NEW EGF RECEPTOR INHIBITORS AND GENISTEIN FOR THE NONSURGICAL TREATMENT OF LEIOMYOMAS

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ABSTRACT:

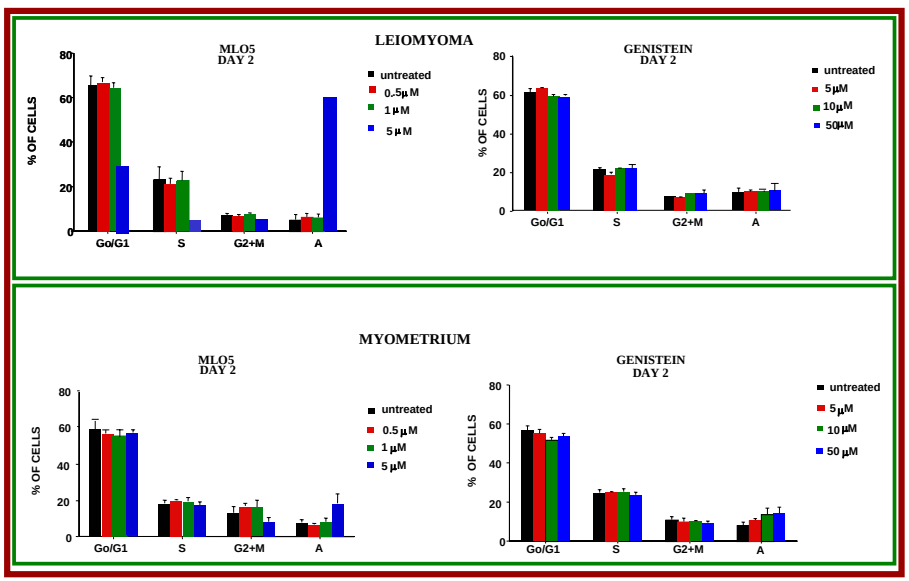
Introduction: Our study aimed to determine the potency of a new EGF receptor (EGFR) tyrosine kinase inhibitor- MLO5, and compare it to the natural PTKs inhibitor genistein-an abundant dietary constituent. We examined their potential as "Signal Transduction Therapeutics" for non-surgical treatment of leiomyomas underlying the effect of ovarian hormones.

MLO5 is more chemically stable and irreversible and is used as a biomarker for molecular imaging of EGRF-positive tumors. Genistein is an iso-flavinoid phytoestrogen, serves as a model for the design of synthetic PTKs inhibitors.

Results: Paired cultures of leiomyoma and normal myometrium samples were established and the suppressive effect of MLO5 and genistein on the cells prior and subsequent to steroidal hormone treatment was examined: cell proliferation, recovery after treatment, cell cycle analysis and WB analysis of relevant proteins were performed.

MLO5 very effectively suppressed cell proliferation, altered cell cycle distribution, induced apoptosis and inhibition of EGFR autophosphorylation. Genistein suppressed leiomyoma cell growth at 50μM and the cells did not recover after cessation of treatment, had no effect on cell cycle distribution, apoptosis and EGFR autophosphorylation . The inhibitory effects of MLO5 and genistein are unaffected by physiological concentrations of 17-β estradiol.

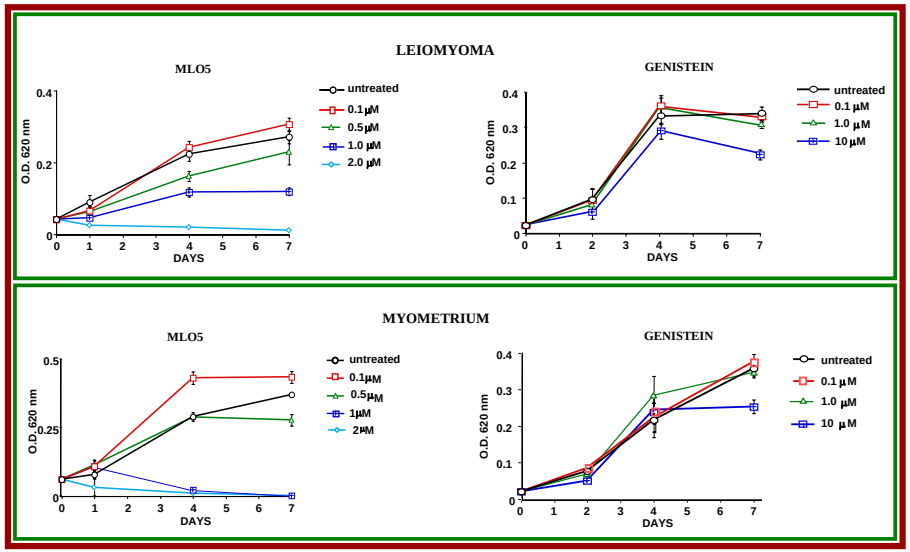
Conclusions: The suppressive properties of MLO5, unaffected by ovarian steroidal hormones, identifies it as a new potential agent for the non-surgical management of leiomyomas. The inhibitory action of newly developed inhibitors may be useful as a future non-chemotherapeutic therapy of leiomyomas.



The effect of MLO5 and genistein on the cell cycle phase distribution and apoptosis of leiomyoma and myometrial cell cultures at day 2.

MLO5 alters the distribution of leiomyoma cells in the cell cycle with a significant increase in the apoptotic cells. This effect is less significant on myometrium cells.

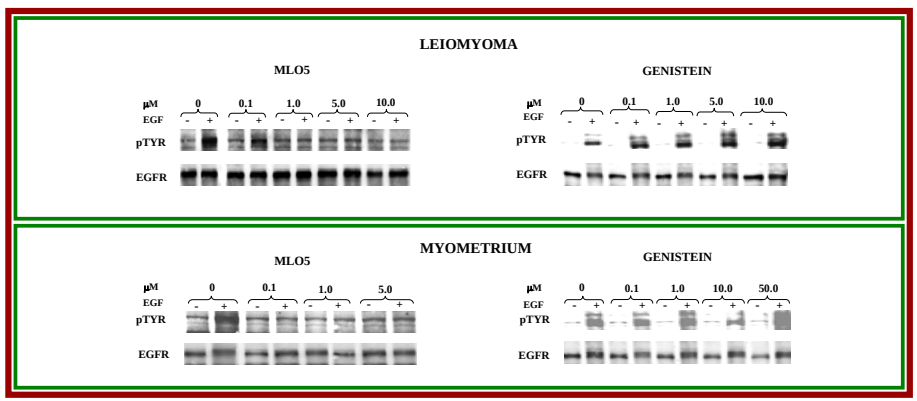
Genistein does not alter cell cycle phase distribution at concentrations up to 50μM.



The inhibitory effect of MLO5 and genistein on the proliferation and rescue of leiomyoma and myometrial cell cultures.

MLO5 at 2μM completely suppressed proliferation and the cells did not recover after cessation of treatment.

Genistein at 10μM caused about 38% growth inhibition.



The effect of MLO5 and genistein on EGFR and autophosphorylation–WB analysis.

MLO5 inhibited EGFR autophosphorylation in a dose-dependent manner.

Genistein had no effect on EGFR autophosphorylation.