



## Where Traditional Drug Discovery Meets Modern Technology in the Quest for New Drugs

Mohammed M Al Qaraghuli<sup>1,2\*</sup>, Abdullah R Alzahrani<sup>1,3</sup>, Kanidta Niwasabutra<sup>1</sup>, Mohammad A Obeid<sup>1</sup> and Valerie A Ferro<sup>1</sup>

<sup>1</sup>Department of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, UK

<sup>2</sup>Department of Chemical & Process Engineering, University of Strathclyde, 75 Montrose Street, UK

<sup>3</sup>Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al-Qura University, Saudi Arabia

### Abstract

Identifying novel compounds or improving bioavailability of drugs requires extensive screening, *in vitro* and *in vivo* testing and subsequent commercialisation. Traditional methods can be labour intensive and time-consuming. Use of modern technologies can reduce these challenges and is best achieved through collaboration with researchers specialising in different research fields. The range of research activities carried out in our lab is outlined and demonstrates the diversity of techniques used in our drug discovery programme.

**Keywords:** Drug discovery; Natural products; Biotherapeutics; Nanoparticles; Molecular dynamics simulations

### Background

Development of new medicines are aimed at curing or preventing diseases or conditions without suitable therapeutic product availability, reducing side effects, improving quality of life, shrinking the cost on healthcare systems, while significantly extending patients' lives. However, the sophisticated process of drug discovery and development can be an extensive process lasting over 7-10 years, with a striking average cost of \$2.6 billion for each successful drug that reaches the market [1]. These daunting cost and time parameters originate from the scientific, technical, and regulatory challenges needed to understand drug mechanism of action for complex diseases at molecular level. Achieving tangible success subsequently requires investment in highly sophisticated technologies, advanced manufacturing processes, and creative research approaches to tackle the ever-growing cost and time of the entire process.

Academic research is often the starting point to develop a hypothesis that correlates the activation or inhibition of a protein or signalling pathway to achieve a therapeutic end-point [2]. This proceeds to basic research to identify a target and to validate the selection. Progression to a lead discovery phase to justify a particular drug development effort follows on from the target selection and validation steps. The lead discovery steps undoubtedly require intensive and robust searches to find a drug-like small molecule or biological candidate that can progress into preclinical, and if successful, into clinical trial, and eventual progression to an approved medicine.

Our research group's activities are diverse and carefully designed to cover both ends of the lead identification spectrum; through the separation and evaluation of novel compounds from natural sources, structural analysis of bio therapeutics, and conjugation of nanoparticles to small molecules, antibodies, DNA, and peptides to generate ground-breaking vaccines or "nano-Trojan horses" [3-8]. Our approach is in basic research, lead discovery and preclinical development (Figure 1). We then generally collaborate with industry (small or large Pharma) to achieve the clinical development phase. This approach applies, whether dealing with natural products, bio therapeutics or nanoparticles.

### Natural Product Research

One abundant source of natural products is derived from the plant kingdom, which have fuelled the drug discovery process with numerous molecules (small drug-like to complex polymers) over the past decades [9,10]. The World Health Organization (WHO) has highlighted the wide utilisation of traditional medicine in developing countries [11]. Our group exploits the rich biodiversity of

### OPEN ACCESS

#### \*Correspondence:

Mohammed M Al Qaraghuli,  
Department of Pharmacy and  
Biomedical Sciences, University of  
Strathclyde, 161 Cathedral Street, UK,  
E-mail: mohammed.al-qaraghuli@  
strath.ac.uk

**Received Date:** 02 Mar 2017

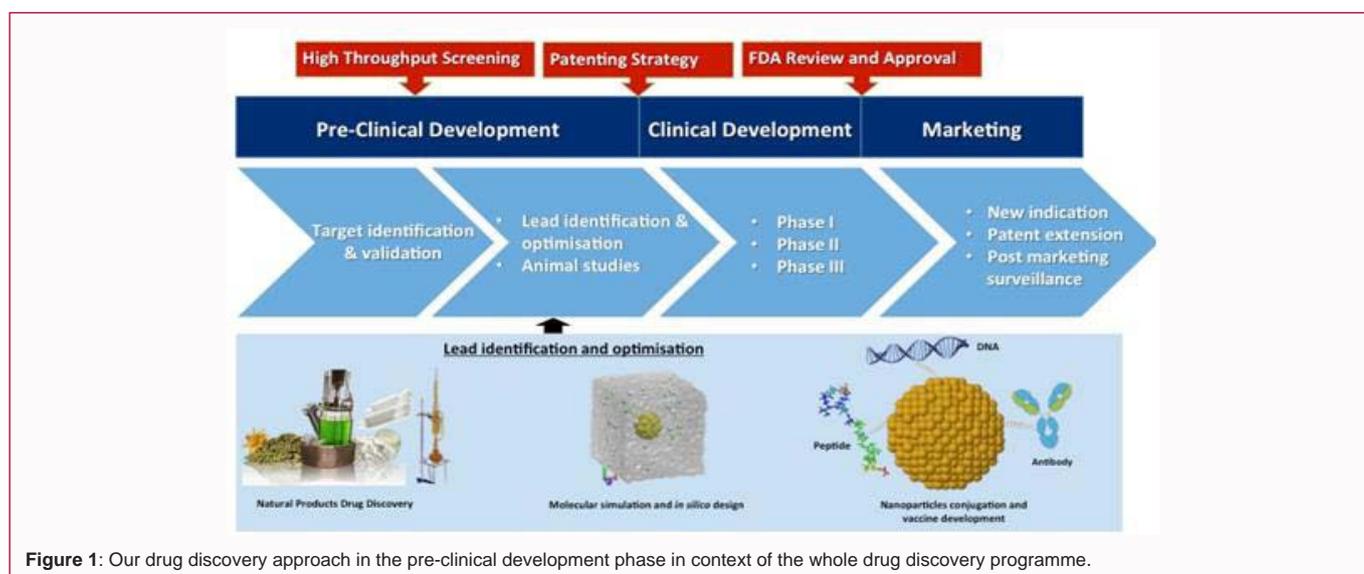
**Accepted Date:** 02 Jun 2017

**Published Date:** 04 Jun 2017

#### Citation:

Al Qaraghuli MM, Alzahrani AR,  
Niwasabutra K, Obeid MA, Ferro VA.  
Where Traditional Drug Discovery  
Meets Modern Technology in the Quest  
for New Drugs. *Ann Pharmacol Pharm.*  
2017; 2(11): 1061.

**Copyright** © 2017 Al Qaraghuli  
MM. This is an open access article  
distributed under the Creative  
Commons Attribution License, which  
permits unrestricted use, distribution,  
and reproduction in any medium,  
provided the original work is properly  
cited.



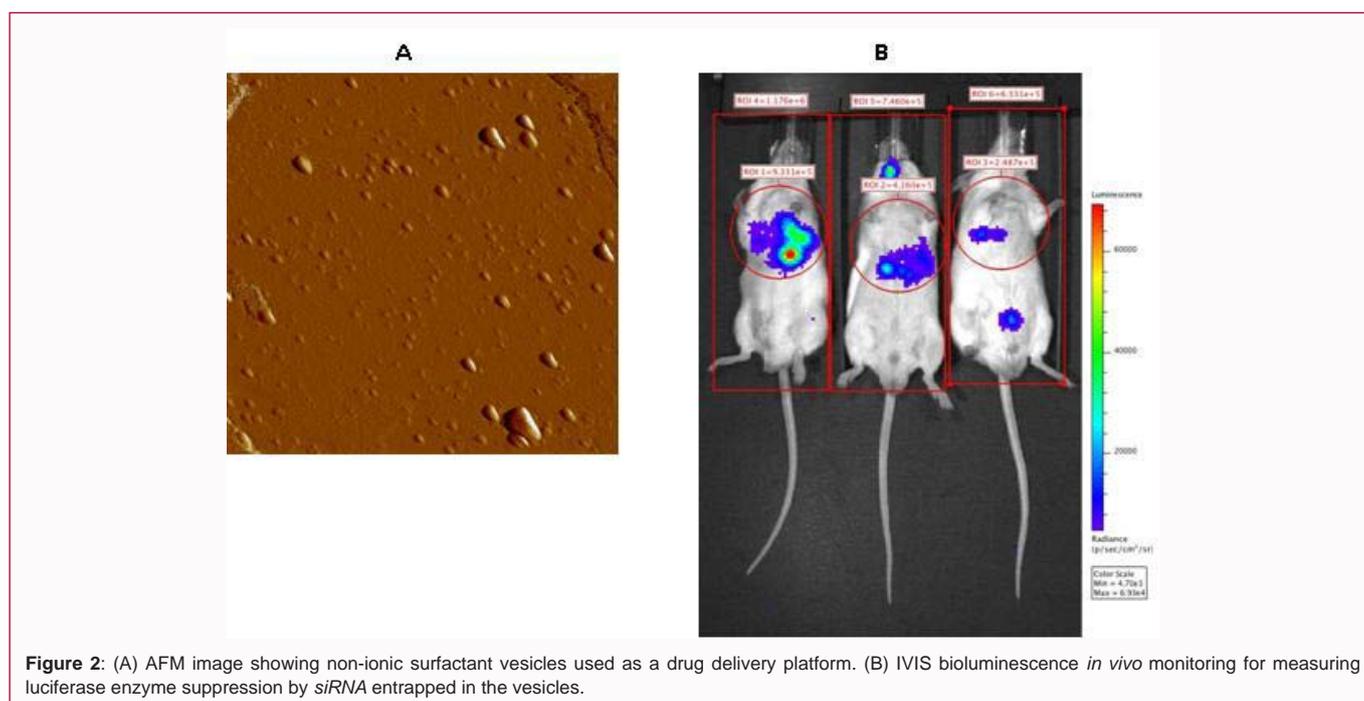
natural sources such as plants, marine organisms, fungi, microbes and insects which are crucial resources for identifying key candidate molecules [12]. The natural products field was estimated to produce or be involved in ~50% of all small drug molecules between the years 2000-2006, and 10 out of the 44 approved small molecules in 2014 were derived from natural products [13,14]. Traditionally, natural products are extracted from source materials, concentrated, fractionated, and purified. Various traditional and advanced techniques have been developed to isolate pure natural products, and the pros and cons of each technique have been comprehensively addressed [9,15-17]. Our group utilizes traditional techniques, such as Soxhlet solvent extraction or infusions to extract constituents, followed by thin layer chromatography (TLC) and nuclear magnetic resonance (NMR) analysis for chemical structure elucidation, mass spectrometry as a confirmatory technique. Open column chromatography (gel filtration, vacuum liquid chromatography), is also used. These techniques are employed in the early part to achieve extraction, isolation and characterisation of compounds. For further separation and isolation of pure compounds we utilize modern chromatography (medium pressure and high pressure liquid chromatography systems) and to identify compound location within tissues we employ matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). Compounds isolated in this way from different natural sources have consistently shown promising therapeutic potential against various microorganisms, cancer, and diabetes [3,4,18,18-22]. A range of bioassays are employed including 96-well plate high throughput screening (HTS), enzymatic assays such as  $\alpha$ -amylase,  $\alpha$ -glucosidase, dipeptidyl peptidase IV (DPPIV), protein tyrosine phosphatase 1B (PTP1B), and lipase assays to investigate the anti-diabetic and anti-obesity activities. Active compounds from HTS are investigated further for their ability to enhance glucose uptake in cell lines such as Caco-2, 3T3 L1 and HepG2 cells. For subsequent evaluation of mechanisms of action we have introduced new technologies such as molecular biology (polymerase chain reaction (PCR) and ribonucleic acid (RNA) sequencing) which can show which genes are affected and therefore the subsequent research can be tailored towards specific disease pathways. Metabolomics is used to advance our understanding and development of any potential lead molecules [3,23-25].

## Bio Therapeutic Developments

The other face of the drug discovery coin relies on the development of novel bio therapeutics, including innovative vaccine formulations, which have recently gained significant momentum. The shift in prominence toward the development of protein therapeutics or antibodies is in part reflected by the growing prevalence of biologic agents in the portfolios of major biopharmaceutical companies. The annual number of first approvals was in the range of 5-8 in 2014 onwards, with 53 novel antibody therapeutics in Phase 3 studies in 2016, and ~ 210 novel antibody therapeutics in each of Phase 1 and 2 of clinical development [26]. Financially, the global sales revenue for all monoclonal antibody products was nearly \$75 billion in 2013, and expected to reach \$125 billion by 2020 [27]. This unprecedented attraction to antibodies originates from the remarkable structural flexibility of these proteins to selectively recognise different antigen classes such as proteins, carbohydrates, and lipids, and challenging happens like pharmaceutical small molecules, pesticides, and even biomarkers that can contribute to the potential detection of life on other planets like Mars [8,28-37]. Antibodies not only represent potential therapeutics, but can be implemented in diverse bespoke applications such as immunodiagnostics, biosensors, photo thermal therapies, and nanoparticle conjugation for drug delivery. Such approaches are illustrated through projects we have been developing in collaboration with a number of small and medium enterprises. These projects are based on optimising the conjugation of antibodies to nanoparticles and solid surfaces, and will exploit sophisticated computational and laboratory techniques to incorporate such platforms within point-of-care testing (POCT) diagnostic kits.

## Drug Delivery Formulations

Drug delivery is another concept that is laterally implemented with drug discovery in our group if the newly discovered compounds are inactive, toxic, or unselective [32]. Improving the bioavailability and effects of these compounds, or reducing their toxicities, can be achieved by loading them into different types of delivery systems [33]. These have the ability to deliver a therapeutic agent to a particular site of the body at a specific rate [34]. A wide range of delivery systems are available such as lipid nanoparticles, carbon nanotubes, and metal nanoparticles [35]. The characteristics of the delivery system with its load can be optimised in terms of size, charge, loading efficiency,



**Figure 2:** (A) AFM image showing non-ionic surfactant vesicles used as a drug delivery platform. (B) IVIS bioluminescence *in vivo* monitoring for measuring luciferase enzyme suppression by *siRNA* entrapped in the vesicles.

stability, and drug release [36]. Our group has developed a wide range of delivery systems being mindful of the changing pharmaceutical and market needs, for example the desire for mucosal delivery to replace parenteral administration [5,37]. Moreover, our group utilises the most advanced techniques for nanoparticle characterisations such as dynamic light scattering and Nansizer for determination of particle size and atomic force microscopy (AFM) for morphological analysis [5]. Figure 2A shows AFM morphology of one of our non-ionic surfactant vesicles (NISV) that is currently being used in our lab for the delivery of different therapeutic agents. We are constantly utilising new innovations and have moved away from traditional thin film hydration methods used commonly in lipid particle manufacture to highly advanced microfluidic [5,6]. Moreover, various other delivery approaches have been adopted for the selective delivery of vaccines against influenza, tetanus toxoid, and mucosal tolerance [7,9,37]. Currently, we are working on the development of highly advanced lipid nanoparticles for effective delivery of short interfering RNA (*siRNA*) using advanced techniques for evaluating the delivery system such as PCR, fluorescence activated cell sorting and *in vivo* bioluminescence imaging. Figure 2B shows one of our experiments for monitoring luciferase enzyme suppression by *siRNA* by measuring the bioluminescence through an *in vivo* imaging system (IVIS).

Both drug discovery and delivery processes have benefited from the continuous efforts to apply computational power to the combined chemical and biological space in order to streamline drug discovery and development. In the biomedical arena, computer-aided or *in silico* design is being utilised to accelerate and facilitate hit identification, hit-to-lead selection, optimise the pharmacokinetic/pharmacodynamics profile, anticipate binding modes, structural analysis, and to avoid safety issues [38]. In the post genomic era, computer-aided drug design has significantly diversified its range of applications, spanning most stages of target identification to lead discovery, and from lead optimisation to preclinical or clinical trials [39-40]. Furthermore, molecular dynamics and computer simulations have been successfully used to analyse interfacial dynamics and

electrostatics, and binding of small molecules, macro-bio molecules, or DNA to nanoparticles [41-48]. These advanced computational technologies can be highly beneficial to investigate best epitope presentation to the immune system. In this respect we have identified a number of peptide antigens using molecular dynamics simulations to provide comprehensive conformational and structural analysis of these peptides for an optimum bespoke conjugation to nanoparticles, and to use these conjugates in the development of highly effective contraceptive or cancer vaccines.

## Conclusion

From our experience, drug discovery programmes have to evolve with advances in new technologies. While traditional techniques have their place, modernisation can provide new insights that could never be realised using the older and established methodologies. We need to embrace the “omics” era and the plethora of tools it provides, but be open and flexible to expand our approaches. This necessitates collaboration, not only in multidisciplinary networks, but also requires closer links to be established with academic-industrial or academic-NHS partnerships. In this way, the time taken to achieve a successful viable end-product can be realised quicker and at lower overall cost.

## References

1. Peters S. Tufts CSDD R&D Cost Study Now Published | Tufts Center for the Study of Drug Development. 2016.
2. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. *Br J Pharmacol.* 2011;162(6):1239-49.
3. Siheri W, Zhang T, Ebiloma GU, Biddau M, Woods N. Chemical and Antimicrobial Profiling of Propolis from Different Regions within Libya. *PLoS One.* 2016;11(5):e0155355.
4. Mamoon-Ur-Rashid null, Ali S, Alamzeb M, Igoli J, Clements C, Shah SQ, et al. Phytochemical and antitypanosomal investigation of the fractions and compounds isolated from *Artemisia elegantissima*. *Pharm Biol.* 2014;52(8):983-7.

5. Obeid MA, Gebril AM, Tate RJ, Mullen AB, Ferro VA. Comparison of the Physical Characteristics of Monodisperse Non-ionic Surfactant Vesicles (NISV) Prepared Using Different Manufacturing Methods. *Int J Pharm.* 2017;521(1-2):54-60.
6. Obeid MA, Khadra I, Mullen AB, Tate RJ, Ferro VA. The effects of hydration media on the characteristics of non-ionic surfactant vesicles (NISV) prepared by microfluidics. *Int J Pharm.* 2017;516(1-2):52-60.
7. Mann JFS, Ferro VA, Mullen AB, Tetley L, Mullen M, Carter KC, et al. Optimisation of a lipid based oral delivery system containing A/Panama influenza haemagglutinin. *Vaccine.* 2004;22(19):2425-9.
8. Al Qaraghuli MM, Ferro VA. Analysis of the binding loops configuration and surface adaptation of different crystallized single-domain antibodies in response to various antigens. *J Mol Recognit.* 2016.
9. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol Adv.* 2015; 33(8): 1582-614.
10. Shen B. A New Golden Age of Natural Products Drug Discovery. *Cell.* 2015;163(6):1297-300.
11. WHO. World Health Organization-Traditional Medicine Strategy 2014-2023 [Internet]. WHO. 2013.
12. Cragg GM, Newman DJ. Natural product drug discovery in the next millennium. *Pharm Biol.* 2001;39(1):8-17.
13. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. *J Nat Prod.* 2007;70(3):461-77.
14. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs from 1981 to 2014. *J Nat Prod.* 2016;79(3):629-61.
15. Bucar F, Wube A, Schmid M. Natural product isolation--how to get from biological material to pure compounds. *Nat Prod Rep.* 2013; 30(4): 525-45.
16. Sasidharan S, Chen Y, Saravanan D, Sundram KM, Yoga Latha L. Extraction, Isolation and Characterization of Bioactive Compounds from Plants' Extracts. *Afr J Tradit Complement Altern Med.* 2010;8(1):1-10.
17. McRae J, Yang Q, Crawford R, Palombo E. Review of the methods used for isolating pharmaceutical lead compounds from traditional medicinal plants. *The Environmentalist.* 2007;27(1):165-74.
18. Alzahrani A, Abbott G, Young LC, Igoli J, Gray AI, Ferro VA. Phytochemical and biological investigation of *Calliandra surinamensis* as a potential treatment for diabetes. *Planta Med.* 2016;81(S 01):S1-381.
19. Ali S, Igoli J, Clements C, Semaan D, Alamzeb M, Rashid MU, et al. Antidiabetic and antimicrobial activities of fractions and compounds isolated from *Berberis brevissima* Jafri and *Berberis parkeriana* Schneid. *Bangladesh J Pharmacol.* 2013;8(3):336-42.
20. Kasim LS, Ferro V, Odukoya OA, Ukpo GE, Seidel V, Gray AI, et al. Cytotoxicity of isolated compounds from the extracts of *Struchium sparganophora* (Linn) Ktze asteraceae. *Pak J Pharm Sci.* 2011;24(4):475-8.
21. Habeeb F, Shakir E, Bradbury F, Cameron P, Taravati MR, Drummond AJ, et al. Screening methods used to determine the anti-microbial properties of Aloe vera inner gel. *Methods.* 2007;42(4):315-20.
22. Niwasabutra K, Igoli JO, Young L, Gray AI, Ferro VA. Effects of crude extracts from mushrooms on different cancer cell lines. *Planta Med.* 2016;81(S 01):S1-381.
23. Ben Zaed SA. Chemical and Molecular Analysis of Libyan Desert Plants used in Camel Feed. University of Strathclyde PhD thesis. 2016.
24. Tusiimire J, Wallace J, Woods N, Dufton MJ, Parkinson JA, Abbott G, et al. Effect of Bee Venom and Its Fractions on the Release of Pro-Inflammatory Cytokines in PMA-Differentiated U937 Cells Co-Stimulated with LPS. *Vaccines.* 2016;19(2):4-16.
25. Alonezi S, Tusiimire J, Wallace J, Dufton MJ, Parkinson JA, Young LC, et al. Metabolomic Profiling of the Effects of Melittin on Cisplatin Resistant and Cisplatin Sensitive Ovarian Cancer Cells Using Mass Spectrometry and Biolog Microarray Technology. *Metabolites.* 2016;13:6.
26. Reichert JM. Antibodies to watch in 2016. *M Abs.* 2016;8(2):197-204.
27. Ecker DM, Jones SD, Levine HL. The therapeutic monoclonal antibody market. *M Abs.* 2015;7(1):9-14.
28. Al Qaraghuli MM, Palliyil S, Broadbent G, Cullen DC, Charlton KA, Porter AJ. Defining the complementarities between antibodies and haptens to refine our understanding and aid the prediction of a successful binding interaction. *BMC Biotechnol.* 2015;15:99.
29. MacKenzie R, To R. The role of valency in the selection of anti-carbohydrate single-chain Fvs from phage display libraries. *J Immunol Methods.* 1998;220(1-2):39-49.
30. Wong-Baeza C, Reséndiz-Mora A, Donis-Maturano L, Wong-Baeza I, Zárate-Neira L, Yam-Puc JC, et al. Anti-Lipid IgG Antibodies Are Produced via Germinal Centers in a Murine Model Resembling Human Lupus. *Front Immunol [Internet].* 2016.
31. Kang HJ, Kim HJ, Cha SH. Isolation of human anti-serum albumin Fab antibodies with an extended serum-half life. *Immunol Lett.* 2016;169:33-40.
32. Cragg GM, Grothaus PG, Newman DJ. Impact of natural products on developing new anti-cancer agents. *Chem Rev.* 2009;109(7):3012-43.
33. Aqil F, Munagala R, Jeyabalan J, Vadhanam MV. Bioavailability of phytochemicals and its enhancement by drug delivery systems. *Cancer Lett.* 2013;334(1):133-41.
34. Parveen S, Misra R, Sahoo SK. Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. *Nanomedicine.* 2012;8(2):147-66.
35. Ranade V, Cannon J. *Drug Delivery Systems, Third Edition [Internet].* CRC Press. 2011.
36. Pradhan P, Guan J, Lu D, Wang PG, Lee LJ, Lee RJ. A facile microfluidic method for production of liposomes. *Anticancer Res.* 2008;28(2A):943-7.
37. Mann JF, Acevedo R, Campo J del, Pérez O, Ferro VA. Delivery systems: a vaccine strategy for overcoming mucosal tolerance? *Expert Rev Vaccines.* 2009;8(1):103-12.
38. Rahman MM, Karim MR, Ahsan MQ, Khalipha ABR, Chowdhury MR, Saifuzzaman M. Use of computer in drug design and drug discovery: A review. *Int J Pharm Life Sci [Internet].* 2012.
39. Tang Y, Zhu W, Chen K, Jiang H. New technologies in computer-aided drug design: Toward target identification and new chemical entity discovery. *Drug Discov Today Technol.* 2006;3(3):307-13.
40. Sliwoski G, Kothiwale S, Meiler J, Lowe EW. Computational methods in drug discovery. *Pharmacol Rev.* 2013;66(1):334-95.
41. Lee KH, Ytreberg FM. Effect of Gold Nanoparticle Conjugation on Peptide Dynamics and Structure. *Entropy.* 2012;14(4):630-41.
42. Pasquinelli DMA, Yingling DY. Molecular Dynamics Simulations of Nano-Bio Materials. In: Bhushan PB, editor. *Encyclopedia of Nanotechnology [Internet].* Springer Netherlands. 2012.
43. Ramezani F, Habibi M, Rafi-Tabar H, Amanlou M. Effect of peptide length on the conjugation to the gold nanoparticle surface: a molecular dynamic study. *DARU J Pharm Sci.* 2015;23:9.
44. Mhashal AR, Roy S. Effect of gold nanoparticle on structure and fluidity of lipid membrane. *PLoS One.* 2014;9(12):e114152.
45. Lee B, Richards FM. The interpretation of protein structures: estimation of static accessibility. *J Mol Biol.* 1971;55(3):379-400.
46. Chen J, Chen L, Wang Y, Chen S. Molecular dynamics simulations of the adsorption of DNA segments onto graphene oxide. *J Phys Appl Phys.* 2014;47(50):505401.

47. Margreitter C, Mayrhofer P, Kunert R, Oostenbrink C. Antibody humanization by molecular dynamics simulations—in-silico guided selection of critical backmutations. *J Mol Recognit.* 2016;29(6):266-75.
48. Comer J, Chen R, Poblete H, Vergara-Jaque A, Riviere JE. Predicting Adsorption Affinities of Small Molecules on Carbon Nanotubes Using Molecular Dynamics Simulation. *ACS Nano.* 2015;9(12):11761-74.