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Colorectal cancer inhibition by BET inhibitor JQ1 is MYC-independent and not improved by nanoencapsulation
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Abstract
Bromodomain and extraterminal domain protein inhibitors (BETi) for cancer treatment did not convince during their first clinical trials. Their epigenetic mechanism of action is still not well understood, even if MYC is generally considered as its main downstream target. In this context, we intended to assess two new nanoformulations of the BETi JQ1 for the treatment of colorectal cancer (CRC). JQ1 was encapsulated at 10 mg/mL in lipid nanocapsules (LNC) or polymeric micelles (PM), both compatible for an intravenous administration. Their effect was compared with free JQ1 on several CRC cell lines in vitro and with daily intraperitoneal cyclodextrin (CD)-loaded JQ1 on the CT26 CRC tumor model in vivo. We showed that LNC preferentially accumulated in tumor, liver, and lymph nodes. LNC-JQ1 and CD-JQ1 similarly delayed tumor growth and increased median survival from 15 to 23 or 20.5 days. JQ1 altered MYC in only two among four CRC cell lines. This MYC-independence found in CT26 was confirmed in vivo by PCR and immunohistochemistry. The main explanation of the JQ1 anticancer effect was an increase in apoptosis. The investigation of its impact on the tumor microenvironment did not show significant effects. Finally, JQ1 association with irinotecan did not synergize in vivo with JQ1 nanoformulations. In conclusion, we demonstrated that the JQ1 anticancer effect was not improved by nanoencapsulation even if their tumor delivery was probably higher. MYC inhibition was not associated to JQ1 efficacy in the case of the CT26 CRC murine model. © 2022 Elsevier B.V.

Author Keywords
BET inhibitor; Colorectal cancer; JQ1; Lipid nanocapsule; Polymeric micelle

Index Keywords
4 (4 chlorophenyl) 2,3,9 trimethyl 6h thieno[3,2 f][1,2,4]triazolo[4,3 a][1,4]diazepine 6 acetic acid tert butyl ester, alpha2 integrin, bovine serum albumin, caspase 3, CD11b antigen, CD16 antigen, CD32 antigen, collagenase, cyclodextrin, deoxyribonuclease I, irinotecan, ketamine, Ki 67 antigen, lactic acid, lipid nanoparticle, Myc protein, nanocapsule, natural cytotoxicity triggering receptor 1, nimatek, platelet endothelial cell adhesion molecule 1, poloxamer, polysorbate 80, polyvinylidene fluoride, programmed death 1 ligand 1, sulforhodamine B, vinculin, xylazine, (+)-JQ1 compound, antineoplastic agent, azepine derivative, bromodomain and extra-terminal domain protein, human, Lipid Nanoparticles, liposome, Myc protein, MYC protein, human, nanoparticle, protein, triazole derivative; animal cell, animal experiment, animal model, animal tissue, antineoplastic activity, apoptosis, Article, biocompatibility, cancer inhibition, cancer survival, cancer transplantation, clinical assessment, colorectal cancer, comparative study, controlled study, CT26 cell line, drug delivery system, drug effect, drug efficacy, drug formulation, female, high performance liquid chromatography, HT-29 cell line, human, human cell, HuTu 80 cell line, immunohistochemistry, in vitro study, liver tissue, lymph node, MC-38 cell line, mouse, nanoencapsulation, nonhuman, oncogene myc, polymerase chain reaction, polymerization, real time polymerase chain reaction, reverse micelle, transmission electron microscopy, treatment failure, treatment indication, tumor growth, tumor microenvironment, tumor model, tumor vascularization, tumor-associated macrophage, animal, Bagg albino mouse, colorectal tumor, drug delivery system, intravenous drug administration, metabolism, tumor cell line; Animals, Antineoplastic Agents, Azepines, Cell Line, Tumor, Colorectal Neoplasms, Drug Delivery Systems, Female, Humans, Infusions, Intravenous, Liposomes, Mice, Mice, Inbred BALB C, Nanoparticles, Proteins, Proto-Oncogene Proteins c-myc, Triazoles

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