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Anti-proliferative effects of GW441756, a novel inhibitor of NGFreceptor tyrosine kinase a (TRKA), in human sarcoma

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Several experimental data have shown a relevant involvement of Nerve Growth Factor (NGF) in neoplastic proliferation and survival. NGF acts through two receptors and two distinct transduction pathways: high affinity TrKA receptor connected to proliferation via AKT, and low-affinity p75 receptor connected to apoptosis via caspases.

Our previous studies have shown that TrKA inhibitors have a relevant anti-proliferative effects in neoplasia. GW441756 is a novel TrKA-inhibitor (IC_{50} = 2nM) that displays an higher selectivity on TrKA respect to previous inhibitors and a 100-fold selectivity over a range of other kinases. However, its biological effects in cancer cells is still unknown.

The aim of our study was to investigate in vitro the biological effects of this new inhibitor in human muscle sarcoma cancer cell line HTB114, at basal condition and following GW441756 administration.

As revealed by thymidine incorporation, GW441756 induced a dose-dependent decrease in neoplastic proliferation. Contemporaneously, Annexin V assay demonstrated a dramatic dose-dependent increase in apoptosis.

To further characterize these results, we studied AKT and caspases activation by cytofluorimetric analysis. In agreement to its anti-proliferative-pro-apoptotic effects, GW441756 did not induce AKT activation, but produced a relevant increase of caspase-3 that, in turn, leads to apoptosis.

In conclusion, GW441756 has a comparable anti-neoplastic effect respect to previous TrKA inhibitors, but with a lower effective dosage (10 μM vs 50 μM of other TrKA-inhibitors). Our data have a preclinical relevance to achieve anti-proliferative effects in muscular sarcomas by TrKA-inhibitors administration.

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Key words
GW441756, TrKA, Proliferation, Apoptosis, Sarcoma