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Authors

Meyskens, Frank L
Liu-Smith, Feng
Fagundes, Tcharles

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Reversal of BRAF Resistance via Re-Establishment of Redox Balance Using a Unique Anti-Oxidant Strategy

Frank L Meyskens Jr[1], *Feng Liu-Smith*[1], *and Tcharles Fagundes*[1]
[1]*UCIrvine, USA*

The long term objective of our work is to develop novel combinatorial approaches that will prevent or cure patients with melanoma. The objective of this study is to lay out a mechanistic-based foundation for combination treatment co-targeting BRAF and NRAS in melanoma that has emanated from our chemoprevention approach. Inhibitors of BRAF kinase have produced high response rates in patients with BRAF mutant disease, but with rapid relapse; the addition of a MEK Inhibitor has led to a very modest increase in survival. Nevertheless, the majority of tumors progress in most patients as the malignancy adopts alternative survival signals to avoid extinction. NRAS plays an essential survival role when BRAF is inhibited; our data indicates that NRAS is regulated by the NRF2 transcription factor. A mt-ROS/NOX1/c-ROS/NRF2/NRAS signal cascade enables the Plx4032 treated cell to regain redox balance, thus resulting in resistance. We discovered that a specific flavonoid luteolin inhibits NRAS expression, perhaps via NRF2. Combinatorial treatment of Plx4032 with luteolin exhibited superb synergistic effect *in vitro* and excellent tumor regression effects *in vivo*. Hence, we hypothesize that a NRF2-mediated novel "redox adaptive response" after Plx4032 treatment modulates NRAS expression and activity; combination treatment with Plx4032 and luteolin disrupts this redox adaptive response by simultaneously co-targeting BRAF via Plx4032 and NRAS (perhaps via Nrf2). If you will, an intelligent shot-gun. Our ongoing work will investigate mechanisms related to redox adaptation as a basis for drug resistance, provide new data to strengthen this approach and propose to develop novel combinatorial treatment methods based on our additional understanding of these processes. Completion of this study will not only advance our knowledge of novel molecular mechanisms that underlie acquired drug resistance, but also yield novel combinatorial treatment methods for clinical use in patients with BRAF mutant melanoma, and may even extend the clinical usefulness of Vemurafnib to BRAF wild type patients or other cancer types harboring mutant BRAF.

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