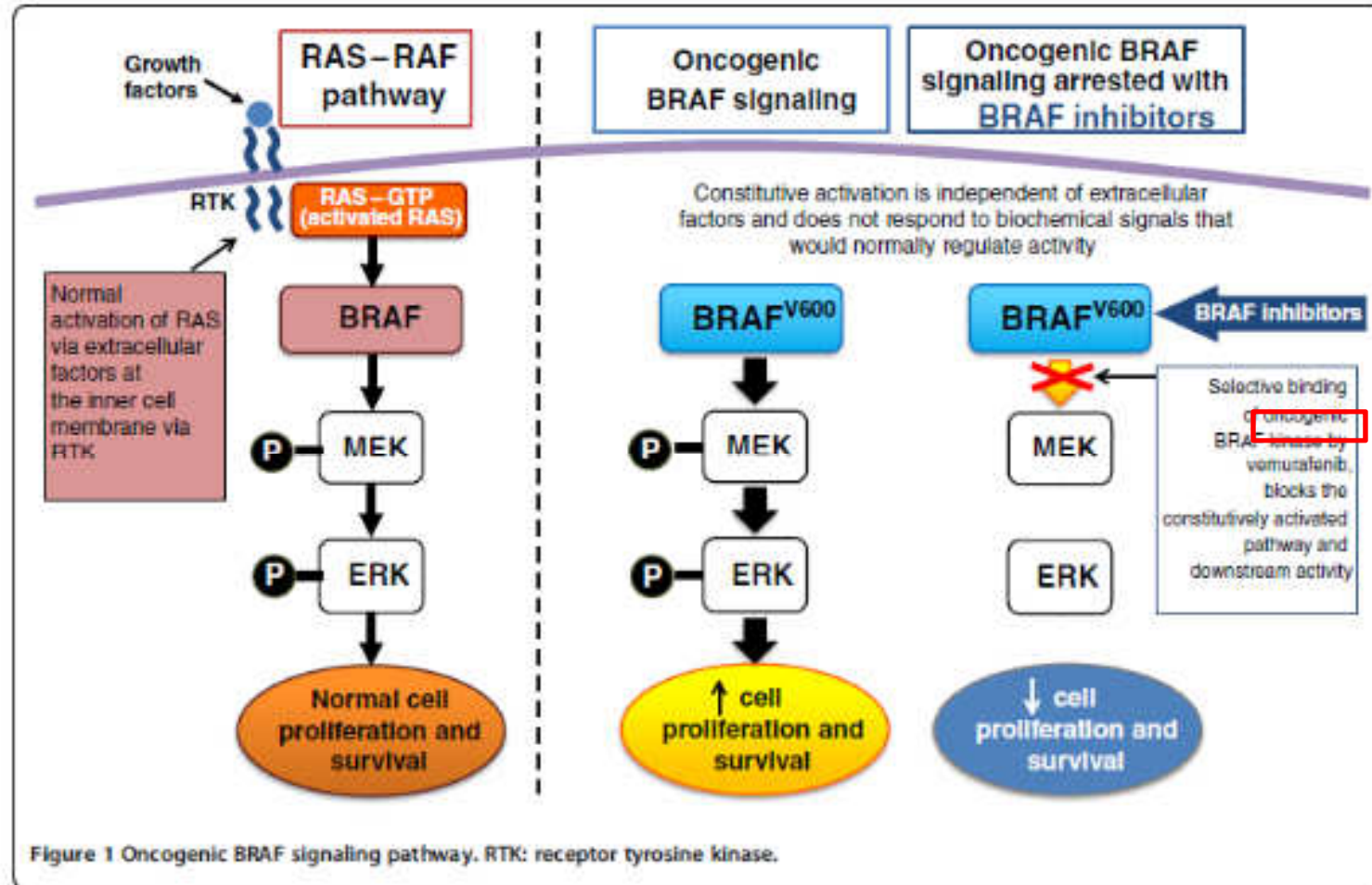
↓ decreased **PMCA4b** expression in
colon and breast cancer cells

Ribitzey et al., Cell Calcium, 42 (2007) 590-605

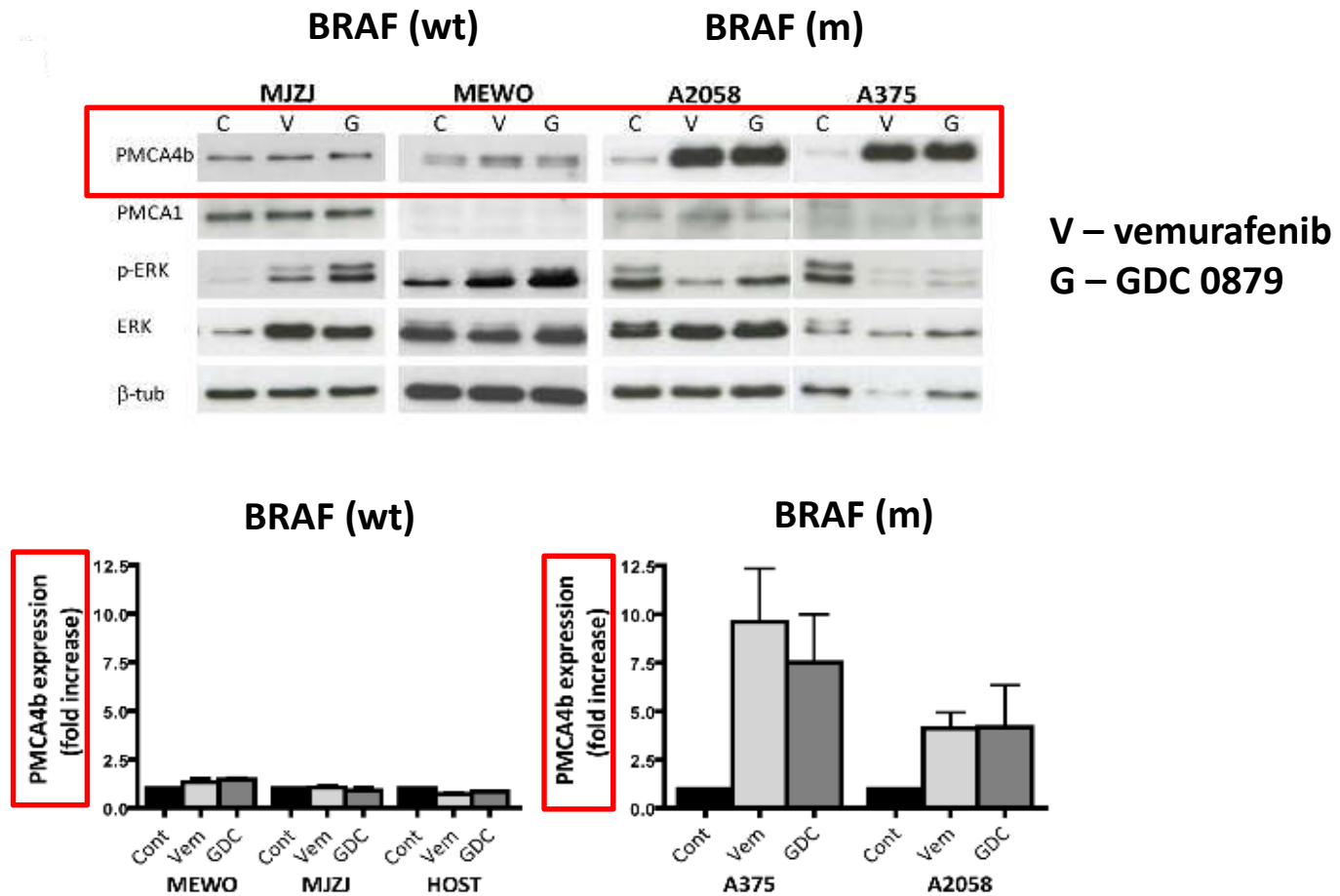
Lee et al., Cell physiology, 301 (2011) C969-976

Varga et al., Cell Calcium, 55 (2014) 78-92.

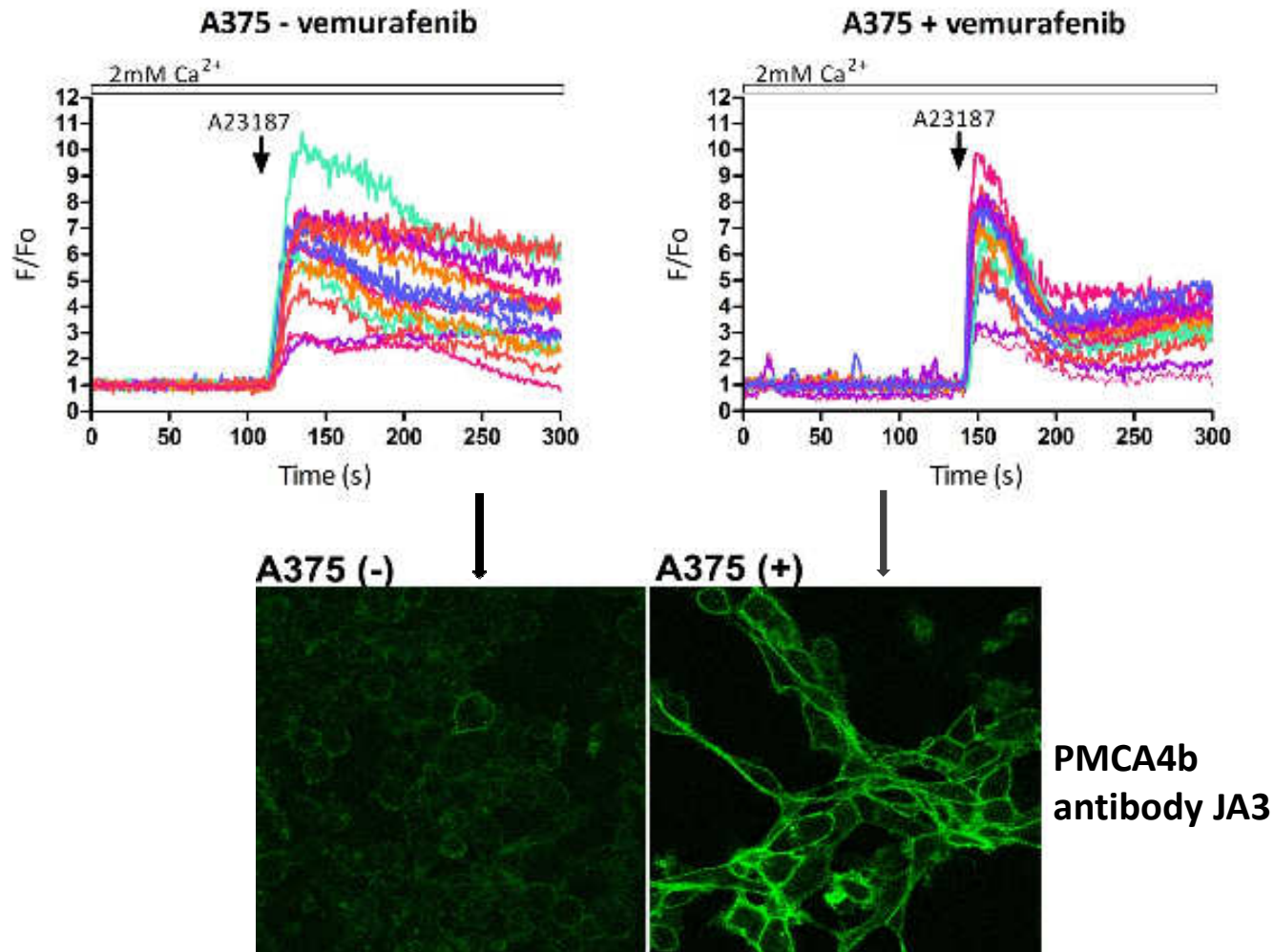
BRAF signaling in melanoma



PMCA4b is upregulated in BRAF mutant melanoma cells after BRAF inhibition

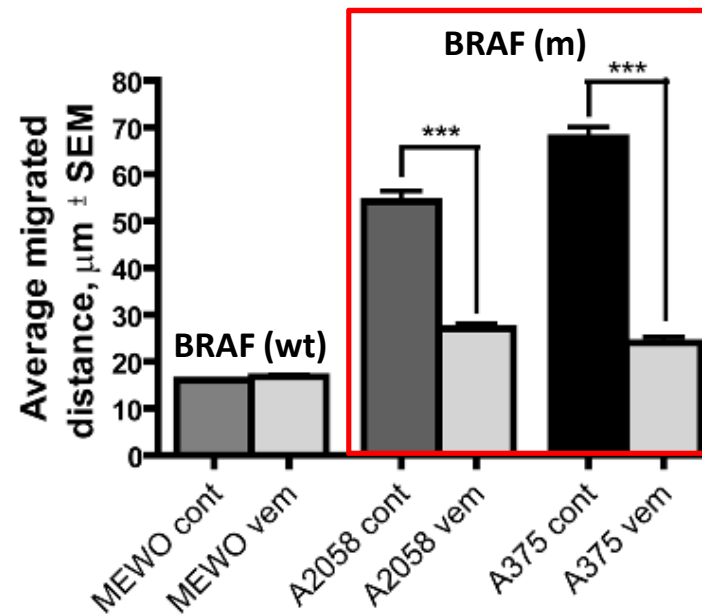
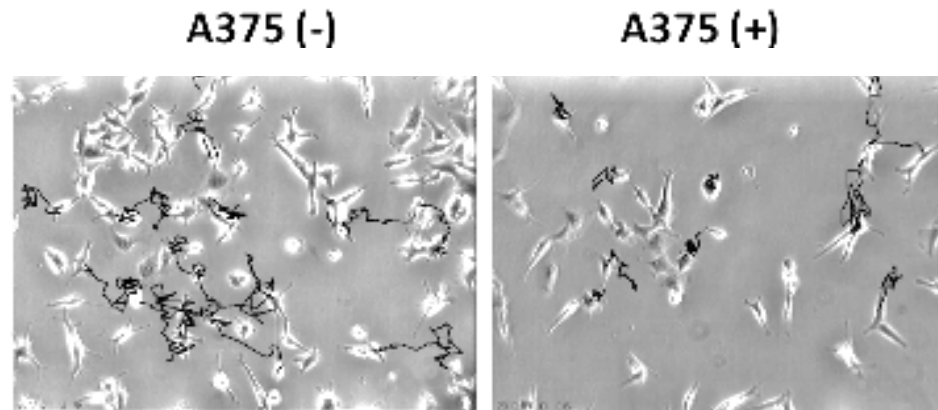


High PMCA4b abundance is associated with fast Ca^{2+} clearance

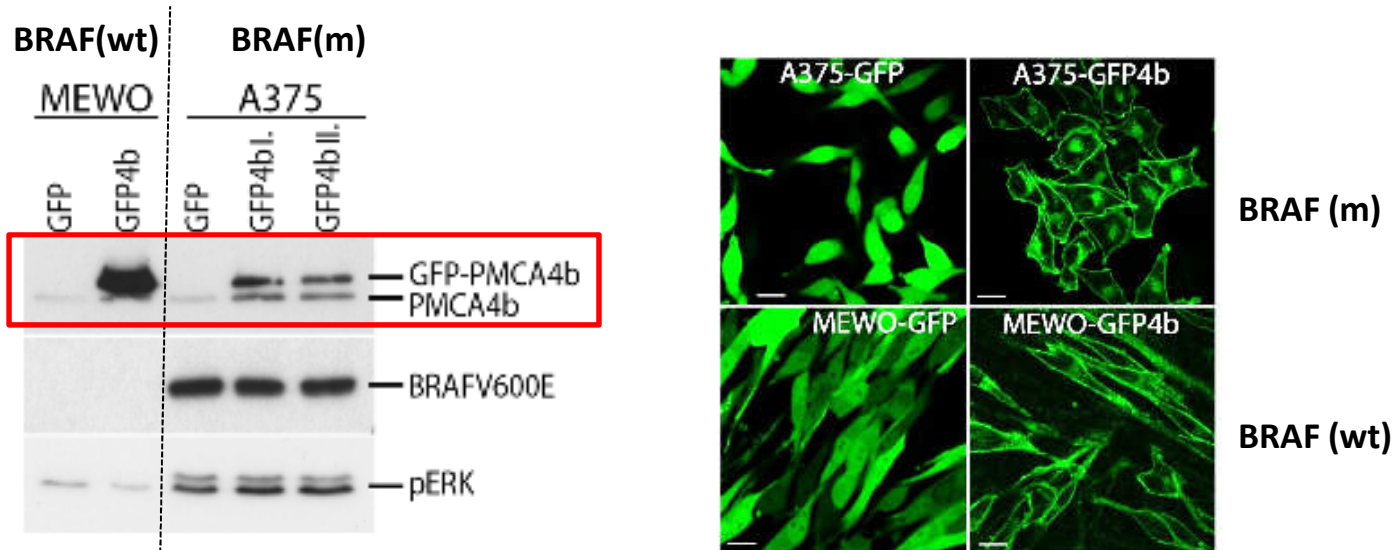


Luca Hegedűs et al, Journal of Cell Science, under revision

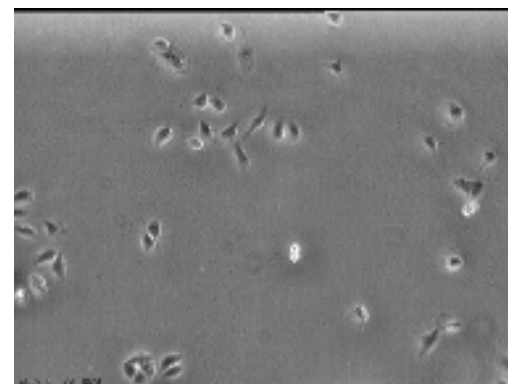
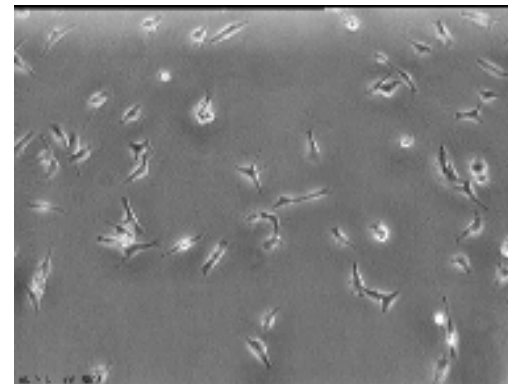
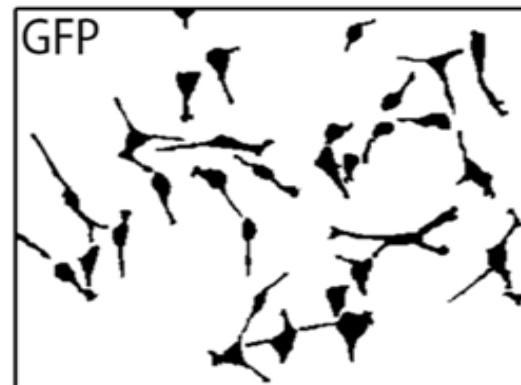
Vemurafenib inhibits migration of BRAF mutant A375 cells



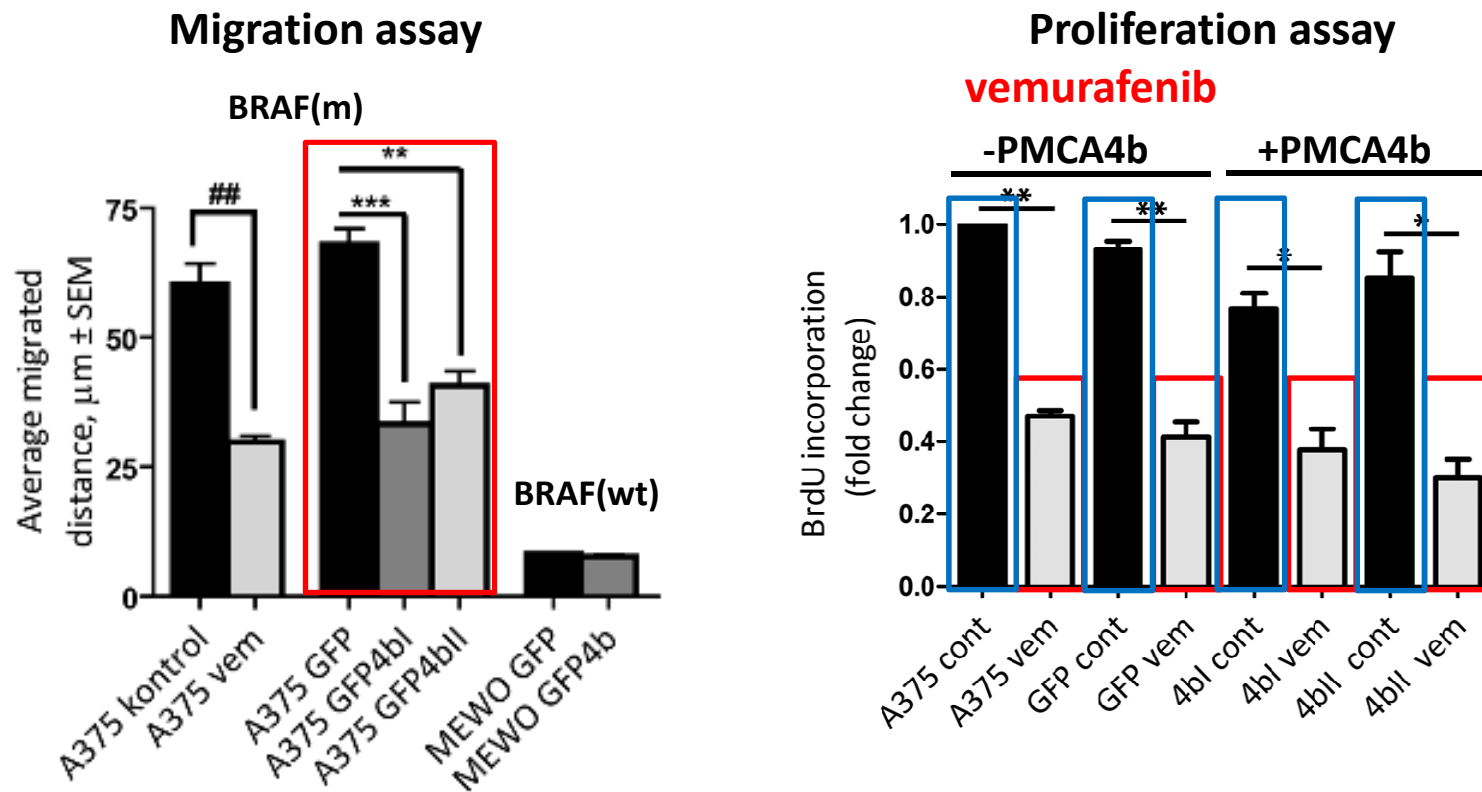
GFP-PMCA4b over-expression in melanoma cells



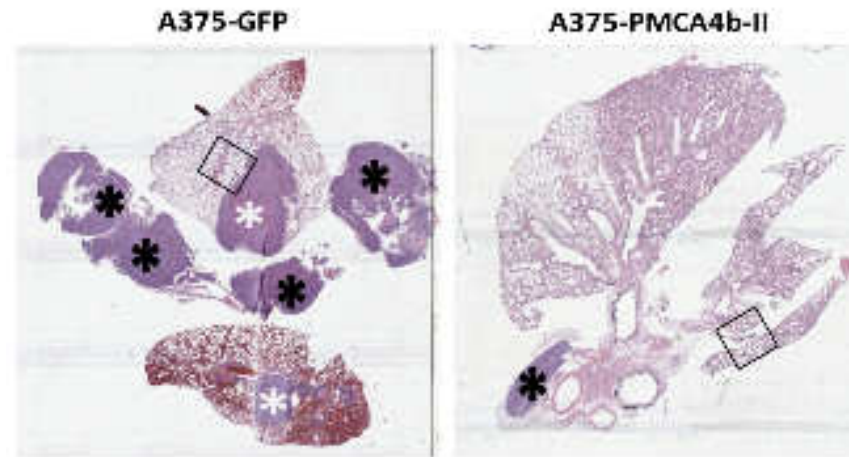
PMCA4b inhibits migration of BRAF mutant A375 cells



PMCA4b inhibits migration but does not affect proliferation of BRAF mutant A375 cells

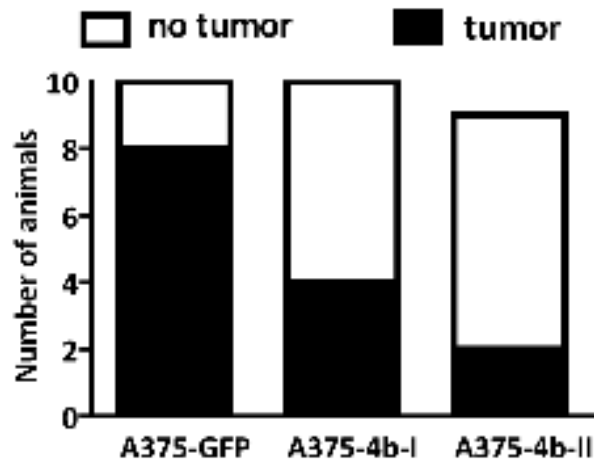


PMCA4b decreases metastasis *in vivo*



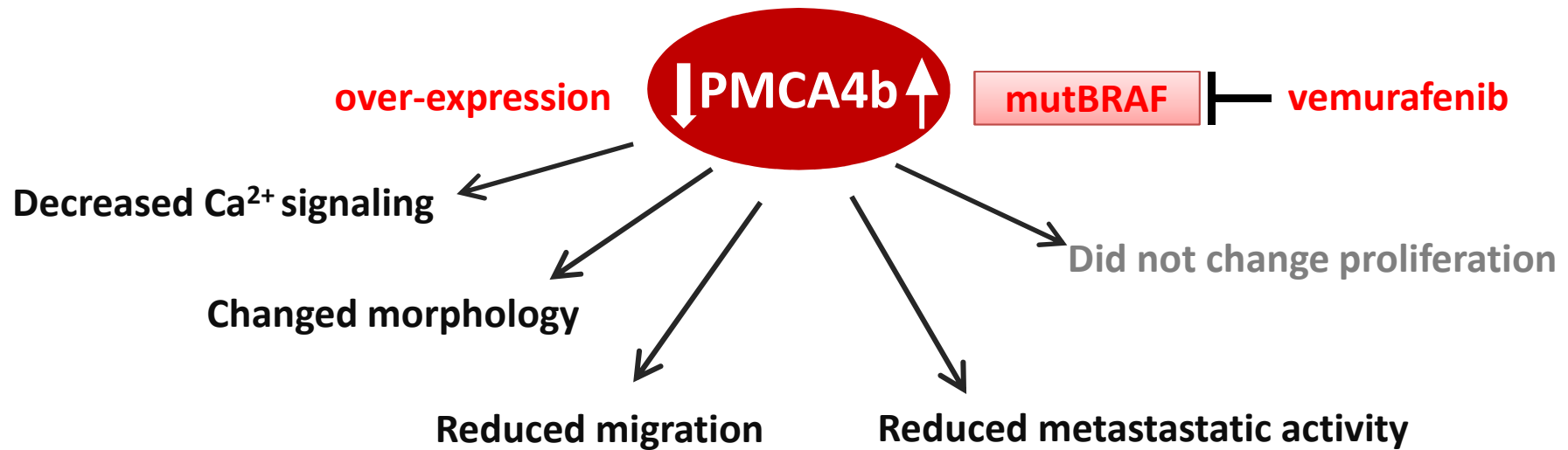
SCID mouse

Number of animals with lung metastasis



Luca Hegedűs et al, Journal of Cell Science, under revision

Conclusion



PMCA4b is a putative metastasis suppressor

Acknowledgement

Molecular Oncology Research Group
of HAS-SE, Budapest

Ágnes Enyedi
Luca Hegedűs
Krisztina Lór
Katalin Pászty
Rita Padányi
Karolina Varga

Balázs Hegedűs
Tamás Garay
Eszter Molnár
Agnes Bilecz

József Tímár

National Koranyi Institute of Pulmonology,
Budapest
Balazs Döme
Szilvia Török

Medical University of Vienna

Eniko Kallay
Luca Hegedűs
Walter Berger
Michael Grusch
Matthias Wolf

Funding

OTKA K101064
OTKA ANN110922
KTIA AIK12-1-2012-0025
TRANSRAT KMR-12-1-2012-0112