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Introduction of improvement in TB therapy with addition of nanoparticles

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Abstract. Tuberculosis (TB) is a major global infectious disease. The challenges faced in current treatment often include the development of drug resistance, long treatment periods and serious side effects. At the same time, Nanotechnology offers innovative solutions to enhance TB treatment. With the help of nanoparticles such as liposomes, polymeric nanoparticles and inorganic nanoparticles, the drug delivery system can be improved, which leads to higher concentrations of drugs at the site of infection. In this way, side effects are minimized and treatment time is potentially shortened.

Keywords: Tuberculosis, mycobacterium tuberculosis, nanoparticles, delivery system, antituberculosis drugs, tuberculosis treatment.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by droplet transmission and can affect any part of the body. It is caused by one of the two bacteria: Mycobacterium tuberculosis or Mycobacterium bovis. The bacteria are usually found in the lungs because these are the first sites of infection. Most infected people will have latent TB at first. These people do not show symptoms as soon as their immune system becomes weaker, the bacteria will be activated. There are several symptoms shown by people who have active TB: tiredness, presence of coughing, shortness of breath, loss of weight, and so on. According to the World Health Organization, TB causes about 1.6 million deaths in 2021. In addition to some economic or technical problems, the recent COVID-19 pandemic has seriously disrupted the protection for TB over the world. The combination of all the factors has resulted in the global TB response still falling short of WHO targets. So the efforts in inventing more advanced methods in TB therapy to enhance the effectiveness is really important to be made [1]. Tuberculosis treatment is a long-term treatment. And it usually takes six months. When the therapy starts, most of the situation can lead to drug resistance, and this will make the treatment more complicated. There are also some drugs for treating tuberculosis that have a lot of side effects. Which will lead to some troubles during the period of the therapy. However, experts are now trying to use nanotechnology to fix these problems.

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Nanoparticles enhance drug delivery by increasing the bioavailability of drugs. And it can target the infectious place effectively. Now there are a lot of different ways to use nanotechnologies to deliver drugs. For example, liposomes and polymeric nanoparticles. They could carry the drugs and make sure they can release them, then kill the bacteria. This targeted approach improves drug efficacy and decreases the risk of drug resistance [2].

Nanoparticles are tiny particles, typically between 1 and 100 nanometers, that exhibit unique physical and chemical properties due to their small size and high surface area. These properties make them useful in many fields, including medicine, where they can be used for targeted drug delivery, diagnostics and as a carrier for therapeutic agents. Nanoparticles offer significant advantages in TB treatment by enabling targeted drug delivery, where they can be designed to deliver drugs directly to infected cells like macrophages, where TB bacteria often reside. This targeted approach increases drug concentration at the infection site, enhancing bacterial killing and reducing the risk of drug resistance. Additionally, nanoparticles can provide sustained and controlled release of anti-TB drugs, ensuring therapeutic levels are maintained over extended periods. This reduces the need for frequent dosing and helps maintain consistent drug pressure on the bacteria, further preventing resistance. Beyond these benefits, nanoparticles can also be engineered for combination therapy, reduced side effects, and enhanced penetration into protective bacterial structures [3].

In this article, we will explore the role of nanoparticles in improving TB therapy and focus more on types of nanoparticles and their relating mechanisms.

2. Current treatment to tuberculosis and the challenges

Conventional TB treatment presents several drawbacks. Firstly, the prolonged treatment period, which typically lasts for six months often leads to poor patient adherence. Apart from this, the anti-TB drugs may cause some side effects, such as allergy, arthralgia, hepatotoxicity, and gastrointestinal disorders. These symptoms also keep the patients from completing the therapy. Treating drug-resistant (DR) TB and multidrug-resistant (MDR) TB is even more complex. For example, isoniazid-monoresistant TB frequently causes failure with standard treatment. In that case, isoniazid is replaced by a later-generation fluoroquinolone and used with rifampicin, pyrazinamide, and ethambutol for at least six months. For MDR-TB, the treatment involves combinations of drugs from different classes: bedaquiline, fluoroquinolones, clofazimine, linezolid, and carbapenems. Three groups of combinations of those drugs are made and ready to be used according to different situations. The complex treatment regimen mentioned shows the treatment for drug-resistant TB is time-consuming and difficult [4]. However, although mycobacterium tuberculosis (Mtb) has a low mutation rate, limited genetic diversity, and no environmental advantage, the growing epidemic of DR Mtb remains a severe concern. This highlights the urgent need to halt the spread of these DR strains. The resistance of Mtb to any TB drug is multifaceted, influenced by biological, clinical, and microbiological factors. This complicates pharmaceutical chemistry, and the rate at which Mycobacterium tuberculosis is developing resistance appears to accelerate the rate of finding of new drugs. In addition to the traditional methods of developing new drugs, other strategies must be pursued at the same time. Significant efforts must be made to identify key bacterial and host pathways and targets [5]. So in this paper, we introduce the combination of anti-TB drugs and different types of nanoparticles, aiming to overcome the existing problems in conventional TB therapy mentioned.

3. Types of nanoparticles

3.1. Lipid-base nanoparticle:

Lipid nanoparticles have emerged as a promising approach, as indicated by scientific data. Made from biodegradable and biocompatible materials, these nanoparticles can potentially reduce dosage and enable controlled drug delivery compared to free drugs. Additionally, modifying the particle surface could improve the targeting power towards the lungs, which are the primary organs affected by the disease [6].

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The most investigated nanocarrier for medical cargoes is called liposome. These kinds of particles consist of natural or synthetic phospholipids and cholesterol. The general shape formed by these materials is spherical. This structure improves stability in both vitro and vivo situations. In the environment of aqueous dispersion, the hydrophilic heads have hydrogen bonds with water molecules while the hydrophobic tails face inwards, leading to spontaneous formation of phospholipid bilayer. So that the hydrophobic drugs can be saved in the lipid bilayer, at the same time, the aqueous core is able to contain hydrophilic ones. Due to the differences in morphology, liposomes are distinguished into giant unilamellar vesicles (GUV≥1μm), large unilamellar vesicles (100nm<LUV<1μm), small unilamellar vesicles (SUV≤100nm), and multilamellar vesicles (have more than five lamellae), oligolamellar vesicles (have two to five concentric lamellae). Microscopy imaging can be used to observe these different structures. The role of each type of liposome as a carrier will be slightly different. For example, Multilamelar vesicles are more appropriate for lipophilic drugs while the unilamellar vesicles are suitable for carrying hydrophilic drugs as they contain a large aqueous core. Liposomes have been widely used in many diseases, including TB and perform as a safe and effective drug delivery system, which enhances the targeting ability of the drugs, especially in pulmonary delivery [7].

Currently, liposomes are used the most widely as carriers for delivering bioactive compounds and antimicrobials. They can bring lots of benefits, including biocompatibility and non-immunogenicity. Liposomes can carry large drug payloads, self-assemble, and have various biophysical and physicochemical properties that can be modified to enhance their delivery capabilities. Encapsulating therapeutic agents in liposomes protects them from degradation, early inactivation and attenuation in blood [8].

There was a research article about an experiment on the ideal material for the liposome as the carrier for isoniazid which is an anti-TB drug. The authors used a mixture of hydrogenated soy phosphatidylcholine (HSPC) and 1,2-Dipalmitoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DPPG). After a series of experiments, the results indicated that interaction between INH and HSPC can increase the loading capacity of the carrier. This is because the INH-HSPC dipole-dipole interaction facilitate the modification of lipid packing and ordering. While the mixture favors the condensation of an HSPC-richer state in an environment of excess DPPG [9].

Liposomal drug delivery systems have shown significant curative effects in the treatment of TB by enhancing the effectiveness and reducing the toxicity of anti-TB drugs. Studies using M. avium and M. tuberculosis models demonstrated that liposomal formulations of drugs like rifabutin and clofazimine slowed disease progression and reduced bacterial loads in various organs, suggesting potential for both pulmonary and extrapulmonary TB treatment [2]. A study concluded that the inhalable liposomal formulation of isoniazid significantly enhances the carriage of the drug towards the alveoli, providing continuous release, leading to higher drug concentration at the infection site. Specifically, the drugs with encapsulation of liposomal formulation achieved a 3.7-fold more in isoniazid concentration in the lungs than that when uptaking free drugs. What's more, the formulation exhibited a sustained release of 83% of the drugs over 24 hours. These results show that this targeted delivery system is able to improve the effectiveness of treatment by lowering the frequency of dosing. In this way, the side effects produced by the drugs can also be decreased [10]. Liposomal packaging of anti-TB drugs improved their penetration in the alveoli, reduced systemic toxicity, and extended pulmonary residence time [2].

Another study concluded that liposomal encapsulation of rifampicin significantly increases the chance of uptaking by macrophages and enhances its antimycobacterial activity while limiting inflammation, which enables the patients to have sustained drug levels in the body [11].

In the 1990s, solid lipid nanoparticles (SLNs) were developed as an alternative nanocarrier to liposomes. SLNs are composed of solid lipids (fatty acids, steroids, triglycerides, or waxes.), water, and surfactant or emulsifiers. What's more, in these formulations, sodium cholate and phosphatidylcholine are commonly used as stabilizers. SLNs are generally safe in terms of toxicity. And the biocompatibility of SLNs is also ideal. In addition, whether the solid lipid is made of natural or synthetic, it is biodegradable [12].

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3.2. Polymeric Nanoparticles:

Polymer nanoparticles are tiny particles made of polymers that can be used to deliver drugs or other therapeutics in a controlled and targeted manner. They have a very small size, usually between 10 and 1000 nanometers, which means they can easily interact with biological systems in different ways than others, which is a great way to treat TB [13].

Tuberculosis treatment often involves long-term antibiotic therapy, which could be very challenging due to medication adherence and side effect issues [14]. Polymeric nanoparticles can be designed to deliver anti-tuberculosis drugs more efficiently. Polymeric nanoparticles can encapsulate anti-tuberculosis drugs. This targeted dosing helps ensure that the drug is released in a controlled manner over time, increasing the success of treatment and reducing side effects [15,16]. Nanocarriers with optimized physical, chemical, and biological properties are more easily absorbed by cells than other macromolecules, so they are very good delivery tools for currently usable bioactive compounds [17].

For the TB bacteria, like Mycobacterium tuberculosis, they can hide within the cells and tissues, so it is very hard for traditional drugs to reach them. However, polymeric nanoparticles can target these bacteria more effectively [18]. The advantage of applying the polymeric nanoparticles is that it could reduce the toxicity. By putting the drugs in nanoparticles, it is possible to reduce the dose required and minimize the exposure of healthy tissues to the drugs. Which is very important for drugs with huge side effects [19]. On the other hand, another advantage of using polymeric nanoparticles is, it can also solve the problem of drug resistance, for example MDR-TB and XDR-TB strains of TB disease are main problems in the TB treatment. Polymeric nanoparticles can be used to deliver combination therapies or new drugs more effectively; it could overcome some forms of drug resistance [20]. Nowadays there are still many problems of treating TB, like there's many anti-TB drugs, they don't get absorbed well in the body. But polymeric nanoparticles can improve the solubility and stability of these drugs to ensure they reach their target more efficiently.

3.3. Inorganic particles

To address the challenges of TB, novel approaches utilizing inorganic/metallic nanomaterials have been developed to improve drug delivery to target alveolar macrophages, where Mycobacterium tuberculosis resides. These nanomaterials have shown effectiveness against various TB strains, providing advantages such as enhanced drug efficacy, reduced side effects, and sustained release of drugs at the site of infection [21].

Gold nanoparticles (GNP) are commonly utilized in targeted drug delivery because of their minute size, compatibility with living organisms, and absence of harmful effects on cells. Surface modifications can be tailored specifically to target macrophages in the lungs where Mycobacterium tuberculosis (Mtb) usually infiltrates, increasing drug concentration at infection sites while decreasing potential side effects in general [22]. Green nanoparticle synthesis offers great promise in treating tuberculosis due to its ability to efficiently eliminate bacteria [23]. Studies have demonstrated that Mycobacterium tuberculosis can be inhibited at concentrations as low as 10mg/ml with this medication; however, they do not work against strains that are resistant to rifampicin. Mesoporous silica nanoparticles (MSNs) containing gold nanoparticles have been discovered to inhibit Mycobacterium tuberculosis growth and may offer an effective means for treating tuberculosis. GNP can also play an instrumental role in diagnosing tuberculosis, including an iron magnetic GNP-based immunodiagnostic system to detect Mycobacterium bovis and GNPs loaded with tetrameric DNA motifs to diagnose Mycobacterium tuberculosis from sputum samples. Furthermore, magnetic bead and GNP-based immuno-PCR technologies have also been created to detect Mycobacterium tuberculosis antigens [22].

Gold nanoparticles possess unique optical and electronic characteristics, making them well-suited to imaging and thermal therapy applications. Modifying gold nanoparticle surface modifications can boost imaging signals for greater diagnostic precision; additionally, these nanoparticles absorb infrared light at infection sites to produce heat at infection sites eradicating Mycobacterium tuberculosis more effectively - these photothermal effects may even be combined with drug therapies to maximize treatment efficacy [22].

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Gold nanoparticles offer promise in treating tuberculosis, but their implementation requires careful consideration of several factors. First and foremost, gold nanoparticles must be safe for human use with minimal toxicity; secondly, surface modifications may enhance targeting specific areas while decreasing non-specific effects; furthermore, understanding their distribution, metabolism, and excretion is also key to understanding the pharmacokinetics of treatment effects is also critical. Reaching gold nanoparticles is also crucial. By customizing their dimensions and linking polyethylene glycol molecules onto their surfaces, their accumulation within tumors can be increased through the EPR effect [24].

Passive targeting involves conjugating a targeting molecule, such as a peptide, antibody, or other biological component, to the cover of the carrier for selective binding to overexpressed receptors on the cell membrane. Many cancer cells exhibit elevated levels of transferrin receptors (TLRs) due to their rapid proliferation and heightened demand for iron [24]. By functionalizing Au nanoparticles with human holo-transferrin, the intracellular delivery efficiency of these carriers is significantly augmented compared to non-targeted counterparts.

A study focuses on the biosynthesis of gold nanoparticles using medicinal plant extracts as reducing and stabilizing agents. The nanoparticles were tested for anti-tuberculosis (anti-TB) activity against *Mycobacterium tuberculosis*, particularly targeting opportunistic infections common in HIV patients. Seven out of 15 tested nanoparticles and seven out of 12 nanoconjugates showed exceptional anti-TB activity, with a Minimum Inhibitory Concentration (MIC) of 6.42 μg/ml, indicating significant potential for treating TB in immunocompromised patients [25].

Silica nanoparticles can be internalized by macrophages and confer immune benefits. Rifampicin-loaded polyethyleneimine (PEI) coated mesoporous silica nanoparticles (MSN) have shown efficient targeted delivery into cells with reduced toxicity. MSN loaded with first-line anti-tuberculosis drugs can eliminate Mycobacterium tuberculosis-infected macrophages. MSN containing NZX (Mycobacterium peptide) can effectively treat tuberculosis by eradicating multidrug-resistant strains of Mycobacterium tuberculosis. Tenland et al. found that MSNs can enhance antibacterial activity against M. bovis and M. tuberculosis H37Rv both in vitro and in vivo. NapFab, an antimicrobial peptide isolated from bronchoalveolar lavage fluid, exhibited outstanding anti-mycobacterial activity when introduced to dendritic MSN. MSN can act as a carrier for delivering silver nanoparticles to specific locations due to their extremely high bactericidal potency. Two-dimensional hexagonal MSN containing silver bromide also displayed promising anti-mycobacterial activity [22].

In the 1990s, researchers at Mobil Oil developed mesoporous silica materials through colloidal chemistry and evaporation-induced self-assembly [23]. These nanoparticles are characterized by their uniformity, porosity, and dispersibility, and have found widespread applications in drug delivery to cells, diagnosis, and bioimaging. They also demonstrate exceptional stability against heat, pH variations, and mechanical stress, effectively safeguarding drug molecules until they are released within the cell. The substantial surface areas of mesoporous silica (exceeding 1,000 m^2/g and 500 m^2/g) enable independent adjustment of pore size and surface chemistry [23]. This unique capability allows for accommodating diverse single or combined drug loads that surpass those achievable with other common drug delivery carriers such as liposomes or polymer conjugates. The loading capacity is attributed to non-covalent electrostatic interactions between the drug and the internal surface of the mesopore as well as hydrogen bonding and physical adsorption due to van der Waals forces which exceed the solubility limit of the drug in solution.

For nanocarriers to be efficacious in biomedical applications, they must concurrently possess multiple functionalities and characteristics. These encompass (1) facile visibility; (2) dispersibility; (3) specificity; (4) capacity to carry and transport diverse high-concentration cargo; and (5) biocompatibility with low toxicity [24]. In this context, mesoporous silica nanomaterials emerge as promising candidates for nanocarrier platforms owing to their expansive surface area, versatile surface chemistry, and minimal toxicity. Mesoporous silica can be employed for direct imaging and targeting, enabling tracking of biological distribution, cancer cell targeting efficiency, internalization pathways, cytotoxicity assessment, and therapeutic monitoring under physiologically relevant conditions. Furthermore,

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mesoporous silica exhibits active targeting capabilities to minimize non-specific binding while enhancing specific internalization into the target cell or tissue site.

Passive and active targeting can be achieved through the utilization of functionalized mesoporous silica nanoparticles. For example, coating mesoporous silica nanoparticles with polyethyleneimine (PEI) has been shown to significantly increase the absorption rate of the particles. Furthermore, precise control over particle size and surface coatings using PEI/PEG copolymers has also been demonstrated to enhance EPR effects and reduce RES uptake in xenograft models [23].

A study explores the use of mesoporous silica nanoparticles (MCM-41) as carriers for poorly soluble anti-tuberculosis drugs, pretomanid and MCC7433. By modifying the nanoparticles with amine and phosphonate groups and using a rotary evaporation method, high encapsulation efficiency (≥86%) and drug loading (8–10%) were achieved. The nanoparticles significantly enhanced drug solubility and maintained pharmacological activity against *Mycobacterium tuberculosis*. In vivo, amino-functionalized MCM-41 improved the systemic exposure of MCC7433 in mice, showing promise for oral delivery of anti-TB drugs, particularly in resource-limited settings [26].

4. Conclusion

Tuberculosis (TB) continues to pose a formidable threat to global health, underscoring the urgent need for intensified global efforts to combat this infectious disease. Despite advancements in rapid diagnostic tests, preventive treatments, and some progress made in certain areas, the TB epidemic remains a major public health challenge, particularly in low- and middle-income countries where access to healthcare and financial resources are limited. The 2019 coronavirus pandemic has caused disruptions in identifying and managing tuberculosis cases, leading to more deaths related to tuberculosis cases and its spread within communities. World Health Organization-set goals to control tuberculosis have not been reached despite worldwide efforts, highlighting the necessity for increased funding, resource allocation, and collaboration across nations. Treating tuberculosis is complex and challenging for patients, highlighting the need for innovative approaches and comprehensive care models to increase success rates of treatment. Furthermore, in order to be truly effective, prevention and control require sustained, global efforts aimed at eliminating this infectious scourge.

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Sen Yu, Xiaohan Lu and Jiahao Zhou contributed equally to this work and should be considered co-first authors.

References

[1] Joan Stephenson, P. (2022, November 15). Who report: Years of progress in global tuberculosis upset by COVID-19 pandemic. JAMA Health Forum. https://jamanetwork.com/journals/jama-health-forum/fullarticle/2798878

[2] Nair, A., Greeny, A., Nandan, A., Sah, R. K., Jose, A., Dyawanapelly, S., Junnuthula, V., V., A. K., & Sadanandan, P. (2023, November 9). Advanced Drug Delivery and therapeutic strategies for tuberculosis treatment - journal of nanobiotechnology. BioMed Central. https://jnanobiotechnology.biomedcentral.com/articles/10.1186/s12951-023-02156-y

[3] Kumar, M., Virmani, T., Kumar, G., Deshmukh, R., Sharma, A., Duarte, S., Brandão, P., & Fonte, P. (2023, September 26). Nanocarriers in tuberculosis treatment: Challenges and Delivery Strategies. MDPI. https://www.mdpi.com/1424-8247/16/10/1360

[4] Hatae , A. C., Roque-Borda, C. A., & Pavan , F. R. (2023, June 30). Strategies for lipid-based nanocomposites with potential activity against mycobacterium tuberculosis: Microbial Resistance Challenge and Drug Delivery Trends. OpenNano. https://www.sciencedirect.com/science/article/pii/S2352952023000506

[5] Singh, V., & Chibale, K. (n.d.-b). Strategies to Combat Multi-Drug Resistance in Tuberculosis. https://pubs.acs.org/doi/10.1021/acs.accounts.0c00878

[6] Aldemar Gordillo-Galeano, Andrade, L. M., Beloqui, A., Bhandari, R., Bunjes, H., Cardona, P. J., Costa, A., Crespo, F., Dheda, K., Dumas, F., Ganesan, P., Garcia-Fuentes, M., Gaspar, D. P., Genina, N., Gordillo-Galeano, A., Gupta, U. D., Haag, S. F., Hershkovitz, I., Hoal, E. G. , … Weber, S. (2021, February 2). Lipid nanoparticles with improved biopharmaceutical attributes for tuberculosis treatment. International Journal of https://www.sciencedirect.com/science/article/abs/pii/S0378517321001253

[7] Buya, A. B., Witika, B. A., Bapolisi, A. M., Mwila, C., Mukubwa, G. K., Memvanga, P. B., Makoni, P. A., & Nkanga, C. I. (2021a, November 30). Application of lipid-based nanocarriers for antitubercular drug delivery: A Review. MDPI. https://www.mdpi.com/1999-4923/13/12/2041

[8] Shrivastava, P., Gautam, L., Vyas, S., & Vyas, S. P. (1970b, January 1). Liposomes for delivery of antitubercular drugs. SpringerLink. https://link.springer.com/chapter/10.1007/978-3-031-14100-3_8#Sec9

[9] Sciolla, F., Chauveau, E., Marzio, L. D., Sarra, A., Bordi, F., Truzzolillo, D., Trabalzini, S., Carafa, M., & Marianecci, C. (n.d.). Influence of drug/lipid interaction on the entrapment efficiency of isoniazid in liposomes for antitubercular therapy: A multi-faced investigation. ar5iv. https://ar5iv.labs.arxiv.org/html/2101.10900v1

[10] Liu, G., Gao, N., Zhou, Y., Nie, J., Cheng, W., Luo, M., Mei, L., Zeng, X., & Deng, W. (2019, October 1). Polydopamine-based “four-in-one” versatile nanoplatforms for targeted dual chemo and photothermal synergistic cancer therapy. MDPI. https://www.mdpi.com/1999-4923/11/10/507

[11] Espana-Agusti, J., Zou, X., Wong, K., Fu, B., Yang, F., Tuveson, D. A., Adams, D. J., & Matakidou, A. (n.d.). Generation and characterisation of a PAX8-CREERT2 transgenic line and a SLC22A6-CREERT2 knock-in line for inducible and specific genetic manipulation of renal tubular epithelial cells. PLOSONE https://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0148055

[12] Author links open overlay Rana, D., Salave, S., Patel, R., Khunt, D., Misra, M., Prajapati, B., Patel, G., & Patel, J. (1970, January 1). Solid lipid nanoparticles in tuberculosis. SpringerLink. https://link.springer.com/chapter/10.1007/978-3-031-14100-3_6#Sec15

[13] Varma, J. N. R., Kumar, T. S., Prasanthi, B., & Ratna, J. V. (2015). Formulation and characterization of pyrazinamide polymeric nanoparticles for pulmonary tuberculosis: Efficiency for alveolar macrophage targeting. Indian journal of pharmaceutical sciences. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4502139/#ref7

[14] Xia, W., Tao, Z., Zhu, B., Zhang, W., Liu, C., Chen, S., & Song, M. (2021, August 24). Targeted delivery of drugs and genes using polymer nanocarriers for cancer therapy. MDPI. https://www.mdpi.com/1422-0067/22/17/9118

[15] Subjakova, V., Oravczova, V., & Hianik, T. (2021, January 21). Polymer nanoparticles and nanomotors modified by DNA/RNA aptamers and antibodies in targeted therapy of cancer. MDPI. https://www.mdpi.com/2073-4360/13/3/341

[16] Caster, J. M., Yu, S. K., Patel, A. N., Newman, N. J., Lee, Z. J., Warner, S. B., Wagner, K. T., Roche, K. C., Tian, X., Min, Y., & Wang, A. Z. (2017). Effect of particle size on the biodistribution, toxicity, and efficacy of drug-loaded polymeric nanoparticles in chemoradiotherapy. Nanomedicine Nanotechnology Biology and Medicine, 13(5), 1673–1683. https://doi.org/10.1016/j.nano.2017.03.002

[17] Suri, S. S., Fenniri, H., & Singh, B. (2007, December 1). Nanotechnology-based drug delivery systems - journal of occupational medicine and toxicology. SpringerLink. https://link.springer.com/article/10.1186/1745-6673-2-16

[18] Hickey, J. W., Santos, J. L., Williford, J., & Mao, H. (2015). Control of polymeric nanoparticle size to improve therapeutic delivery. Journal of Controlled Release, 219, 536–547. https://doi.org/10.1016/j.jconrel.2015.10.006

[19] Liao, Z., Wong, S. W., Yeo, H. L., & Zhao, Y. (2020). Smart nanocarriers for cancer treatment: Clinical impact and safety. NanoImpact, 20, 100253. https://doi.org/10.1016/j.impact.2020.100253

[20] Xu, S., Wang, L., & Liu, Z. (2020). Molecularly Imprinted Polymer Nanoparticles: an emerging versatile platform for cancer therapy. Angewandte Chemie International Edition, 60(8), 3858–3869. https://doi.org/10.1002/anie.202005309

[21] Dastidar, D. G., Roy, A., Ghosh, G., & Mandal, S. (2024). Applications of inorganic nanomaterials against tuberculosis: A comprehensive review. Current Drug Delivery, 21. https://doi.org/10.2174/0115672018295247240426055330

[22] Nair, A., Greeny, A., Nandan, A. et al. Advanced drug delivery and therapeutic strategies for tuberculosis treatment. J Nanobiotechnol 21, 414 (2023). https://doi.org/10.1186/s12951-023-02156-y

[23] Gupta, A., Pandey, S., & Yadav, J. S. (2020). A review on recent trends in green synthesis of gold nanoparticles for tuberculosis. Advanced Pharmaceutical Bulletin, 11(1), 10–27. https://doi.org/10.34172/apb.2021.002

[24] Santos, H. A., Bimbo, L. M., Peltonen, L., & Hirvonen, J. (2014). Inorganic nanoparticles in targeted drug delivery and imaging. Advances in Delivery Science and Technology, 571–613. https://doi.org/10.1007/978-3-319-11355-5_18

[25] Mubarak, M. M., Makane, V. B., Banu, A., Sloan, D. J., Tăbăran, A. F., Nasiruddin, M., Varghese, S., & Baranyai, Z. (2022b, September 17). Determination of anti-tuberculosis activity of biosynthesized gold nanocompounds against M. tuberculosis H37RV. Indian Journal of Tuberculosis.https://www.sciencedirect.com/science/article/abs/pii/S001957072200110X#preview-section-snippets

[26] Ang, C. W., Tan, L., Qu, Z., West, N. P., Copper, M. A., Popat , A., & Mark A.T. Blaskovich. (n. d.-b). ACS Publications: Chemistry journals, books, and references published ... http://pubs.acs.org/doi/full/10.1021/acsbiomaterials.7b00683