Review Article

Feasibility of Nano-Scaffold for Covid-19 infected lung tissue regeneration: A review

K. Jeevika, R. A. Sobiya, T. Indhumathi*, S. Kathiravan

Department of Biochemistry, Dr. N.G.P. Arts and Science College (Autonomous), Coimbatore - 641048, Tamil Nadu, India

Received: 7 April 2021 Revised: 27 June 2021 Accepted: 28 June 2021

Abstract

In December 2019, a cluster of cases of pneumonia of unknown origin was identified in Wuhan, China which was named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses. The Covid-19 attacks the respiratory system of the infected people leading to its severe damage by eliciting a vigorous immune response by our body. The disease has spread worldwide and affects human health. Covid-19, a newly reported virus is 96% similar to bat CoV. Upon inhalation, the virus enters the respiratory region by unlocking ACE2 protein. Type 2 alveolar cell leading to collapse of alveolus which leads to fluid accumulation, it causes ARDS, SIRS, multi organ failure which cause fatal consequences. In this review, the scope of nanoscaffold in the Covid-19 infected lung tissue regeneration was discussed. Tissue engineering and nanotechnology can help in formation of tissue and guide cellular activities. Damaged tissue can be regenerated by nanoscaffolds that have potential to be risk-free, antiviral and also biological therapeutics. Scaffolds provide intra and extracellular cell contact in regenerative medicine and can provide mechanical strength, oxygen and nutrients for cell metabolism, cell adhesion, and progressive maturation and remove metabolic waste products. It also has some limitations like short circulation half-life of bioactive molecules,inadequate extrinsic factors, variable toxicity, poor regulation and degradation rate. These nanoscaffolds for lung tissue damage due to Covid-19 improve adsorption of ECM protein, new tissue formation, and enhance biological regulation *of cell behavior for regeneration and help to recover from lung damage.*

Keywords: SARS, Covid-19, Lung tissue damage, Tissue engineering, Nanoscaffold

Introduction

On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARS- CoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from there (Xinhua, 2020). The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring (Huang et al, 2020).

In 2020, the typical respiratory syndrome known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a covid-19 disease which is a global challenge (Lofti et al., 2020). In the current pandemic, this disease majorly infects the respiratory system, especially the low respiratory system. This virus threatens human health which leads to increase in mortality rate of humans worldwide (Cascella et al., 2020). Covid-19 patients may suffer by chronic diseases like cardiovascular and cerebrovascular diseases and in severe cases it may infect endocrine system, digestive system and mostly affects respiratory system and nervous system. Usually, novel coronaviruses increase complications like organ function damage, respiratory injury, renal injury, ARDS (Acute Respiratory Distress Syndrome).

In the first case of SARS-Cov-2 identified in seafood market, Wuhan, China in late December 2019, presumed as pneumonia a highly infective disease (Li et al., 2020). Pulmonary disease (damage parts of lungs and other respiratory parts) globally, a health issue that reduces the life period as well as causes premature death. These problems injure lungs, so it gives rise to shortage of lungs for transplantation (Soriano, 2020). Masses of people were

Address for Corresponding Author:
Dr. T. Indhumathi
Professor, Department of Biochemistry,
Dr. N.G.P. Arts and Science College (Autonomous), Coimbatore - 641048,TamilNadu, India
Email: indhumathi@drngpasc.ac.in

DOI: https://doi.org/10.31024/ajpp.2021.7.3.2

facing long-term lung damage which makes a vast difference to Covid-19 patients. In severe Covid-19 infection the patients are affected by permanent lung damage (Pallab, 2020). During covid-19 infection, the respiratory system showed inflammation, which made it difficult to control the inflammation in the initial stage. Till now, numerous studies have been conducted to evaluate the safety, technique, vaccines, methods, etc. in wide range of research field. Researchers are suggesting therapeutical applications for Covid-19 using tissue engineering and regenerative medicine (TERM) products like stem cells, growth hormone, their derivatives (eg: exosomes) (Shafiee et al., 2021). Tissue engineering scaffolds greatly regenerate the damaged tissues and organs in our body. The usage of scaffolds with nanomaterial efficiently works on inflammation caused by lung tissue damages in Covid-19. This article examines various attributes like lung tissue damage regeneration using tissue engineering with nanomaterial applied for Covid-19 disease (Padmanabhan et al., 2015).

Covid-19

Severe acute respiratory syndrome coronavirus 2 is a highly transmissible and highly infective virus (Tatara, 2020).It originated in Wuhan city of China (Shereen et al., 2020). First they presumed it was started in the wet market, Huanan seafood market (Wang et al., 2020). It was a cause for the covid-19 disease (Zoonotic origin-Infection transfer from animal to human) (MacKenzie et al., 2020). SARS-CoV-2 genome was 96% similar to bat-Cov (Guo et al., 2020). Coronavirus has crown-like spikes on the outer wall and it has a size of 65-120nm in diameter. It has a single-stranded RNA material which sized from 26 to 32 kb. The coronavirus enters into other organisms with the help of genes for viral replication, nucleocapsid and spikes formation. To enter into humans this SARS coronavirus uses exopeptidase as a receptor. The genes like trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) will help the virus to transmit. The 394 glutamine residue in the RBD region of SARS-CoV-2 is recognized by the critical lysine 31 residue on the human ACE2 receptor and the virus will enter into human. The incubation period of this virus is about 1 to 14 days (Tatara, 2020). Transmission of virus has two chances one is droplet and fomite Transmission. Viral particles enter through the nose, eyes or mouth and bind to the ACE2 receptor in our body in lungs, kidney, intestinal (WHO. 2020). After the antigen entry, our body's two main immune lines (innate and adaptive immune response) get an impulse. It shows some clinical manifestations like high fever, tiredness, dry cough, sore throat, difficulty breathing, chills, loss of taste and smell and so on. In some cases, patients may be asymptomatic too. When it triggers our immune system, it has the ability to kill most viral particles quickly and show inflammation to trap viruses to spill out from our body. To destroy the virus, T Cells and B Cells may produce antibodies to kill the virus. Release, secreted protein cytokines to infect the targeted cell (Chowdhury et al., 2020).

Lung tissue damage due to Covid-19

When a virus enters the body, it gets contact with a mucous membrane that lines nose, mouth and eyes. After virus entry makes new virus parts by using healthy cell and infects nearby cells. The virus affects the airways and multiplies along the cells. Initial stage, the patient has respiratory symptoms directly impacts the lungs (Hosseini et al., 2020). Covid-19 captures the lungs cells and adjoining cells of it. Low respiratory infection travels down the airways of alveoli,a tiny air sac (Science Daily, 2020; Neha, 2020). SARS-CoV-2 causes infection of ACE2 assertion cells lies on epithelial cells of alveolar type 2 cells (Ptompetchara et al, 2020). Tissue-Engineeredinside type 2 cells the virus infects and multiple within the cells (Shravanti, 2020). Lungs become filled with fluid accumulation (Panagis, 2020). In some cases, studies of Covid-19 showed tissue damage with edema, bleeding and intra-alveolar fibrin settling with hyaline membrane (Laguipo et al., 2020). The respiratory tract infection includes nasal congestion, runny nose, fever and dyspnea (National Jewish Health, 2021; Yuki et al., 2020). In some extensive cases patients affected by blood clotting of lung arteries, veins and lung cells were abnormally large, leading to syncytia (The Hindu, 2020). Globally recognized that respiratory disease will damage pulmonary interstitial arteriolar walls (Li et al., 2020). After multiplication of cells, it infects tissues in airways and increases levels of BALFs, serum in covid-19 also increases cytokines levels like CCL-2, IFN-1, IFN-11, IL-6, etc., leads to cell death. These all cause multi organ damages and may lead to myocardial inflammation and fibrotic lungs ARDS (Harrison et al., 2020). Even though the patient in recovered state of Covid-19, lungs are still in damaged state, they need the ventilation and gas exchange is not completely functioning like a healthy people and in severe cases causes death due to this disease including central nervous system, cardiac, liver, kidney may also affect (The Economic Times, 2020; Zheng et al.,2020).

Tissue engineering in lungs

Many tissue engineering techniques are used to treat pulmonary diseases which are worldwide public health problems (Kubo, 2012). Scaffolds composed with natural or synthetic polymers can be used to treat the lung damage. Tissue engineering helps to limit lung transplantation (Tebyanian et al., 2019). For tissue engineering we need a scaffold to incorporate cells, source of stem cells (such as embryonic stem cells, endogenous pulmonary stem cells,

extra pulmonary stem cells, growth factors and bioreactor to cultivate cells. The cells are placed inside the scaffold and cultured in a bioreactor. When the patient's cells are placed in the biomaterials and used in affected lung tissue this will make the lung compatible to targeted immune system and cures the damage caused by infection (Tsuchiya et al., 2020). Recently, a human lung culture model was made from the human lung cells which is used to study the infections caused to lungs such as SARS COV -2 (Salahudeen et al., 2020). To study fibrosis in the lung due to infection, aviral infection microtissue was designed which detects the changes in stiffness of the lung tissue (Jane, 2020; Azimietal, 2020). Scaffold with poly (vinylidene fluoride-co-trifluoroethylene) [P(VDF-TrFE)] incorporating zinc oxide (ZnO), in the form of electrospun fiber meshes showed the anti-inflammatory, antimicrobial activity, increases the cell growth in the lungs (Aiyelabegan et al., 2016).The albumin loaded on the scaffolds will be effective in treating the lungs (Singh et al.,2020). So lung tissue engineering reduces the lung transplantation and it can be used to treat some inflammations caused by viral diseases. These tissue engineering can contribute in this time of Covid-19 pandemic to lead the way to prevent and treat (Meyer, 2020). Tissue engineering widely a great path for detecting future viral diseases (Tatara et al., 2016). This tissue engineering technique helps to know about infection, design in DDS and increases biocompatibility (Henderson et al., 2020). Biofabrication gives proper disease models to discover medicine for disease. For example, 2D and 3D models of lung are used to find medicines for Covid-19 (Farre et al., 2020). 3D models can be used to study the progression of disease and in drug discovery (Alsafadi et al., 2017). The 3D models are better than animal models and 2D models, as they provide 3D multi cell interactions (Laura Elizabeth Lansdowne, 2020). 3-D bioprinted models help to check how the drug response in tissue. For infections such as virus, 3D bioprinted lung model is used widely (Gerckens et al., 2019). Recently for Covid-19 patients computational lung model was developed (Jakob Richter, 2020).

Nanoscaffolds for lung tissue damage

SARS-CoV-2 primarily infects the respiratory system first after then extending to other organs of the body like heart, kidney, liver and so on (Li et al., 2020). Although, this virus affects directly our tissue when we observed in covid-19 patients, the virus can reach the organs of the body as these organs expressACE2 receptors (Hamming et al., 2004). In our body, highly expel ACE2 receptors present in lungs, bronchial cells act as entry site and binding site for SARS-CoV-2 virus (Turner et al., 2004). Nanoscaffold directly safe and effective for eliminating the spreading of virus through initial interactions of virus spike protein with human cell surface ACE2 receptor and disrupt the virus replication (Chauhan et al., 2020).Currently various vaccines, technique are suggesting for global health, we are in an urgent situation to develop advanced therapeutics options for Covid-19 cases on account of we can't control the spreading of virus still now (Cortiella et al., 2006; Ghoraishizadeh et al., 2014). Cell therapy has some possibilities to regenerate the function of myocardial tissue because the lung tissue damage is most commonly in Covid-19 patients (Buxton, 2009; Letizia et al., 2013). Many studies were going on in this field like stem cell isolation for making a scaffold with great effective nanotechnology (Solchaga et al., 2011). The experts were saying that nanoscaffold can provide a nanofibre to produce an actual regenerative medicine using tissue engineering with nanomaterials (Kunisaki et al., 2006). Nanotechnology was widely used for pulmonary therapies,in effluxing of cancer cells, blockading the apoptosis in sepsis (Raji et al., 2020). These scaffolds can work on intra and extracellular cell contact.Nanomaterial scaffolds are manufactured through various methods like electrospinning which can display the properties for the purpose (Campos et al., 2020). In lung tissue damage, the *ex vivo* method of nanoscaffold is frequently used in regeneration of lung tissue (Ahn et al., 2020). So some studies explaining the sources for airways and alveolar like structured scaffolds production for lung tissue regeneration. These scaffolds can be worn for the present pandemic Covid-19 patients, especially gold nanoparticles which have a unique property in biomedical applications. The AuNPs scaffold is the finest for virus-infected tissue regeneration for all respiratory systems (Kostarelos, 2020). Nanoscaffold, it's a greatest strategy to regenerate the lung tissue damage in Covid-19 patients which gives a thousands of benefits to improve the potential of lung tissue regeneration and blood diseases too. Covid-19 majorly infects lower respiratory tract and some viral organs such as cardiac, liver, kidney, GIT, CNS and causes various organ damage and complication which all leads to death (Lurie et al., 2020). Table 1. depicts the applications of nanocarriers in tissue engineering.

Prominent role of nanoscaffolds in Covid-19

Nanotechnology plays a crucial role in therapeutics for the current outbreak which fast-tracks the Covid-19 research (Singh et al., 2017). Nanoscaffolds are a great approach for designing the nanocarriers. Nanocarriers are having a potential to antiviral and biological therapeutics for Covid-19 patients (Hisatoshi et al., 2008). Nanoscaffolds discharge the overcoming tissue barriers and play an important function in loaded antigens (Cortiella et al., 2006). While using the nanoscaffolds for lung tissue damage and even for other organs it targets both the two main lines of defense of our body, innate and adaptive

Table 1. Applications of Nanocarriers in Tissue Engineering

S.No	Nanocarrier	Advantages	Disadvantages	Reference
1	Liposomes	Biocompatible; It is used for both polar and nonpolar agents.	Less stability; Large scale production is difficult due to high cost.	Karami *et al*., 2018
2	Gold	Adaptable size; Biocompatible; Can synthesize and bind with multiple agents; Good electrical and mechanical property.	High cost for large scale production; Not biodegradable.	Ding *et al*., 2014
3	Carbon nanotube	Can integrate with multiple bioactive agents; Can able to enclose and deliver multiple agents; Large surface area.	Toxic; Not biodegradable; Less soluble in water.	Kirkpatrick *et al*., 2012
4	Quantum dots	Tunable size; Imaging property; High photo stability; Long lifetime with high quantum yield.	Less stable; Toxic in *invivo* system; Multi exponential of fluorescence.	Shan et al., 2011
5	Silica	High bioavailability; Well defined surface properties.	Preparation of well-ordered material is difficult; Disintegrate in size distribution.	Jafari et al., 2019
6	Polymeric micells	Increase the solubility of high lipophilic drugs; Decrease surface free energy.	Low loading capability; Uses only lipophilic drug.	Kahraman et al., 2017
7	Dendrimer	Provides multifunctional nanomaterial; Used for targeting, imaging system.	High cost for their synthesis; Toxicity in cellular function.	Mehta *et al*., 2019

immunity. These nanomedicine scaffolds are restrained antigens from active cells. It implies the drug discovery for SARS-CoV-2. Nanoscaffolds are advantageous in application of detection, diagnosis, treatment for lung tissue damage due to viral infections (Fathi-Achachelouei et al., 2019; Tabata, 2009). Nanotechnology scaffolds (n-scaffold) is a biodegradable polymer which is beneficial in natural extracellular matrix and nanoscale fibrous structure stimulation (Ferracane and Giannobile, 2014). These provide enormous mechanical strength to monitor the cellular activities in regenerative medicine (Zhang et al., 2018). Distribute cells with micro ecosystems, enhance and regulate the capability of cell-based tissue engineering majorly functioning on DDS (drug delivery system) (Ebrahimi et al., 2019). Fibrous structure nanoscaffolds are short in diffusional path which leads to high porosity and interconnected with drug delivery for various purposes like transporting the nutrients (Wang et al., 2012). Bioactive glass NP-scaffolds, AuNPs, CP group of scaffolds, silica NP scaffolds are all involved in repair of tissue damage for Covid-19 patients with high eminent resources like biocompatibility, naturally tissue regeneration, high security and cheap (Funda et al., 2020). The major advantage of these NP-scaffolds are uniformly morphological and have chemical stability (Deng et al., 2012). Delicate nanoscaffolds are applied in reinforced cross linking agents and pores in the material allows it to interact with interior tissue which infiltrates within scaffolds. Invasive surgery can be restored by self-hardening biomaterial scaffolds which release the minerals from it and generate apatite crystals too (D'Amora et al., 2017). Nanoscaffolds for lung tissue repair produce vascularization for oxygen supply and nutrients for cells. Sometimes it helps to remove metabolic waste products and regulates the cellular metabolism within the scaffolds (Yancong et al., 2015). Relieves cell adhesion and involves in formation of tissue for scaffolds and it guides the cellular activities. Appropriate physio-chemical properties for tissue regeneration and controlled degradation are assets by using this (Christopher *et al*., 2015). Peculiar events in tissue levels are controlled and endorse the progressive maturation and remodeling take account in kinetics degradation too (Mi et al., 2016; Graham et al., 2015).

Limitation of nanoscaffolds

The nanoscaffolds for lung tissue damage have an enormous benefit even though it has some limitation like low solubility, unstable bioactivity and reduce the life period of bioactive molecules such as growth factors, cytokines, inhibitors, genes, etc., (Hosseinpour et al., 2017). Nanoscaffolds have a contract agent which decreases the bioactive agent delivery and monetization need more attention for it (Ionescu et al., 2010). In tissue regeneration, the major disadvantage is impairment of cellular differentiation because of inadequate production of extrinsic factors produced by nanoscaffolds (Vieira et al., 2017). These have biocompatibility and great regenerative property but it cannot control the framework degradation in every process of repairment (Liu et al., 2008). In the initial stage of action, it frees up a huge amount of diffusion path in a wide range of areas in the scaffolds. Sometimes, some nanoscaffolds with nanoparticles like silica can produce an irregular toxicity. Drug delivery, degradation, mechanical strength, these properties become very poor. Nanoscaffolds can cause very low toughness. The main importance we should maintain is the level of biological factors and drug delivery system in nanoscaffolds making because it makes instability and cause risk factors into scaffolds in the repair process (Carbone et al., 2014).

Conclusion

Pneumonia can decrease the oxygen and can increase the lipid accumulation in the lung thus damaging the lung tissue. It reduces the alveolar capillary barrier function and develops the intestinal lung edema. Infections like Covid-19 cause damage to the lungs that occurs with edema and bleeding;also the intra-alveolar fibrin settles with a hyaline membrane. In this context, tissue engineering and stem cell therapy has a great scope and possibility that they can reduce lung damage. Tissue engineering helps in the design

of disease models to study about the disease and also to discover drugs. The various biomaterials in tissue engineering like scaffolds can be designed to reduce lung damage. These improve the adsorption of ECM proteins like collagen and reduce the damage. Nanoscale structural elements in tissue engineering scaffolds can be effective in promotion of cell distribution and new tissue formation so tissue engineering plays an important role in case of infections like Covid-19 to design the disease models. Lung damage due to infections like SARS Corona Virus 2 can be regenerated using tissue engineering as scaffolds and other biomaterials heal the tissue damage and aid in growth of new cells.

Conflicts of interest

We declare that we have no conflicts of interests

Acknowledgement

The authors wish to express their sincere thanks to the management of Dr.N.G.P. Arts and Science College (Autonomous), Coimbatore for rendering all the facilities and support. Communication Number:DrNGPASC2020-21 BS073

References

Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, Kim BT, Kim SJ. 2020. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). Journal of Microbiology and Biotechnology, 30(3):313-324.

Aiyelabegan HT, Zaidi SS, Fanue Sl, Eatemad Ai, Ebadi MT, Sadroddiny E. 2016. Albumin-based biomaterial for lung tissue engineering applications. International Journal of Polymeric Materials and Polymeric Biomaterials, 65(16):853-861.

Alsafadi HN, Staab-Weijnitz CA, Lehmann M, Lindner M, Peschel B, Königshoff M, Wagner DE. 2017. An ex vivo model to induce early fibrosis-like changes in human precision-cut lung slices. American Journal of Physiology-Lung Cellular and Molecular Physiology, 312(6):L896-L902.

Amora D, Russo U, Gloria T, Rivieccio A, D'Antò V, Negri V, Ambrosio G, De L, Roberto S. 2017. 3D additive-manufactured nanocomposite magnetic scaffolds: Effect of the application mode of a time-dependent magnetic field on hMSCs behavior. Bioactive materials, 09, Vol.2 (3), p.138-145.

Azimi B, Sorayani Bafqi MS, Fusco A, Ricci C, Gallone G, Bagherzadeh R, Donnarumma G, Uddin MJ, Latifi M, Lazzeri A, Danti S. 2020. Electrospun ZnO/poly (vinylidene fluoride-trifluoroethylene) scaffolds for lung tissue engineering. Tissue Engineering Part A 26(23-24).

Buxton DB. 2009. Nanomedicine for the management of lung and blood diseases. Nanomedicine (Lond). 4(3):331-9.

Campos EVR, Pereira AES, de Oliveira JL, Carvalho LB, Guilger-Casagrande M, de Lima R, Fraceto LF. 2020. How can nanotechnology help to combat COVID-19? Opportunities and urgent need. Journal of Nanobiotechnology, 18(1):125.

Carbone EJ, Jiang T, Nelson C, Henry N, Lo KW. 2014. Small molecule delivery through nanofibrous scaffolds for musculoskeletal regenerative engineering. Nanomedicine, 10(8):1691-9.

Chauhan G, Madou MJ, Kalra S, Chopra V, Ghosh D, Martinez-Chapa SO.2020. Nanotechnology for COVID-19: Therapeutics and Vaccine Research. American Chemical Society Nano, 14(7):7760-7782.

Chowdhury MA, Hossain N, Kashem MA, Abdus Shahid Md, Alame A. 2020. Immune response in COVID-19: A review. Journal of Infection and Public Health, 13(11):1619-1629.

Christopher JC, Gregory T, Jennifer T, Saucier-Sawyer K, Mark Saltzman W. 2015. A holistic approach to targeting disease with polymer nanoparticle. Nature Reviews Drug Discovery, 14(4):239–247.

Computer model of the lung enables protective ventilation. 2020. healthcare-in-europe.com. https://healthcare-in-europe.com/en/news/computer-model-of-the-lung-enables-protective-ventilation.html

Coronavirus: Information & Resources. 2021. National Jewish Health. https://www.nationaljewish.org/patients-visitors/patient-info/important-updates/coronavirus-information and-resources/overview

Coronavirus: Lung damage in COVID-19 dead may shed light on 'long COVID': study. The Hindu. All about Covid19. Accessed on 04 November 2020 11:25 IST. https://www.google.com/amp/s/www.thehindu.com/sci-tech/science/lung-damage-in-covid-dead-may-shed-light-on-long-covid-study/article33019642.ece/amp/

Cortiella J, Nichols JE, Kojima K, Bonassar LJ, Dargon P, Roy AK, Vacant MP, Niles JA, Vacanti CA. 2006. Tissue-engineered lung: an in vivo and in vitro comparison of polyglycolic acid and pluronic F-127 hydrogel/somatic lung progenitor cell constructs to support tissue growth. Tissue Engineering, 12(5):1213-25.

Deng M, James R, Laurencin CT, Kumbar SG. 2012. Nanostructured polymeric scaffolds for orthopaedic regenerative engineering. IEEE Trans Nanobioscience, 11(1):3-14.

Ding Y, Jiang Z, Saha K, Kim CS, Kim ST, Landis RF, Rotello VM. 2014. Gold nanoparticles for nucleic acid delivery. Molecular Therapy, 22(6):1075-1083.

Ebrahimi M, Botelho M, Lu W, Monmaturapoj N. 2019. Synthesis and characterization of biomimetic bioceramic

nanoparticles with optimized physicochemical properties for bone tissue engineering. Journal of Biomedical Materials Research A, 107(8):1654-1666.

Emine K, Sevgi G, Yildiz O. 2017. Potential enhancement and targeting strategies of polymeric and lipid-based nanocarriers in dermal drug delivery. Therapeutic Delivery. 8. 967-985.

Farre R, Otero J, Almendros I, Navajas D. 2018. Bioengineered lungs: A challenge and an opportunity. Archivos de Bronconeumologia, 54(1):31–38.

Fathi-Achachelouei M, Knopf-Marques H, Ribeiro da Silva CE, Barthès J, Bat E, Tezcaner A, Vrana NE. 2019. Use of Nanoparticles in Tissue Engineering and Regenerative Medicine. Frontiers in Bioengineering and Biotechnology, 7:113.

Ferracane JL, Giannobile WV. 2014. Novel biomaterials and technologies for the dental, oral, and craniofacial structures. Journal of Dental Research, 93(12):1185-6.

Frontiers. 2020. How COVID-19 kills: Explaining the mechanisms, symptoms, and diagnosis of the new coronavirus. Science Daily. https://www.sciencedaily.com/releases/2020/05/200513081810.htm

Funda G, Taschieri S, Bruno GA, Grecchi E, Paolo S, Girolamo D, Del Fabbro M. 2020. Nanotechnology Scaffolds for Alveolar Bone Regeneration. Materials (Basel), 13(1):201.

Galiatsatos P. 2020. What Coronavirus Does to the Lungs? John Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/what-coronavirus-does-to-the-lungs

Gerckens M, Alsafadi HN, Wagner DE, Lindner M, Burgstaller G, Königshoff M. 2019. Generation of Human 3D Lung Tissue Cultures (3D-LTCs) for Disease Modeling. Journal of visualized experiments; Feb 12;(144).

Ghoraishizadeh S, Ghorishizadeh A, Ghoraishizadeh P, Daneshvar N, Boroojerdi MH. 2014. Application of Nanoscaffolds in Mesenchymal Stem Cell-Based Therapy. Advances in Regenerative Medicine, vol. 2014, Article ID 369498, 14 pages.

Ghosh P. 2020. Covid-19: Lung damage 'identified' in study. BBC News. https://www.bbc.com/news/health-55017301.

Graham G. Walmsley, McArdle A, Tevlin R, Momeni A, Atashroo D, Michael S, Abdullah Hu, Feroze H, Victor W, Peter W, Lorenz H, Michael TL, Derrick C, Wan MD. 2015. Nanotechnology in bone tissue engineering. Nanomedicine, 11(5):1253–1263.

Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. 2020. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Medical Research, 7(11).

Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology, 203(2):631-7.

Harrison AG, Lin T, Wang P. 2020. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends in Immunology, 41(12):1100-1115.

Henderson E. 2020. Tissue engineering can play an important role during COVID-19 pandemic, News Medical Life Sciences. https://www.news-medical.net/news/20200508/Tissue-engineering-can-play-an-important-role-during-COVID-19-pandemic.aspx

Hosseini ES, Kashani NR, Nikzad H, Azadbakht J, Bafrani HH, Kashani HH. 2020. The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. Virology 551: 1–9.

Hosseinpour S, Ghazizadeh Ahsaie M, Rezai Rad M, Baghani MT, Motamedian SR, Khojasteh A. 2017. Application of selected scaffolds for bone tissue engineering: a systematic review. Oral and Maxillofacial Surgery. 21(2):109-129. doi: 10.1007/s10006-017-0608-3. Epub 2017 Feb 13. PMID: 28194530.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. 2019. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet Journal. 2020; 395:497–506. doi: 10.1016/S0140-6736(20)30183-5.

Jafari S, Derakhshankhah H, Alaei L, Fattahi A, Varnamkhasti BS, Saboury AA. 2019. Mesoporous silica nanoparticles for therapeutic/diagnostic applications. Biomedicine and Pharmacotherapy, 109:1100-1111.

Karami, N, Moghimipour E, Salimi A. 2018. Liposomes as a Novel Drug Delivery System: Fundamental and Pharmaceutical Application. Asian Journal of Pharmaceutics, 12(1):S31-41.

Kirkpatrick DL, Weiss M, Naumov A, Bartholomeusz G, Weisman RB, Gliko O. 2012. Carbon Nanotubes: Solution for the Therapeutic Delivery of siRNA? Materials (Basel). 5(2):278-301.

Kobayashi H, Yokoyama Y, Yoshikawa C, Igarashi S, Hattori S, Honda T, Koyama H, Takato T. 2008. Nanofiber-based Scaffolds for Tissue Engineering. Biomaterials in Asia, 182-193.

Kostarelos K. 2020. Nanoscale nights of COVID-19.

Nature Nanotechnology, 15(5):343-344.

Kubo H. 2012. Tissue engineering for pulmonary diseases: Insights from the laboratory. Respirology, 17(3):445-454.

Kunisaki SM, Fuchs JR, Kaviani A, Oh JT, LaVan DA, Vacanti JP, Wilson JM, Fauza DO. 2006. Diaphragmatic repair through fetal tissue engineering: a comparison between mesenchymal amniocyte- and myoblast-based constructs. Journal of Pediatric Surgery. 41(1):34-9; discussion 34-9.

Laguipo A. 2020. Persistent and extensive lung damage seen in COVID-19 patients. News-Medical Life Sciences. https://www.news-medical.net/news/20201105/Persistent-and-extensive-lung-damage-seen-in-COVID-19-patients.aspx

Lara CI, Gregory CL, Brian JS, Jason AB, Robert LM. 2010. An anisotropic nanofiber/microsphere composite with controlled release of biomolecules for fibrous tissue engineering. Biomaterials. Volume 31, Issue 14, Pages 4113-4120.

Laura Elizabeth Lansdowne, Senior Science Writer, Technology Networks. 2020. Using Bioprinted Tissue Models to Test Drugs Against Diseases Including COVID-19.

Li G, Fan Y, Yanni Lai Y, Han T, Li Z, Zhou P, Pan P, Wang W, Hu D, Liu X, Zhang Q, Wu J. 2020. Coronavirus infections and immune responses. Journal of Medical Virology, 92(4):424-432.

Li H, Zhe Liu Z, Ge J. 2020. Scientific research progress of COVID-19/SARS-CoV-2 in the first five months. Journal of Cellular and Molecular Medicine, 24:6558–6570.

Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, Shen B, Gong Z. 2020. Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. International Journal of Infectious Diseases, 94:128-132.

Liu L, Liu J, Wang M, Min S, Cai Y, Zhu L, Yao J. 2008. Preparation and characterization of nano-hydroxyapatite/silk fibroin porous scaffolds, Journal of Biomaterials Science, Polymer Edition, 19:3, 325-338.

Lotfi M, Hamblin MR, Rezaei N. 2020. COVID-19: Transmission, prevention, and potential therapeutic opportunities. Clinica Chimica Acta; International Journal of Clinical Chemistry, 508:254–266.

Lurie N, Saville M, Hatchett R, Halton J. 2020. Developing Covid-19 Vaccines at Pandemic Speed. The New England Journal of Medicine, 382(21):1969-1973.

Mackenzie JS, Smith DW. 2020. COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't. Microbiology Australia. 41(1):45-50.

Marco C, Michael R, Abdul A, Scott C, Dulebohn R, Di N. 2020. Features, Evaluation, and Treatment of Coronavirus.In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing

Mehta P, Pawar A, Kadam S, Chellam B. 2019. Dendrimers for pulmonary delivery: Current perspectives and future challenges. New Journal of Chemistry, 43, 8396-8409.

Meyer KC. 2020. Risks of lung transplantation in the SARS-CoV-2 era. The lancet respiratory medicine, 9(3):224-226.

Mi P, Kokuryo D, Cabral H, Wu H, Terada Y, Saga T, Aoki I, Nishiyama N, Kataoka K. 2016. A pH-activatable nanoparticle with signal-amplification capabilities for non-invasive imaging of tumour malignancy. Nature Nanotechnology, Vol. 11(8):724-30.

'Most patients who recovered in Wuhan suffer lung damage'. 2020. Healthworld.com. From the Economic Times. Accessed on August 06, 2020, 07:43. https://www.google.com /amp/s/health.economictimes.indiatimes.com/amp/news/diagnostics/most-patients-who-recovered-in-wuhan-suffer-lung-damage/77383786

Padmanabhan J, Kyriakides TR. 2015. Nanomaterials, inflammation, and tissue engineering. Wiley Interdisciplinary Reviews Nanomedicine Nanobiotechnology, 7(3):355-70.

Pathak N. 2020. What Does COVID-19 Do to Your Lungs? WebMD Medical Reference.

Prompetchara E, Ketloy C, Palaga T. 2020. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pacific Journal of Allergy Immunology, 38(1):1-9

Salahudeen, AA, Choi SS, Rustagi A. 2020. Progenitor identification and SARS-CoV-2 infection in human distal lung organoids. Nature 588,670–675.

Shafiee A, Moradi L, Lim M, Brown J. 2021. Coronavirus disease 2019: A tissue engineering and regenerative medicine perspective. Stem Cells Translational Medicine, 10(1):27-38.

Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. 2020. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research, 24:91-98.

Shravanti S. 2020. What Does Immunity Against COVID-19 Really Mean? Health, The Sciences. https://science.thewire.in/the-sciences/covid-19-individual-herd-immunity-immunoglobulin-antibody-dependent-enhancement/

Singh AK, Mishra G, Maurya A, Kulkarni GT, Awasthi R. 2020. Biofabrication: An interesting tool to create in vitro model for COVID-19 drug targets. Medical Hypotheses, 144 :110059

Singh L, Kruger HG, Maguire GEM, Govender T, Parboosing R. 2017. The role of nanotechnology in the treatment of viral infections. Therapeutic Advances in

Infectious Diseases, 4(4):105-131.

Solchaga LA, Penick KJ, Welter JF. 2011. Chondrogenic differentiation of bone marrow-derived mesenchymal stem cells: tips and tricks. Methods in Molecular Biology, 698:253-78.

Soriano JB, Kendrick PJ, Paulson KR, Gupta V, Vos T. 2020. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.The lancet Respiratory Medicine, 8(6):585-596.

Tabata Y. 2009. Biomaterial technology for tissue engineering applications. Journal of Royal Society Interface. 6 Suppl 3(Suppl 3):S311-24.

Tatara AM, Ratcliffe A, Mark EK, Wong F, Antonios KK Mikos G. 2015. Chapter 12 - Biomaterials in Regenerative Medicine: Considerations in Early Process Development. Translational Regenerative Medicine, 141-149.

Tatara AM. 2020. Role of Tissue Engineering in COVID-19 and Future Viral, Outbreaks. Tissue Engineering Part A 26(9-10):468–474.

Tebyanian H, Karami A, Nourani MR, Motavallian E, Barkhordari A, Yazdanian M, Seifalian A. 2019. Lung tissue engineering: An update. Journal of Cellular Physiology, 234 (11):19256-19270.

Tsuchiya T, Doi R, Obata T, Hitachi G, Nagayasu T. 2020. Lung Microvascular Niche, Repair, and Engineering. Frontiers in Bioengineering Biotechnology 8:105.

Turner AJ, Hiscox JA, Hooper NM. 2004. ACE2: from vasopeptidase to SARS virus receptor. Trends in Pharmacological Sciences, 25(6):291-4.

UB Now, News and views for UB faculty and staff. http://www.buffalo.edu/ubnow/stories/2020/11/engineered-tissue-lung-disease.html

V R, Pal K, Zaheer T, Kalarikkal N, Thomas S, de Souza FG, Si A. 2020. Gold nanoparticles against respiratory diseases: oncogenic and viral pathogens review. Therapeutic Delivery, 11(8):521-534.

Ventrelli L, Ricotti L, Menciassi A, Mazzolai B, Mattoli V. 2013. Nanoscaffolds for Guided Cardiac Repair: The New Therapeutic Challenge of Regenerative Medicine. Journal of Nanomaterials, Vol. 2013, Article ID 108485, 16 pages.

Vieira S, Vial S, Reis RL, Oliveira JM. 2017. Nanoparticles for bone tissue engineering. Biotechnology Progress. 33(3):590-611.

Wang H, Leeuwenburgh SC, Li Y, Jansen JA. 2012. The use of micro- and nanospheres as functional components for bone tissue regeneration. Tissue Engineering Part B Reviews, 18(1):24-39.

Wang H, Li X, Li T, Zhang S, Wang L, Wu X, Liu J. 2020. The genetic sequence, origin, and diagnosis of SARS-CoV-2. European Journal of Clinical Microbiology and Infectious Diseases, 24:1–7.

Welch JS. 2020. Engineers investigate engineered tissue to treat lung disease, University at Buffalo

WHO. 2020. Transmission of SARS-CoV-2: implications for infection prevention precautions. Scientific Brief. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions

Xinhua. China's CDC detects a large number of new coronaviruses in the South China seafood market in Wuhan. Available at: https://www.xinhuanet.com/2020-01/27/c_1125504355.htm. Accessed 20 Feb 2020.

Yuki K, Fujiogi M, Koutsogiannaki S. 2020. COVID-19 pathophysiology: A review. Clinical Immunology 215:108427.

Zhang J, Chen Y, Xu J, Wang J, Li C, Wang L. 2018. Tissue engineering using 3D printed nano-bioactive glass loaded with NELL1 gene for repairing alveolar bone defects. Regenerative Biomaterials, 5(4):213-220.

Zhang Y, Sun H, Song X, Gu X, Sun C. 2015. Biomaterials for Periodontal Tissue Regeneration. Reviews on Advanced Materials Science, 209-214.

Zheng YY, Ma YT, Xie X. 2020. COVID-19 and the cardiovascular system. Nature Reviews. Cardiology 17:259–260.