



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



MONA MAGHRABY



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التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



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CAIRO UNIVERSITY
FACULTY OF VETERINARY MEDICINE
DEPARTMENT OF PHARMACOLOGY



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

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BVSc, Cairo Univ., 2010

MVSc, Cairo Univ., 2013

For the Degree of
Ph.D. of VSc.

(Pharmacology)

Under Supervision of

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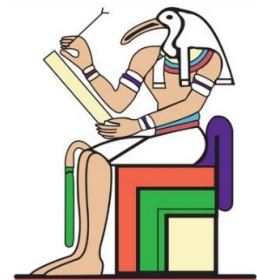
Eugene Applebaum College of Pharmacy and Health Sciences

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(2021)



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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

To the queen of my heart (My Mom) and the inspiring of my soul (My Dad). The success I've had in my life is entirely due to your love, care, support, and encouragement. Thanks for believing in me, putting up with me for so long, and cutting my slack in the tough times. Thanks to the effort you have put into making me who I am today. I would never be here without you, as you are always the secrete behind my achievements.

To my beloved family Dr. Rehab, Ms. Dina, Eng. Ahmed, Miss Razan, Rinad, Yassin, and Kenzy. I can't find the perfect words to thank each one of you for the amount of love you surrounded me with, the amount of courage you push me with, and the amount of confidence you offered me.

Special Thanks to my uncle Ahmed Badr and my cousin Amr Ahmed Badr for your determination in showing me I can do it! Thanks for your perseverance, support, and love.

Acknowledgment

At the moment when all your hard work has been paid off, and in the hope that this work may in some way contribute to alleviating cancer payload, I would like to express my sincerest thanks and gratitude to,

*First and foremost, to **The Almighty ALLAH** for his countless giving to me.*

***Prof. Hosny Awad Hassan Elbanna**, Professor of Pharmacology, Faculty of Veterinary Medicine, Cairo University. Thanks for converting my mistakes into lessons, pressure into productivity, and weakness into strengths. Working with you is an honor; working without you is an absolute horror and working under your supervision is a pleasure and an experience that I truly treasure. Thanks for paving my hard way and bringing out the best of me.*

***Prof. Mohamed Atef Ahmed Shihata**, Professor of Pharmacology, Faculty of Veterinary Medicine, Cairo University. For his unlimited help and support.*

***Dr. Arun K. Iyer**, Associate Professor and Director of U-BiND Systems Laboratory, Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, MI, USA. For giving me the chance to be a part of his team.*

***Dr. Hussein Ali Hussein**, Professor of Virology and Vice Dean of postgraduate and Research Affairs, Faculty of Veterinary Medicine, Cairo University. For his time, effort, and prompt responses.*

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