FAK inhibition combined with the RAF/MEK clamp avutometinib overcomes resistance to BRAF and MEK inhibitors and to immune checkpoint blockade in BRAFV600E mutant cutaneous melanoma

Simone Lubrano[1,2], Farhoud Faraji[1], Daniel Cervantes-Villagrana[1], Sydney Ramirez[1], Kuniaki Sato[1], Adam Officier[1], Nadia Arang[1], R., Damiano C. Rigiracciolo[1], Paola Y. Anguiano Quiroz[1], Sendi R Adame-Garcia[1], Antonietta Bacchiocchi[3], Ruth Halaban[3], Claudia Martini[2], Silvia Coma[4], Sheri Holmen[5], Jonathan A. Pachter[4], Andrew E. Aplin[6], J. Silvio Gutkind[1]

[1]Moores Cancer Center-Department of Pharmacology, University of California San Diego [2]Department of Pharmacy, University of Pisa [3]Department of Dermatology, Yale University [4]Verastem Oncology [5]School of Medicine, University of Utah [6]Department of Cancer Biology, Thomas Jefferson University

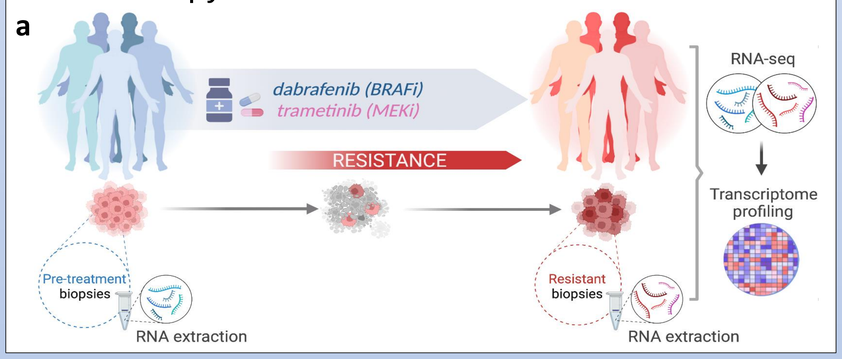
BACKGROUND

Metastatic melanoma is the most aggressive malignancy of the skin and **BRAFV600E** mutation is the most common genetic alteration in cutaneous melanoma[1]. Despite the advent of immune checkpoint inhibition (ICI) immunotherapy, only 40% of patients show long-term responses[2]. As such, combined therapy with BRAF and MEK inhibitors (BRAFi + MEKi) remains the standard of care for BRAFV600E melanoma.

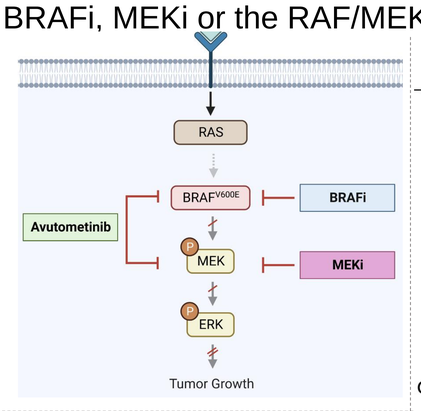
1. JAMA Dermatol. 2022;158(5):495-503. doi:10.1001/jamadermatol.2022.0160
2. N Engl J Med 2017; 377:1345-1356 DOI: 10.1056/NEJMoa1709684

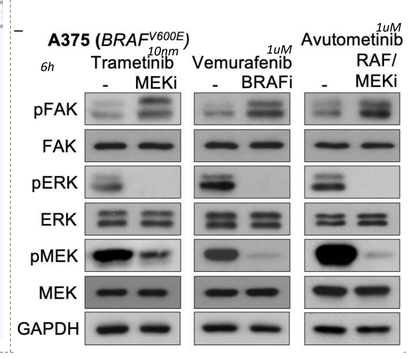
RESULTS

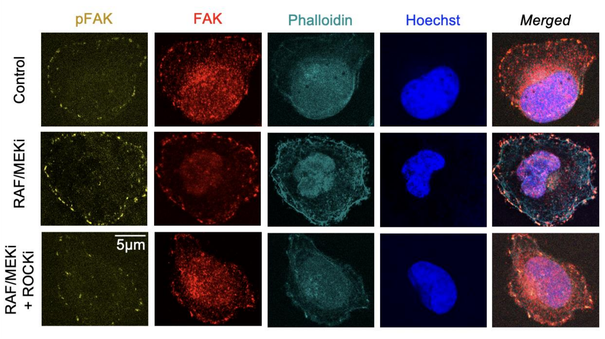
Transcriptome analysis of BRAFV600E (*Fig. a*) melanoma tumors derived from patients revealed that activation of extracellular matrix signaling, including focal adhesion signaling, is highly enriched in patients who experienced disease progression on BRAFi + MEKi therapy.

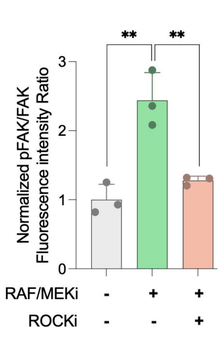


Increased activation of focal adhesion kinase (**FAK**) in human BRAFV600E A375 melanoma cells treated with BRAFi, MEKi or the RAF/MEK clamp avutometinib.









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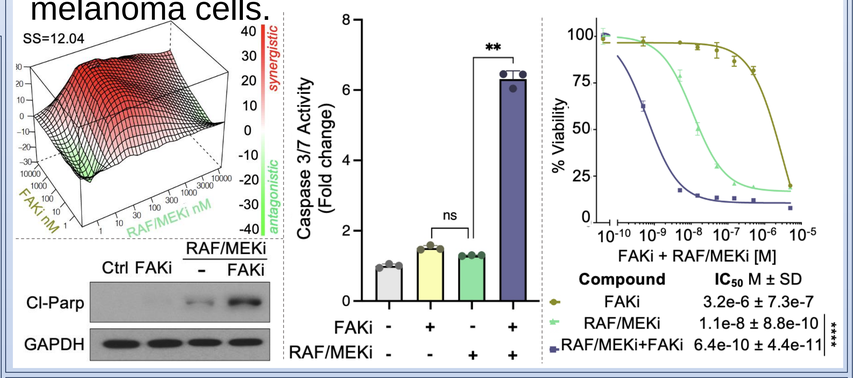
Mechanistically, avutometinib-mediated inhibition of the RAF/MEK/ERK pathway decreased RhoE/Rnd3 expression, thereby unleashing RhoA/FAK/AKT signaling *(data not shown)*.

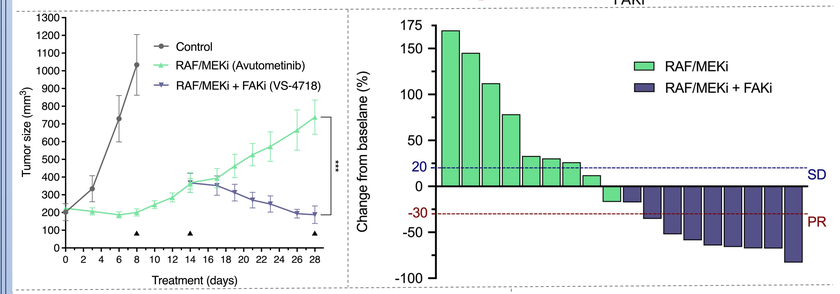
Hypothesis: FAK activation represents a resistance mechanism to BRAFi + MEKi and FAK inhibition (FAKi) might overcome resistance to BRAFi + MEKi.

Avutometinib demonstrated **synergistic** antiproliferative and pro-apoptotic activity when combined with FAKi in human BRAFV600E A375 melanoma cells.

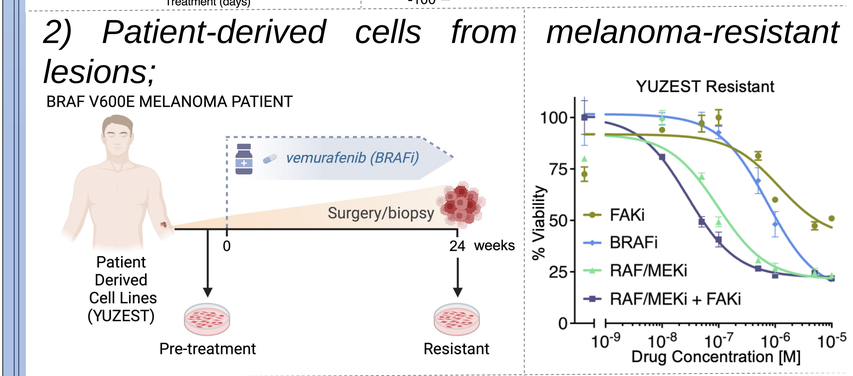


The combination of FAKi + avutometinib **overcame resistance** to MAPKi in:

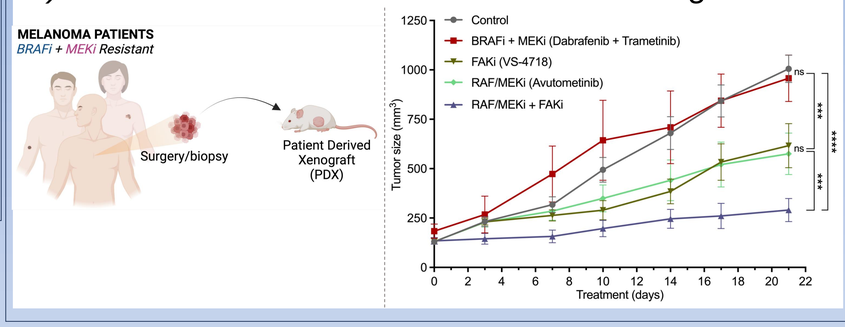
1) Melanoma xenografts;



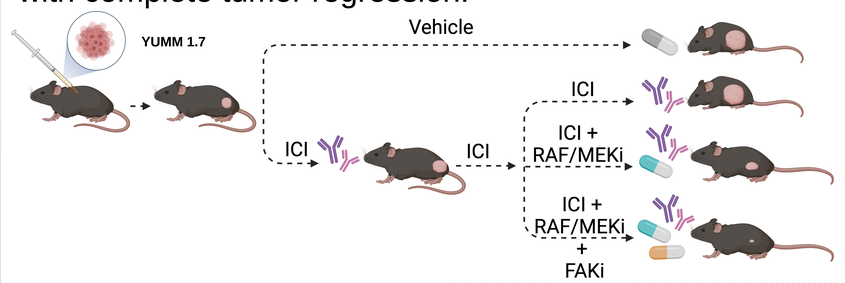
2) Patient-derived cells from melanoma-resistant lesions;

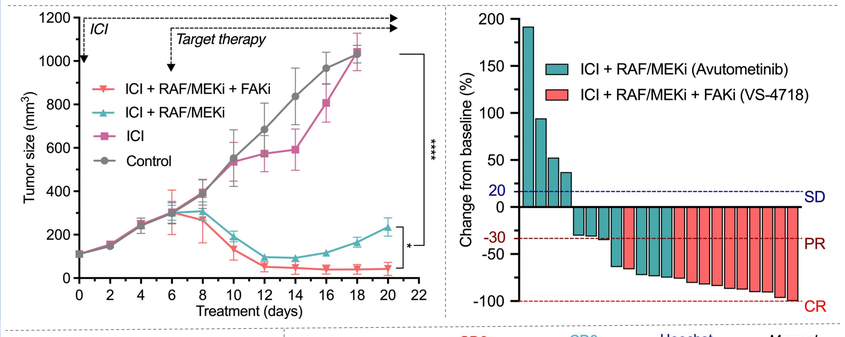


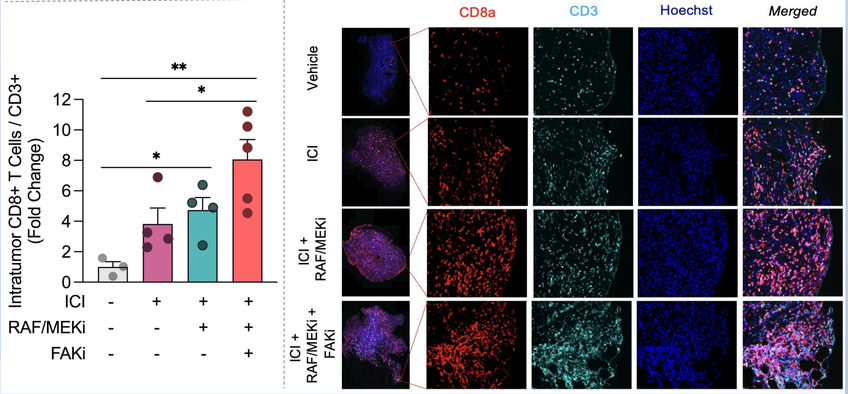
3)Resistant melanoma Patient-Derived Xenograft



While BRAFV600E melanoma YUMM 1.7 syngeneic tumors failed to respond to **ICI therapy**, addition of avutometinib ± FAKi inhibited tumor growth. We observed that tumors treated with ICI + avutometinib eventually developed resistance and escaped growth inhibition, but those treated with ICI + **combined avutometinib and FAKi displayed durable treatment responses**, often with complete tumor regression.







CONCLUSIONS

These findings provide rationale for clinical evaluation of the combination of avutometinib, FAK inhibitor (defactinib) ± ICI for patients with BRAFV600E melanoma, either in the primary setting or in patients who progress on BRAFi + MEKi and/or ICI therapy.