IJAPB International Journal of Advances in Pharmacy and Biotechnology

Journal homepage: http://ijapbjournal.com/

Review Article

Lymphatic System: A Path for Drug Delivery

***Keerthi Reddy Sunkari*[*1], *Pallavi Sunduru*[1]**

[*1]*Department of Pharmaceutics, Center for Pharmaceutical Sciences, IST, JNTUH, Kukatpally, 500085, Hyderabad, Telangana, India.*

ARTICLE INFO

Article history:
Received 05 April 2020
Received in revised form 16 April 2020
Accepted 17 April 2020
doi.org/10.38111/ijapb.20200602003

Keywords:
Drug delivery, Nano-carriers, Lymphatic targeting, Lipophilicity

ABSTRACT

A Lymphatic system is a network like system being extended all over the body and useful targets for efficient drug delivery for drugs having poor oral bioavailability in the intestine and less absorbed into systemic circulation because of drug degradation in GI tract. Lymphatic targeting is not only to treat various infections not limited to pathological conditions like human immunodeficiency virus and other diseases but also used in diagnosis of tumours along with metastasis. Moreover, lymph nodes are the site for faster spread source to tumours via metastasis. Under these circumstances, there is a need for effective delivery of drugs towards and through lymphatic networks. Nano based systems and lipid based systems have unique features as necessary candidates for lymphatic delivery. The review provides information about different routes, drug transport in the lymphatic system, physicochemical properties which give impact on lymphatic delivery.

1. Introduction

According to national Lymphedema network the term “lymph” is derived from Latin word “Lympha” means “connected to water”.[1,2] Lymphatic system is a network of tissues and organs, consists of lymph vessel, lymph nodes and its main function is to carry the lymph. Lymph is colourless and clear fluid plays a significant role in immune response, infection, protein transport, fat metabolism and cancer metastasis, even helps in get rid of body toxins. The organs which are involved in lymphatic system are bone marrow, peyer’s patch, spleen, thymus, tonsils and adenoids.[2] Though tonsils and adenoids are small tissues of combined lymphatic cells (present at the back of the throat and patch at back of nasal cavity) helps in fighting against the infections.

Disorders of lymphatic system includes Obstruction: By lymphedema, filariasis. [3, 4] Infection: By organisms which spread disease through the lymphatic system.[5] Cancer: Tumors block the lymphatic system by metastasis. [6]

It plays an essential role in absorption of long chain fatty acids, triglycerides, cholesterol esters, lipid soluble vitamins and xenobiotics. Cancer cells mainly utilize the lymph nodes as a source of spreading. The portal vein or lymphatic system helps in transporting drugs to the systemic circulation after oral administration.[7] The hydrophobic drugs are best suited for lymphatic delivery by co-administering drugs with lipids gives easy transfer of drug through the lymphatic system.[8] The main purpose of this targeted drug delivery is to kill malignant lymphoid cells deposited in the lymph nodes and lodged viruses. For this, drugs are complexed with high molecular weight carriers in order to deliver them lymphotropically. By lymphatic delivery we can achieve drug targeting with the aim of directing drugs with specific sites and decreasing the dose. Hence, automatically adverse effects are minimized.

2. Physicochemical Properties

Particle Size: The lymphatic system is dependent on particle size ranging from 10 to 100nm. The optimum size reported for lymph target is 10 to 50nm. There is no barrier for lymphatic uptake, only a barrier that limits open junctions. As the part of lymphatic system, peyer's patch absorbs particles of <10nm.[9]

Molecular Weight: As the molecular weight increases, uptake by lymphatics also increases. The similar relationship exists between particle size and molecular weight. Many studies revealed that molecular weight between 1000 & 16000 Da for a molecule to absorb via lymphatic system. For example, fatty acids with 14 carbons or more than that can only be absorbed in this path less than that are more soluble and transported through

* *Corresponding author.* Tel.: 9949633910
E-mail address: keerthireddysunkari@gmail.com

portal vein. When colloids are targeted to lymphatics this parameter becomes negligible.in some of conjugated molecules such as hyaluronan-NIR the optimum molecular weight is between 6.4 KDa to 697 KDa.[10]

Lipophilicity: The most of drugs which are administered orally will be absorbed by portal circulation. But highly lipophilic compounds with high partition coefficients and solubility in triglyceride lipids are transported through lymphatic route. These compounds when combined with lipid vehicles enhance the drugs delivery in the proper way. Considerably drug solubility should be >50mg/ml and logP>5 for excellent intestinal lymphatic transport. Co-administration of drugs with fatty foods increases lymphatic transport and postprandial state is main factor for delivery of drugs to lymphatic system.[11]

Surface Modification: The surface modification can be done for both drug and carrier to improve intestinal absorption lymphatic uptake and relative bioavailability. Surface can be modified with many substances such as polyethylene glycol(PEG), biotin, and ligands. Steric stabilization with PEG coating shows the negative effect on lymph node uptake. Whereas, biotin coated liposomes resulted in greater lymphatic uptake when used along with avidin injection. Subcutaneously, lipid based carrier is coated with non specific antibodies as ligands leads to higher lymphatic absorption.[9, 12]

Surface Charge: Surface charge influences the design of colloidal particles to impart better performance physiological systems. Due to the presence of charge on carrier system, which offers repulsions between particles and prevents aggregation.[13]

Concentration: Drug absorbed into the systemic circulation through portal vein and then undergoes first pass metabolism in the liver. It results in a decrease in the concentration of drugs in plasma. Hence lymphatics the plasma concentration & bioavailability. [14]

3. Carrier Associated with Lymphatic Delivery

Solid lipid nanoparticles:

Solid lipid nanoparticles are colloidal drug carrier systems that act as solid at room and body temperature because they are surfactant stabilized lipids, and have high entrapment efficiency for hydrophobic drugs when compared to liposomes. The lipid core of solid lipid nanoparticles mimics the chylomicrons formed by enterocytes and helps in absorption of lipophilic drugs. Hence acts as a carrier for drugs through the lymphatic system. For example, the praziquantel loaded solid lipid nanoparticles enhanced bioavailability along with reduction in dosing frequency and showed sustained release of drug from the carrier system. Similarly, the drugs like Clozapine, Docetaxal, Etoposide, Idarubicin, Isoniazid, Pyranzinamide, paclitaxel all these improved targeted therapy with reduced toxicity.[15]

Liposomes:

Liposome is a lipid bilayer consisting of hydrophilic heads and hydrophobic tails. The hydrophilic heads face apart from each other saying the inner core is hydrophilic where the drug is incorporated. This carrier enhances the permeability across enterocytes thereby providing stability stability of drug and controlled release. [16,17]

Dendrimers:

Firstly in 1978, vogtle scientists showed a novel and efficient nanotechnology platform for drug delivery. These three dimensional tree-like structures have versatile nature. This multivalency is subjected to possess the terminal surface groups, entrapment/conjugation of drugs and many offer wide potential to treat many problems. Many researches like, improved solubility of paclitaxol when incorporated in polyglycerol dendrimers. Polymeric-drug conjugates, in the form of injectable suspension where paclitaxol drugs are bound with particles and others like doxorubicin in liposomal form. Similarly, methotrexate conjugated with PEGylated & PEGylated poly-L-lysine dendrimers has given targeted delivery. [18]

SEDDS (Self emulsified drug delivery system):

Majority of the drugs are water insoluble which are developed newly. Self emulsified systems shown promising resulted with improved solubility and site targeting. These are isotropic mixtures of oils, hydrophobic surfactant and sometimes contains co-solvents upon gentle agitation or digestive motility at a great rate produces fine o/w emulsion. [19]

Others:

Carbon nanotubes: These are gaining popularity as novel drug delivery systems as well as for biosensing. This resulted in production of biocompatible nanotubes with minimal side effects. The properties like surface area, strength, stiffness and resilience are unique which made CNTs with paclitaxel (single walled CNTs) targeted towards the tumor cells in mice provided high treatment efficiency with low doses. [20]

Quantum dots: The term "Quantum dots" coined by MARK REED. Generally QDs are tiny particles or nanocrystals of semiconductor material core coated with a shell to increase optical properties and solubility in aqueous buffers. Glowing particles with 2-10nm are formed by fine tuning of quantum dots. These when conjugated with antibodies, peptides, proteins, DNA forms the bio-conjugated dots as marked on cells & genes helps in differentiating pathological tissue. It has capability in detecting cancer, preventing metastasis and also targeted treatment. [21]

Table-1: Drugs transported to lymphatics by different carriers

Carriers	Drugs	Route of administration	Inference
Dendrimers	Methotrexate	Subcutaneous administration	Size & surface modification influenced influenced lymphatic permeability. [22]
Liposomes	IgGI	Subcutaneous injection	-IgG-Coupled liposomes entrapped within IgM molecules binding to macrophage Fc-receptor and helped in lymph node retention. [23]
	9-Nitro-Camptothecin	Pulmonary route (Nebulization)	-Effective against the pulmonary metastasis and prevented tumour passage to organs via lymphatic system in mice. [24]
Solid lipid nanoparticles	Praziquantel	Oral route	Improved bioavailability via lymphatic transport to avoid gastric pH antacids/H2-blocker/proton pump inhibitors. [27]
	Efavirenz	Oral route	-Significant amount of drug present in lymphatic organs shown by-pass for portal system indicated reducing first pass effect. Thereby managing HIV. [28]
SEDDS a. self micro emulsified drug delivery system	Nobiletin	Oral administration	-The absorption of nobiletin is higher in smedds dilution. [29]
b. Self nano emulsified drug delivery system	Carvedilol	Oral administration	-As it is BCS class-II drug, improved solubility, permeability and bioavailability by transport through lymphatics. [30]

4. Routes of Administration

The way through which a drug is introduced into the body and comes in contact with the site of action to treat/prevent dysfunction in the body.

Oral route:

Among all other routes of administration, oral route is preferred by patients because other routes show various drawbacks such as pain extravasation of blood thrombosis like problems. This shows commercialization of oral delivery of drugs. Even this route is associated with problems like gastric pH and first pass effect, this is surpassed by nanoscience and nanotechnology in drug delivery. Nanoforms can protect not only drugs from G.I. pH but also G.I. irritation from drugs.

Its exclusive function is more important due to targeted delivery. This is done with help of lipid absorption for lymphatic transport. Hence novel lipid based drug delivery is best suitable for drug transport through intestinal lymphatic system and achieves superior bioavailability, plasma profile and site targeting ability. [31]

Parenteral route:

A Sterile atmosphere is essential for parenteral systems. Now-a-days the novel approaches came into existence wherein drugs and proteins are incorporated within the nano-based carrier systems. The parenteral route may be either by intramuscular/intradermal/subcutaneous. The diffusion of particles present in injection have 2 pathways, one is blood capillaries based on particle size I.e., below 10nm and size of particles which are having range between 10 & 100nm can enter into lymphatic capillaries through active transcytosis or inter endothelial cell junctions. The GALT is the gut-associated lymphoid tissue helps the immune system and protects the body. Subcutaneous absorption was highly studied in sheep model and their protein delivery in them observed more via lymphatic route shown the 70% of therapeutics was bioavailable. [32]

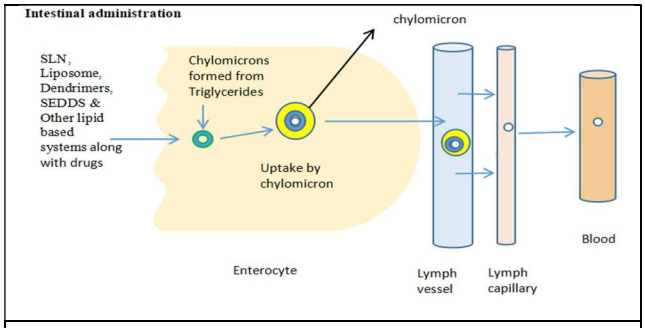

Fig-2: Transport of drug and carrier to lymphatic system via intestinal route

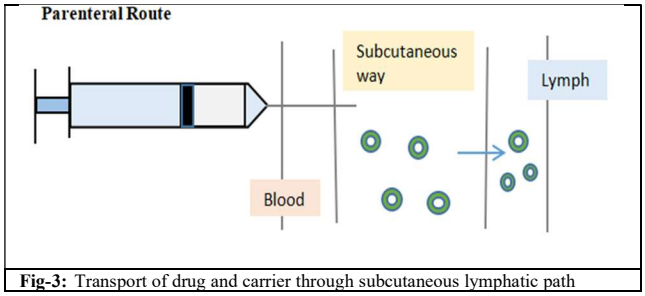

Fig-3: Transport of drug and carrier through subcutaneous lymphatic path

Mucosal Route:

Mucosal surfaces are more vulnerable for microbial infections and induce complex arrays of innate and adaptive immunity. Vaccines delivery is becoming essential in case of immunity suppression diseases and recently lymph nodes present in nasal, pulmonary and genital organs and its lining ease for drug delivery. M-cells cover mucosa associated lymphatic tissues(MALT) show importance in transport of drugs and antigen like particles. After crossing this layer, then enter lymph nodes via lymph capillaries to lymphatic vessels. [33]

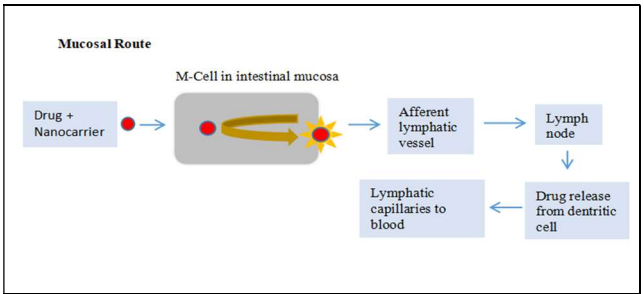

Fig-4: Transport of carrier along the intestinal mucosa to lymphatic path

5. Applications

Cancer therapy:

When chemotherapy is implied as treatment in cancer patients the disadvantage is non specificity in action because of potent agents usage. Hence, there is a need for a proper delivery route i.e.,lymphatic route and to invade the tumour cells endogenous proteins are used. Then the targeted delivery is achieved. Lymphatic drainage is a major site for metastasis. For this reason drugs/isotopes are labelled with the various carriers (mostly liposomes) to target towards tumour. For example, 99MTC labelled liposomes for lymph node imaging. [34]

Infections and their treatment:

Infections are very diverse and caused by bacteria, fungi, parasites, **viruses**, etc. Beneficial effect is seen with lymphatic targeting because, viruses like HIV and parasites mainly reside in lymph nodes and lymph vessels. But there is a restricted penetration of antiretroviral drugs to lymph nodes. For this nanoformulation or surface modifications came into picture and accumulated in lymph nodes, available for treatment.

Whereas coming to parasites, filariasis impairs lymphatic system leads to abnormal enlargement in body parts. To avoid this, drugs are selectively targeted with modified systems. [4]

Novel methods are used to target the antituberculosis drugs to lymph nodes and could reduce time line therapy in treating tubercular lesions. The Mycobacterium tuberculosis mainly settles in the thoracic lymph nodes where anti-tubercular drugs and vaccine entry is somewhat difficult and may retain the infection. Here, the Lymphatic delivery of drugs & vaccines by nanocarriers can definitely encounter problems associated.[35]

Vaccine delivery:

Vaccines are ingested by people in order to prevent diseases and develop the corresponding antibodies accordingly. Barriers to immune response may arise when the lymphatic system is blocked with infectious agents like HIV viruses and cancerous cells (during metastasis). Actually, vaccines are inactivated antigenic material when trapped by the lymph nodes. Where, immune cells are activated such as antigen specific T-cells and memory cells produces adaptive immune response. Hence, the lymphatic path plays a significant role in vaccine delivery through subcutaneous and intradermal routes where an extensive lymphatic system originates.

Carrier surface modification with ligands such as polyethylene glycol and CpG DNA acts as a vaccine adjuvant, improves the function of antigen presenting cell and boosts immune response. This delivered in liposomal carrier for lymphatic system.[36]

6. Conclusion

Currently lymphatic drug delivery system has achieved significant advances in novel levels. All the advanced carriers involved in delivering the drugs, proteins, biomolecules realized to and targeted lymphatic drainage as a targeted delivery. In order to have biocompatibility and high uptake rate, there must be suitable carriers with unique properties that give selective targeting. Mainly the lymphatic system possesses immune cells to fight against the pathogens which can penetrate in. Research on viruses and metastatic tumours multiplication controlling process, respective vehicle for carrying drugs and biodegradability of therapeutics will focus on normalization of immunity to provide active therapy.

Acknowledgements

Authors are thankful to The Principal, Center for Pharmaceutical Sciences, IST, JNTUH, Kukatpally, 500085, Hyderabad, Telangana, India

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

References

1. Indus singh, rajan swami, wahid khan, ramakrishna sistla. Delivery system for lymphatic targeting, *focal controlled drug delivery*, 2014, 429-458.
2. Kim Ann Zimmermann, Lymphatic system: Facts, Functions & Diseases, 2018.
3. Pfarr, K. M., A. Y. Debrah, S. Specht, and A. Hoerauf."Filariasis and lymphoedema." *Parasite Immunol*., 2009, 31(11); 664-672.
4. Anitha, K., and R. K. Shenoy. "Treatment of lymphatic filariasis: Current trends." *Indian J Dermatol Venereol Leprol.*, 2001, 67(2); 60-65.
5. Chachu, Karen A., Anna D. LoBue, David W. Strong, Ralph S. Baric and Herbert Virgin. “Immune mechanisms responsible for vaccination against and clearance of mucosal and lymphatic norovirus infection” *PLoS Pathog*., 2008, 4(12);.
6. Cueni, Leah N., and Michael Detmar. The lymphatic system in health and disease. *Lymphat Res Biol*., 2008, 6(3-4); 109-122.
7. Hari Vardhan Reddy L., and R. S. R. Murthy. Lymphatic transport of orally administered drugs., *Indian J Exp Biol*., 2002, 40(10); 1097-109.
8. Yáñez, Jaime A., Stephen WJ Wang, Ian W. Knemeyer, Mark A. Wirth, and Kevin B. Alton. "Intestinal lymphatic transport for drug delivery." *Adv Drug Deliv Rev.*, 2011, 63(10-11); 923-942.
9. Bora, C., R. Prabhu, and V. Patravale. "Lymphatic delivery: concept, challenges and applications (INDIAN DRUGS best review article award 2017)." *Indian Drugs*, 2017, 54(8); 5-22.
10. Cho, Hyun-Jong, et al. "Surface-modified solid lipid nanoparticles for oral delivery of docetaxel: enhanced intestinal absorption and lymphatic uptake." Int *J Nanomedicine,* 2014, 9; 495-504.
11. Saraf, Swarnlata, Avijit Ghosh, Chanchal Deep Kaur, and Shailendra Saraf. "Novel modified nanosystem based lymphatic targeting." *Res J Nanosci Nanotechnol*, 2011, 1(2); 60-74.
12. Jahan, Sheikh Tasnim, Sams Sadat, Matthew Walliser, and Azita Haddadi. "Targeted therapeutic nanoparticles: an immense promise to fight against cancer." *J Drug Deliv Sci Technol*, 2017.
13. Khan, Arshad Ali, Jahanzeb Mudassir, Noratiqah Mohtar, and Yusrida Darwis. "Advanced drug delivery to the lymphatic system: lipid-based nanoformulations." *Int J Nanomedicine* , 2013, 8; 2733–2744.
14. Yasir, Mohd, Praveen K. Gaur, Dinesh Puri, Preeti Shehkar, and Shanmugam Sadish Kumar. "Solid lipid nanoparticles approach for lymphatic targeting through intraduodenal delivery of quetiapine fumarate." *Curr Drug Deliv*, 2018, 15(6); 818-828.
15. Khoo, Shui-Mei, Glenn A. Edwards, Christopher JH Porter, and William N. Charman. "A conscious dog model for assessing the absorption, enterocyte-based metabolism, and intestinal lymphatic transport of halofantrine." *J Pharm Sci*, 2001, 90(10); 1599-1607.
16. Murakami, Masahiro, Kazutaka Nishina, Chie Watanabe, Kie Yoshida-Tanaka, Wenying Piao, Hiroya Kuwahara, Yuji Horikiri et al. "Enteral siRNA delivery technique for therapeutic gene silencing in the liver via the lymphatic route." *Scientific reports*, 2015, 5; 17035.
17. Hyeongmin Kim, Yeongseok Kim, and Jaehwi Lee. "Liposomal formulations for enhanced lymphatic drug delivery." *Asian journal of pharmaceutical sciences*, 2013, 8(2); 96-103.
18. Zhu, Jingyi, and Xiangyang Shi. "Dendrimer-based nanodevices for targeted drug delivery applications." *J. Mater. Chem. B*, 2013, 1(34); 4199-4211.
19. Liu, Peng. "Modification strategies for carbon nanotubes as a drug delivery system." *Ind. Eng. Chem. Res.,* 2013*,* 52(38); 13517-13527.
20. Peng, Chun-Wei, and Yan Li. "Application of QuantumDots-Based Biotechnology in Cancer Diagnosis: Current Status and Future Perspectives." *J. Nanomater*, (2010).
21. Ryan, Gemma M., Victoria M. McLeod, Dharmini Mehta, Brian D. Kelly, Pauline C. Stanislawski, David J. Owen, Lisa M. Kaminskas, and Christopher JH Porter. "Lymphatic transport and lymph node targeting of methotrexate-conjugated PEGylated dendrimers are enhanced by reducing the length of the drug linker or masking interactions with the injection site." *Nanomedicine*, 2017, 13(8); 2485-2494
22. Hauss, David J., Steven E. Fogal, James V. Ficorilli, Caswall A. Price, Tapon Roy, Andrew A. Jayaraj, and James J. Keirns. "Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor." *J Pharm Sci*, 1998, 87(2); 164-169.
23. Moghimi, S. Moein, and Majid Moghimi. "Enhanced lymph node retention of subcutaneously injected IgG1-PEG2000-liposomes through pentameric IgM antibody-mediated vesicular aggregation." *Biochim Biophys Acta*, 2008, 1778(1); 51-55.
24. Holm, René, Christopher JH Porter, Glenn A. Edwards, Anette Müllertz, Henning G. Kristensen, and William N. Charman. "Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides." *Eur J Pharm Sci*, 2003, 20(1); 91-97.

25. Azzi, Jamil, Li Tang, Robert Moore, Rong Tong, Najib El Haddad, Takurin Akiyoshi, Bechara Mfarrej et al. "Polylactide-cyclosporin A nanoparticles for targeted immunosuppression." *FASEB J*, 2010, 24(10); 3927-3938.
26. Luo, Yue Yuan, Xiang Yuan Xiong, Yuan Tian, Zi Ling Li, Yan Chun Gong, and Yu Ping Li. "A review of biodegradable polymeric systems for oral insulin delivery." *Drug Deliv*, 2016, 23(6); 1882-1891.
27. Mishra, Amit, Parameswara Rao Vuddanda, and Sanjay Singh. "Intestinal lymphatic delivery of praziquantel by solid lipid nanoparticles: formulation design, in vitro and in vivo studies." *J. Nanotechnol*., 2014.
28. Makwana, Vivek, Rashmi Jain, Komal Patel, Manish Nivsarkar, and Amita Joshi. "Solid lipid nanoparticles (SLN) of Efavirenz as lymph targeting drug delivery system: Elucidation of mechanism of uptake using chylomicron flow blocking approach." *Int J Pharm*, 2015, 495(1); 439-446.
29. Yao, Jing, Yun Lu, and Jian Ping Zhou. "*Preparation* of nobiletin in self-microemulsifying systems and its intestinal permeability in rats." *J Pharm Pharm Sc*i, 2008, 11(3); 22-29.
30. Singh, Bhupinder, Lalit Khurana, Shantanu *Bandyopadhyay*, Rishi Kapil, and O. O. P. Katare. "Development of optimized self-nano-emulsifying drug delivery systems (SNEDDS) of carvedilol with enhanced bioavailability potential." *Drug Deliv*, 2011, 18(8); 599-612.
31. Ahn, Hyeji, and Ji-Ho Park., Liposomal delivery systems for intestinal lymphatic drug transport, *Biomater. Res*., 2016, 20(1); 36.
32. Richter, Wolfgang F., and Björn Jacobsen. "Subcutaneous absorption of biotherapeutics: knowns and unknowns." *Drug Metabolism and Disposition*, 2014, 42 (11); 1881-1889.
33. Yáñez, Jaime A., Stephen WJ Wang, Ian W. Knemeyer, Mark A. Wirth, and Kevin B. Alton. "Intestinal lymphatic transport for drug delivery." , *Adv Drug Deliv Rev*, 2011, 63(10-11); 923-942.
34. Murtaza, Ghulam, Kuo Gao, Tiegang Liu, Imran Tariq, Ashif Sajjad, Muhammad Rouf Akram, Meiying Niu, Guokai Liu, Zahid Mehmood, and Guihua Tian. "Current and future lymphatic imaging modalities for tumor staging." *Biomed Res Int*, 2014.
35. Sharie Keanne C. Ganchua, Alexander G. White, Edwin C. Klein, JoAnne L. Flynn, Lymph nodes—The neglected battlefield in tuberculosis, *Plos Pathogens*, 2020, 1-19.
36. Schwendener, Reto A. "Liposomes as vaccine delivery systems: a review of the recent advances." *Ther Adv Vaccines*, 2014, 2(6); 159–182.