BIOGRAPHICAL SKETCH

NAME: Hammouda, Hossam

eRA COMMONS USER NAME (credential, e.g., agency login): hammouda.hossam

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Cairo University	BS	07/2012	Pharmacy
Cairo University	MS	08/2018	Pharmaceutical Chemistry
Dongguk University	PHD	08/2023	Medicinal Chemistry

A. Personal Statement

With more than 12 years of research experience spanning chemical biology, medicinal chemistry, and machine learning, my work is driven by a fundamental question: how can we understand and therapeutically modulate complex immune receptor signaling networks that have historically resisted conventional drug discovery approaches? My research focuses on challenging biological targets, including proteins with disordered extracellular domains, cryptic or transient binding pockets, and signaling pathways mediated through protein–protein interactions rather than classical enzymatic active sites. To address these challenges, I have developed and prospectively validated several open-source machine learning platforms that accelerate key stages of drug discovery, including HTS-Oracle for screening prioritization, LigandForge for de novo ligand generation, and TargetTrace for target engagement and off-target prediction.

Unlike many computational approaches that are evaluated primarily through retrospective benchmarks, these platforms have been tested in prospective drug discovery campaigns against experimentally validated therapeutic targets. HTS-Oracle, for example, reduced experimental screening requirements by more than 99% for TREM2 and CHI3L1 while achieving up to 176-fold enrichment compared with traditional high-throughput screening approaches. These platforms serve as a foundation for the exploration of previously inaccessible therapeutic targets and biological mechanisms. Through the integration of medicinal chemistry, chemical biology, structural biology, and machine learning, I have contributed to the discovery of direct TREM2 agonists, CHI3L1 inhibitors, LAG3 inhibitors, and modulators of additional immune signaling pathways. These studies have provided new insights into the structural basis of receptor modulation while generating promising therapeutic leads for diseases with significant unmet medical need.

As a newly appointed Assistant Professor of Pharmaceutical Sciences at the University of Massachusetts Lowell, my independent research program will focus on understanding the structural and molecular determinants that govern signaling and ligand recognition in difficult-to-drug extracellular and immune-related targets. By integrating machine learning-driven structural prediction, biophysics, chemical biology, and medicinal chemistry, my laboratory will develop generalizable strategies for discovering and optimizing therapeutics against biologically important yet pharmacologically challenging targets. This work will establish a mechanistic framework for targeting currently “undruggable” proteins and accelerate the development of new therapies for cancer, neurodegenerative disorders and other diseases with high unmet clinical need.

1. Nada H, Yuan S, El Gaamouch F, Cho S, Kuncewicz K, Calvo-Barreiro L, Gabr MT. TREM2 activation by first-in-class direct small molecule agonists: DEL screening, optimization, biophysical validation, and functional characterization. Eur J Med Chem. 2026 Jan 15;302(Pt 3):118358. PubMed Central PMCID: PMC12892748.
2. Nada H, Wolber G, Gabr MT. Targeting CAPON to modulate the CAPON-NOS Axis: a computational approach. Comput Struct Biotechnol J. 2025;27:4813-4824. PubMed Central PMCID: PMC12636374.
3. Nada H, Calvo-Barreiro L, Abdel-Rahman SA, Gabr MT. Discovery and validation of LAGi-DEL: A nanomolar LAG-3 inhibitor that reverses immune suppression in tumor-immune co-culture models. Eur J Med Chem. 2026 Jan 5;301:118204. PubMed PMID: 41016188.

4. Nada H, Kim S, Lee K. PT-Finder: A multi-modal neural network approach to target identification. Comput Biol Med. 2024 May;174:108444. PubMed PMID: 38636325.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2026 - Assistant Professor of Pharmaceutical Sciences, University of Massachusetts Lowell, Lowell, MA
2024 - 2026 Postdoctoral Associate, Weill Cornell Medicine
2023 - 2024 Postdoctoral Fellow, Dongguk University

Honors

2023 - 2024 Research excellence award, Dongguk University
2022 - 2023 Best academic performance Award, Korean government Ministry of Education
2021 - 2022 Best academic performance Award, Korean government Ministry of Education

C. Contribution to Science

1. Modulating Immune Receptors with Small Molecules. Despite their significant therapeutic potential, no small-molecule immune checkpoint inhibitors have yet received FDA approval for clinical use. To advance this field toward its first clinically viable candidate, I have led and collaborated on multiple breakthrough discoveries: potent small-molecule CHI3L1 and LAG3 inhibitors reported to date, the first-in-class direct small-molecule TREM2 agonists, and novel small-molecule modulators targeting CD28, SLIT2 and CAPON. These discoveries were the results of the integration of medicinal chemistry, chemical biology, biophysical validation, immunology, pharmacology, computational chemistry, and structural biology. The resulting leads from these investigations have shown effectiveness in modulating diseases such as glioblastoma and Alzheimer's disease with favorable drug-like and pharmacokinetic properties.

    a. Nada H, Zhang L, Kaur B, Vázquez NG, Gabr M. Restoring amyloid clearance: Z17 promotes astrocytes to clear Alzheimer's plaques via CHI3L1 inhibition. Int J Biol Macromol. 2026 Apr;354:151402. PubMed PMID: 41825670.
    b. Nada H, Yuan S, Gaamouch FE, Cho S, Gabr MT. Small Molecule Agonists of TREM2 Reprogram Microglia and Protect Synapses in Human Alzheimer's Models. bioRxiv. 2026 Jan 21; PubMed Central PMCID: PMC12871600.
    c. Nada H, Zhang L, Kaur B, Gabr MT. CHI3L1-targeted small molecules as glioblastoma therapies: Virtual screening-based discovery, biophysical validation, pharmacokinetic profiling, and evaluation in glioblastoma spheroids. Eur J Med Chem. 2025 Nov 5;297:117960. PubMed Central PMCID: PMC12371121.

2. Innovative Machine Learning Platforms for Drug Discovery. The integration of machine learning (ML) into drug discovery is rapidly transforming the field, with early results demonstrating its ability to streamline development timelines, enhance predictive accuracy, and overcome traditional bottlenecks. However, many computational models lack prospective validation which limits their practical utility in real-world drug development. To address this critical gap, I developed three prospectively validated, open-source ML platforms that accelerate key drug discovery processes through improved screening efficiency, predictive accuracy, and target identification. The first platform is HTS-Oracle which showed substantial improvements in both efficiency and discovery quality across three challenging immune-related targets: TREM2, CHI3L1, and CD28. HTS-Oracle was evaluated on three distinct and clinically validated yet undruggable immune targets with no approved small-molecule therapeutics: TREM2 (cryptic binding pockets), CHI3L1 (disordered secreted glycoprotein) and CD28 (PPI-dominated immune checkpoint). HTS-Oracle achieved 176-fold and 87.5-fold enrichment over traditional HTS for CHI3L1 and TREM2, respectively.

More importantly, HTS-Oracle managed to reduce the experimental screening requirements by >99% for TREM2 and CHI3L1, and 70% for CD28. PT-Finder is the second platform which I developed based on a neural network architecture. PT-Finder integrates structural features of small-molecule inhibitors with target sequence data to rapidly identify protein targets, enabling both drug repurposing and efficient compound library screening. The third platform was a Random Forest-based model which predicts biological activity of compounds before their synthesis to reduce the number of compounds synthesized and improve hit optimization outcomes. Prospective validation of the platform in an EGFR study yielded 18 compounds with high potency and antiproliferative activity. Together, these platforms demonstrate how rigorously validated computational approaches can expand chemical space exploration, streamline experimental workflows, and accelerate therapeutic development.

a. Nada H, Sipos-Szabó L, Bajusz D, Keserű GM, Gabr M. LigandForge: A Web Server for Structure-Guided De Novo Drug Design. bioRxiv. 2026 Apr 3; PubMed Central PMCID: PMC13060250.
b. Nada H, Calvo-Barreiro L, Fuchs N, Kaur B, Cho S, Upadhyay S, Meanwell N, Gabr M. HTS-Oracle: Experimentally validated AI-enabled prioritization for generalizable small molecule hit discovery. bioRxiv. 2025 Dec 1; PubMed Central PMCID: PMC12694594.
c. Nada H, Gul AR, Elkamhawy A, Kim S, Kim M, Choi Y, Park TJ, Lee K. Machine Learning-Based Approach to Developing Potent EGFR Inhibitors for Breast Cancer-Design, Synthesis, and In Vitro Evaluation. ACS Omega. 2023 Sep 5;8(35):31784-31800. PubMed Central PMCID: PMC10483653.

3. Computer-Aided Discovery of Selective DDR1 Inhibitors. Dysregulation of the discoidin domain receptor 1 (DDR1), a collagen-activated receptor tyrosine kinase, has been implicated in multiple human cancers, including non-small cell lung carcinoma (NSCLC), ovarian cancer, glioblastoma, and breast cancer, as well as in various inflammatory and neurological disorders. Despite the discovery of several selective DDR1 inhibitors over the past two decades, their clinical advancement has been hindered by challenges such as high cytotoxicity, poor kinome selectivity, and unfavorable drug metabolism and pharmacokinetics profiles. In this work, I employed an integrative approach combining computational and experimental strategies to identify and optimize novel DDR1 inhibitors. The workflow began with ultra-large-scale virtual screening to identify promising small-molecule hits, followed by millisecond-scale molecular dynamics simulations and competitive binding assays to validate predicted hits. By leveraging machine learning (ML)-guided optimization, I successfully improved the potency of the initial hits into the nanomolar range while enhancing pharmacokinetic (PK) and pharmacodynamic (PD) properties. Notably, I discovered a shallow cryptic pocket within the DDR1 binding interface, which plays a crucial role in small-molecule interactions with the target. These projects demonstrate my ability to integrate multidisciplinary expertise to drive advancements in drug discovery.

   a. Nada H, Dayem AA, Kim S, Park Y, Jaemin C, Park Y, Bin Lee S, Gabr M, Cho SG, Lee K. Targeting DDR1 with novel synthesized antagonists delays cellular aging and enhances wound healing in mesenchymal stem cells. Biomed Pharmacother. 2026 Apr;197:119182. PubMed PMID: 41793971.
   b. Nada H, Kim S, Jaemin C, Park S, Choi Y, Lee MY, Lee K. From pixels to druggable leads: A CADD strategy for the design and synthesis of potent DDR1 inhibitors. Comput Methods Programs Biomed. 2024 Sep;254:108318. PubMed PMID: 38991374.
   c. Nada H, Lee K, Gotina L, Pae AN, Elkamhawy A. Identification of novel discoidin domain receptor 1 (DDR1) inhibitors using E-pharmacophore modeling, structure-based virtual screening, molecular dynamics simulation and MM-GBSA approaches. Comput Biol Med. 2022 Mar;142:105217. PubMed PMID: 35032738.

4. Carbonic Anhydrase Inhibitor Discovery and Development. Carbonic anhydrases (CAs) regulate a wide range of physiological processes, including respiration, pH homeostasis, ion transport, bone resorption, and gastric fluid secretion. Dysregulation of these enzymes has been implicated in multiple diseases, making carbonic anhydrase inhibitors (CAIs) an important therapeutic class. Over the past few decades, CAIs have been developed for diverse clinical applications, including as anticonvulsants, topically acting antiglaucoma agents, and anticancer drugs. In my research, I discovered several novel classes of small-molecule CA inhibitors and demonstrated their therapeutic potential by evaluating their effects on cell

proliferation and signaling pathways. Furthermore, I provided key evidence that non-primary sulfonamides can effectively inhibit carbonic anhydrases, broadening the chemical space for CA-targeted drug discovery and paving the way for a new class of therapeutics. These findings highlight my ability to integrate medicinal chemistry and chemical biology to uncover novel inhibitors and advance drug discovery for critical enzyme targets.

a. Lee HY, Elkamhawy A, Al-Karmalawy AA, Nada H, Giovannuzzi S, Supuran CT, Lee K. Chalcone-based benzenesulfonamides as potent and selective inhibitors for human carbonic anhydrase II: Design, synthesis, in vitro, and in silico studies. Arch Pharm (Weinheim). 2024 Nov;357(11):e2400069. PubMed PMID: 39240035.

b. Nada H, Elkamhawy A, Abdellattif MH, Angeli A, Lee CH, Supuran CT, Lee K. 4-Anilinoquinazoline-based benzenesulfonamides as nanomolar inhibitors of carbonic anhydrase isoforms I, II, IX, and XII: design, synthesis, in-vitro, and in-silico biological studies. J Enzyme Inhib Med Chem. 2022 Dec;37(1):994-1004. PubMed Central PMCID: PMC8973350.

c. Awadallah FM, Bua S, Mahmoud WR, Nada HH, Nocentini A, Supuran CT. Inhibition studies on a panel of human carbonic anhydrases with N1-substituted secondary sulfonamides incorporating thiazolinone or imidazolone-indole tails. J Enzyme Inhib Med Chem. 2018 Dec;33(1):629-638. PubMed Central PMCID: PMC6009853.