Preclinical antitumor activity of novel DNA polymerase 1 (POLA1) inhibitors

Claudio Pisano, Lucio Merlini, Sergio Penco, Raffaella Cincinelli, Nadine Darwiche, Mario B. Guglielmi, Ilaria La Porta, Giacomo Signorino, Gabriele De Rubis, Fabiana Colelli, Francesco Cardile, Alessandra Fucci, Egildo L. D'Andrea and Sabrina Dallavalle

Abstract

The anti-proliferative and pro-apoptotic effects of Retinoid-Related Molecules (RRMs) are described as independent from Retinoids' receptors-mediated transcriptional activity. Prototypes of this class are CD437 and its more potent analogue ST1926, which have a strong antitumor activity by targeting DNA polymerase 1 alpha (POLA1) (Han et al. Nat Chem Biol. 2016; Abdel-Samad et al. AJCR, in press).

With aim to identify new RRMs with an improved pharmacological profile, we synthetized and screened a library of RRMs for their antitumor properties and inhibitory activity on POLA1. From this screening, four molecules, MIR002, MIR020, MIR072 and MIR075, were selected. All exert a potent anti-proliferative effect, with G1/S arrest and apoptosis, in more than 50 cancer cell lines derived from human hematological and solid tumors. From a mechanistic point of view, these RRMs modulate, at different extent, POLA1 activity and/or expression.

Notably, NSCLC cells harboring POLA1-L764F mutation (H460-R9A), are resistant to both CD437 and ST1926 (IC50>50 higher than the one of wild type H460 cells), while they are sensitive to MIR002, showing for this RRM-derivative an improved/different pharmacological profile with respect to CD437 and ST1926.

Hints on the possibility of these new RRMs to be orally absorbed were obtained using cancer cells overexpressing or not P-glycoprotein (Pgp), known as the major player limiting the oral absorption of several chemotherapeutic agents. Results from these experiments revealed that the Tested compounds are not Pgp substrate thus suggesting the possibility for their absorption via oral route

MIR002 in vivo activity was assessed in tumors from Malignant Mesothelioma derived cells (MM487), and lung cancer cells (H460 and H460-R9A). In all the evaluated models, MIR002 induced a strong Tumor Growth Inhibition either alone or in combination with cisplatin (TGI>61% and TGI>80-100%, respectively).

The treatment of orthotopic models of malignant mesothelioma (MM487) with MIR072 in combination with Cisplatin, resulted in a impressive synergic antitumor activity if compared to Cisplatin monotherapy (TGI 95% vs 55%).

Tests on orthotopic transplants of hepatocellular carcinoma cells (HepG2), showed that MIR020 has significant antitumor effects (TGI 72%).

Finally, the activity of MIR075 was evaluated on glioblastoma luciferase-expressing cells (U-87MG) intracranically injected. Also this compound displayed a significant tumor growth inhibition (TGI 72%), as measured by IVIS imaging system.

Taken together, the results from in vitro and in vivo experiments indicate that this new class of RRMs, including MIR002, MIR072, MIR020, and MIR075, modulate POLA1 functions and activate pro-apoptotic pathways. The large spectrum of antitumor activity, together with the high tolerability observed, opens the possibility for their clinical investigation in different population of cancer patients