بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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MONA MAGHRABY

CAIRO UNIVERSITY
FACULTY OF VETERINARY MEDICINE
DEPARTMENT OF PHARMACOLOGY

Novel Study of The Application of Nano-Pharmacology on The Field of Oncology

THESIS PRESENTED BY

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BVSc, Cairo Univ., 2010
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For the Degree of
Ph.D. of VSc.

(Pharmacology)

Under Supervision of

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The defense committee on 11-2-2021 decided to nominate Ms.Ghazal Nabil Abdelmonsif Khaleifa for Ph.D. degree in Veterinary Medicine Sciences (Pharmacology). The proposed thesis was entitled **"Novel Study of The Application of Nano-Pharmacology on The Field of Oncology".**

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Abstract

Breast cancer is the second leading cause of cancer-related death among American women after lung cancer. Breast cancer is molecularly classified based on the presence or absence of specific receptors to luminal A, luminal B, HER-2+, and TNBC. TNBC represents about 15-20% of whole breast cancer cases. Due to the absence of these receptors, TNBC has limited therapeutic options. Our study focused on the combination strategy to better tackle these issues, which has remarkable strides in improving patient outcomes and survivability. The ability of momelotinib (MMB), a JAK/STAT inhibitor, to sensitize the TNBC to apoptosis inducer (CFM-4.16) was evaluated in MDA-MB-231 and MDA-MB-468. MMB + CFM-4.16 combinations with a combination index (CI) less than or equal to 0.5, was selected for *in vitro* and *in vivo* studies. MMB was combined with CD44 directed polymeric nanoparticles (NPs) loaded with CFM-4.16, namely CD44-T-PNPs, which selectively delivered the payload to CD44 overexpressing TNBC with a significant decrease in cell viability associated with a high dose reduction index (DRI). The mechanism underlying their synergism is based on the simultaneous downregulation of P-STAT3 and the up-regulation of CARP-1, which induced ROS-dependent apoptosis leading to caspase 3/7 elevation, cell shrinkage, DNA damage, and suppressed migration. CD44-T-PNPs showed a remarkable cellular internalization, demonstrated by uptake of a rhodamine B dye *in vitro* and S0456 (NIR dye) *in vivo*. S0456 was conjugated to NPs to form CD44-T-PNPs/S0456 that simultaneously delivered CFM-4.16 and S0456 parenterally with selective tumor targeting, prolonged circulation, minimized off-target distribution. This study investigates a promising NPs platform for CD44 mediated theranostic that can be combined with JAK/STAT inhibitors to treat TNBC.

Keywords: TNBC; Theranostic; Nanomaterial; Momelotinib; CFM-4.16; JAK/STAT3; CARP-1; Esterase-responsive nanoparticle; Combination therapy.

Dedication

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