# Advanced Hydrogel Systems for Encapsulation and Co-Delivery of Therapeutic Compounds, Cells, and Nanomaterials

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## Abstract

As many medications are administered jointly, they often give larger benefits, counteract disadvantages, and enhance treatment results compared to monotherapy. Whether natural or synthetic, injectable biomaterials can form degradable networks in situ, decreasing patient pain and cost while presenting new and promising possibilities for minimally invasive surgery. Biomaterials' ability to create and manufacture injectable systems is strongly impacted by their physicochemical and mechanical properties. The design and manufacture of injectable systems containing cells, therapeutic molecules, particles, and biomolecules that can be injected into geometrically complex body tissue regions poses a significant challenge as they must ensure drug/biomolecule/material bioactivity, cell survival and retention. Hydrogels are a promising choice in this case given their amazing ability to manipulate, encapsulate and co-deliver pharmaceutical chemicals, cells, biomolecules, and nanomaterials. Hydrogels can alter their mechanical and deteriorating qualities by adjusting the cross-linking technique and chemical composition. The ability to modify IH's mechanical strength permits co-encapsulation of medicinal compounds, cells, nanomaterials, and growth factors in the matrix in situ, allowing for multimodal synergistic therapies.

To boost the prospects of translating IHs into normal clinics, various barriers and outstanding scientific issues must be tackled in the future. Future investigations, including the application of IHs in multimodal synergistic treatment, should start with large animal models such as monkeys and dogs or even ex vivo human tissue models. In addition, the period of in vivo evaluations should be prolonged from weeks to months for trustworthy and accurate data to be translated to clinical trials. On the one hand, the toxicity of certain crosslinking agents used in IH synthesis must be considered, as the residues will cause unwanted in vivo reactions.Toxic crosslinkers, on the other hand, may interact with therapeutic molecules/biomolecules or nanomaterials trapped in the hydrogel matrix, causing loss of bioactivity. Similarly, IHs' sol–gel transition is a vital issue requiring much investigation. A quick sol–gel transition of precursor solutions might cause the fluid to be caught in the needle, whereas high-viscosity precursor solutions need high injection force, resulting in physician hand fatigue and patient annoyance. Other concerns for clinical IH translation include fast release and rate of degradation. Degradation rate is critical in controlling therapeutic drug release and tissue regeneration. Fast hydrogel breakdown may trigger early inflammatory reaction due to breakdown products, whereas delayed degradation may result in insufficient release of therapeutic drugs. Changing the composition, structure, and crystallinity of polymers must be employed to customize the breakdown rate. Expert researchers will be better equipped to tackle these challenges if they have a deeper knowledge of polymers' physiochemical features. Overall, future IH design should focus on building simple, well-defined 3D networks with low toxicity, high biodegradation rate, and acceptable functionality.

## 1 Introduction

Changes in lifestyle, nutrition, physiological, and environmental conditions have led to an increase in difficult-to-treat diseases and socioeconomic challenges around the world. These changes have resulted in an increase in conditions such as cancer, cardiovascular disorders, neurodegenerative disorders, and infectious diseases, all of which pose a threat of death to humans. 1 and 2 Due to the physiological complexity of hard-to-treat disorders, clinical experience and exploratory investigations have shown over the past decade that a single therapy approach may be unable to sufficiently battle them. This conclusion was reached as a result of the fact that a single therapy method has been demonstrated to be unable to adequately combat them. (3) Because the synergy of therapeutic substances or procedures creates large superadditive (that is, "1 + 1 > 2") therapeutic effects, recent discoveries have increasingly drifted away from monotherapy and toward combination or multiple treatments. (4) As a consequence of this, the use of combined or multiple therapies has been proposed as an alternative to monotherapy in order to mitigate the negative effects. (5) In spite of the many advantages they offer, existing combinations of treatments or multiple treatments each have a number of drawbacks that may limit how they can be utilized in clinical settings. For example, the potentiation of certain pharmaceuticals for combined or multiple therapy is significantly sequence dependent; as a result, the simultaneous combination of certain medications does not provide synergistic benefits in the fight against difficult-to-treat illnesses. (6) In addition, the challenges that come with the creation of new formulations have hindered the expansion of multi-therapeutics. For instance, the Gliadel wafer is a post-surgical drug delivery implant that is intended to prevent tumor recurrence; however, it has a number of drawbacks, such as rapid drug release, inability to adapt to the shape and anatomy of the desired site, and subsequent implant dislodgement; high rigidity of the structure; and consequently, the requirement for a large resection cavity size (especially for the treatment of glioblastoma). (8) As a consequence of this, new platforms need to be developed in order to make it possible to load many therapeutic compounds into implants at the same time. For instance, this may be done in order to provide antibacterial and anti-inflammatory properties while simultaneously destroying cancer cells after cancer tissue has been surgically removed. (9) There is an immediate need in this field for new injectable platforms that have adhesion capabilities and the ability to enable for the controlled and sustained release of medicinal chemicals. (9)

In order to realize, specificity, and durability of combination or multiple treatments to achieve positive synergistic effects, the proper integration of numerous therapeutic molecules in a single platform, rather than simple mixing, is critical. (9) Rapid breakthroughs in nanotechnology and biomaterials have made it possible to assemble a platform from a variety of medications, growth factors, and particles via chemical interactions or simple physical adsorption without labile interactions. (12) Hydrogels are three-dimensional networks of cross-linked polymer chains that have the ability to absorb huge quantities of water and biological fluids. These networks have the potential to be utilized as controlled drug delivery platforms or as an artificial extracellular matrix (ECM) for the purposes of tissue engineering. (13)

In addition, many polymeric hydrogel systems have shear thinning and self-recovery capabilities, or they can be formed in situ within the body after being injected as a liquid. These systems can also be described as having self-recovery characteristics. (14) As a result of these characteristics, it is possible to produce injectable hydrogels (IHs), (15, 16) which are promising candidates for cancer therapy, cartilage repair, angiogenesis and vascularization, (19-21) tissue engineering, (22) repair of the nervous system, (19) therapeutic delivery, (23, 24) wound healing, (25, 26), and other applications. The formation of in situ forming hydrogels can be accomplished by the use of physical contacts (including ionic and hydrophobic contacts, as well as supramolecular chemistry), non-toxic chemical crosslinkers, or biological cross-linking via enzymes. (27)

IHs are excellent candidates for use in biomedical applications due to their outstanding properties, which include ease of handling and use, minimal invasiveness, the capability for simple and long-term cell and growth factor encapsulation without the need for chemical cross-linking, shape adaptability, proper adherence to the surrounding tissues during in situ formation, and improved patient compliance. IHs also have the ability to encapsulate cells and growth factors without the need for chemical cross-linking. 16, 28

The concept of modifying and optimizing IHs for use in various therapies is still in its infancy stage. The peculiar structure of IHs enables the efficient trapping of large payloads of a variety of therapeutic agents, as well as the protection of these payloads against enzymatic degradation and the regulated release of these payloads in the target region. 11 and 29 In this review, we discuss the methodologies for synthesizing and characterizing IHs, in addition to recent advancements in their usage for multitherapy of cancer, wound healing, and other illnesses.

2 Methods for the Preparation of IHs In general, IHs can be manufactured by either chemical or physical cross-linking processes. Secondary forces, in which non-covalent interactions lead to the creation of polymeric networks without the requirement for chemical stimuli, can be used to accomplish the feat of physically cross-linking two different polymeric molecules. Non-covalent interactions such hydrophobic contacts, hydrogen bonding, ion cross-linking, and host–guest interactions were used in the construction of the physically cross-linked IHs. Despite the fact that IHs that have been physically cross-linked are biocompatible and pose a low risk to human health in terms of cytotoxicity, they frequently have mechanically unstable features as a result of temporary junctions between the chains. On the other hand, chemically cross-linked IHs are produced by creating new covalent connections between polymer chains. This process results in junctions that are permanent, stable, and have great mechanical qualities.

However, the usage of these hydrogels in vivo may be restricted due to the presence of potentially dangerous substances, including as cross-linking monomers, photo-initiators, organic solvents, and catalysts, which are required in the manufacturing process. According to the research that has been done, the process of chemical cross-linking can be carried out in a number of different methods. (31)

These technologies produce hydrogels with strong mechanical capabilities, which can be used to build IHs with long-lasting features. These IHs can be used in a variety of applications. (32) Traditional cross-linking processes may not be specialized enough to make injectable gels, but they are sufficient for the creation of ordinary hydrogels. This is because injectable gels require a higher molecular weight than regular hydrogels. When it comes to bulk gel molding as well as injectability and mass transfer, the gelling kinetics can have a significant impact.

2.1 Methods That Involve Physical Cross-Linking

2.1.1 Hydrogels That Are Linked Together By Ionic Forces

Ionic cross-linked hydrogels are the outcome of combining ionizable polymers with counter-ions in a mixing process. The injectability of these hydrogels can be affected by alterations in ion concentrations, gelator concentrations, electrical density, pH, and temperature, amongst other variables. In a similar vein, the mechanical strength of the structure can be affected by both the cross-linking density and the molecular weight of the polymers. Certain macromolecules, such as alginate, are capable of undergoing the process of cross-linking when cationic donors, such as calcium chloride, are introduced into their structures because their structures contain a substantial number of carboxyl groups. An further method for producing an ionic cross-linking hydrogel (HA) is by combining polyelectrolytes that have charges that are opposite to one another, such as sodium alginate, polylysine, and hyaluronic acid. (33) One of the most significant drawbacks of this procedure is that it produces an inhomogeneous mixture that is rich in large aggregates as a result of the powerful interaction between two polyelectrolytes that have opposite charges. (34) In order to overcome this problem (CS), Wu et al. utilized a method known as static mixing to produce polyelectrolyte complex (PEC) IHs that contained chitosan and polyglutamate. (34) The same group of researchers utilized a method of mild gelation to add spherical hydroxyapatite to PEC IHs. They found that this combination had a high capacity for injection with a needle of 27G and improved the regeneration of soft tissue. (35)

2.1.2 Interactions With Hydrophobic Particles

Amphiphilic polymers can be made using a variety of methods, including block or random copolymerizations, as well as the decoration of hydrophilic macromolecules with pendant hydrophobic moieties. (36). The development of hydrogels can be facilitated by the hydrophobic moieties of amphiphilic polymers. Since a shift in the ambient temperature produces a sol–gel transition and then hydrogel formation, polymeric amphiphiles with an upper critical solution temperature (UCST) or a lower critical solution temperature (LCST) may be viable options for injectability. "37" Because the condition of gelation of such polymers is temperature dependent, it is essential to select a critical temperature that is close to the environment of the body. (38)

2.1.3 Interaction with Stacking

Stacking bonds can be created when relatively electron-rich groups of aromatic compounds contact with comparatively electron-deficient groups of aromatic compounds. Depending on the geometry of aromatic interactions, the – stacking interaction can be broken down into three different types: I stacked face-to-surface, ii stacked edge-to-face (T-shaped), and iii stacked offset. (40) Plane-to-plane and edge-to-plane interactions are the two types of – stacking interactions that have been reported in hydrogels. (40) Because of the high proportion of water in hydrogels, some amino acids, such as tyrosine, tryptophan, and phenylalanine, would be good candidates for the role of aiding the stacking of molecules. Consequently, using gelling materials that already include pre-designed peptides is the only way to ensure that IHs will be formed as a result of the -stacking interaction. (41)

2.1.4 Hydrogen Bonding

Because it enables the simultaneous synthesis of IHs with thermoplasticity and self-healing properties, hydrogen bonding has been proposed as a potential method for cross-linking. This is due to the fact that it allows for these properties. On the other hand, the bonding between hydrogen atoms is dynamic in nature, and it can be broken at high temperatures. (42) The poor stability of hydrogen bonding cross-linked hydrogels in water, which is related to hydration and hydrogen bonding segregation between polymer segments, is a fundamental issue that may restrict their usage in biological applications. This may be the case because hydration and hydrogen bonding segregation between polymer segments can only occur in discrete groups. Several solutions have been suggested in order to address this problem and enhance the mechanical properties of hydrogen-bonding cross-linked hydrogels. Examples of this include utilizing macromolecules with two amide moieties (which forms dual hydrogen bonding structures) or utilizing nanoclays as bioink for the purpose of modifying the structural viscosity. (42-44). Several different functional moieties, such as 2-ureido-4-(1H)-pyrimidinone (UPy), diaminotriazine (DAT), and 6-aminocaproic acid (6-ACA), can be used to construct hydrogen (H) bond-based hydrogels that have diverse stimuli reactivity and the ability to shear thin. (43, 45) These hydrogels can also be made to have shear thinning capabilities.

UPy is widely regarded as one of the most promising functional moieties for the synthesis of H-bonding cross-linked IHs (45). This moiety is capable of forming a UPy–UPy dimer through the formation of triple H-bonds. Because of the unique properties of UPy, it is possible to modify the sol–gel transition of IHs by making adjustments to the temperature and pH of the system. (45, 46) Another functional moiety called 6-ACA has the ability to be used in the production of H-bond cross-linked IHs that have the capability of reversible self-healing in the event that pH-induced damage has occurred. Self-healing in hydrogels is caused by H-bonds formed between the amide and carboxylic acid moieties of two different regions of the hydrogel. IHs formed by 6-ACA have a high capacity for self-healing and a strong adherence to new gastric mucosa. As a result, they are useful platforms for the sustained release of therapeutic substances in an environment with a low pH, and they are also appropriate tissue adhesives for stomach perforations. (47)

2.1.5 Communication between the host and the visitor to the home

In host–guest chemistry, which is another method for physically cross-linking molecules, typical host molecules such crown ethers, cyclodextrins, and cucurbiturils are grafted onto polymer backbones as pendent or end moieties. This creates cross-links between the polymer chains. (48) Since the host–guest chemistry has a number of advantages, such as reversibility, the ability to prevent burst release, and the capture of therapeutic molecules by the host moieties, it is an intriguing cross-linking strategy for the creation of IHs that can be used for drug delivery and tissue engineering. (49, 50) On the other hand, IHs that are formed by host–guest interactions go through a mild gelation processing without the use of cross-linking agents or the generation of heat during polymerization. This is because cross-linking agents and heat generation during polymerization can impede the denaturation of incorporated proteins and cause damage to encapsulated cells at the gelation site. (Fifty)

2.2 Techniques for Cross-Linking That Make Use of Chemicals

Click for the 2.2.1 version of Chemistry.

Click chemistry is one of the methods of chemical cross-linking, and it is one of the approaches that has reasonably quick kinetics. Because of its biocompatibility, selectivity, flexibility, spontaneous reactions, rapid reaction rates, high product yields, and high capacity for in situ gel formation, the click chemistry technique is a potential option for the production of IHs. These characteristics include rapid reaction rates, spontaneous reactions, high product yields, and high capacity for in situ gel formation. (51)

To make hydrogels, researchers employed a variety of click chemistry techniques, including non-alkyl carbonyl chemistry, nucleophilic ring-opening reaction, thiol–ene addition, azide–nitrile addition, carboncarbon multi-bond addition reaction, and cycloaddition reaction.(52) The requirement for the presence of an initiator and/or a catalyst for the reaction, which might obstruct its bioactive use, is a key barrier for this method. The production of IHs that are ecologically acceptable is currently the subject of a number of people's efforts to use reactions that do not require a catalyst or initiator. (53) A notable advantage of using click chemistry is that it makes it possible to produce hydrogels with a high water content (90 percent) that are strong and can have changeable mechanical and stiffness characteristics. (54)

2.2.2 Photographic Hyperlinking and Related Images

Photo cross-linking is a chemical cross-linking strategy for preparing IHs in which electromagnetic light in the UV and visible ranges is used to induce cross-linking by activating photo-initiators and producing cations or free radicals. (55) an Initiation (excitation of photoinitiators and development of free radicals), propagation (interaction with photocurable macromers and synthesis of reactive species), and termination are the three processes that make up this technique (the (56) One of the benefits of photo-crosslinked hydrogels is that the encapsulated cells retain a high level of vitality. This is possible thanks to the mild gelation settings and the exquisite temporal and spatial control that can be exerted over the gelation process. (57)

On the basis of the polymerization reaction, photoinitiation can be broken down into a large number of subcategories. Some examples of these subcategories are radical photopolymerization by hydrogen abstraction, cationic polymerization, and radical photopolymerization by photocleavage. It has been argued that one of the most significant drawbacks of using this procedure is the low rate of light penetration that occurs in the gelling mixture. (58) Visible light has been preferred over ultraviolet (UV) light by a number of research institutions because it has a greater rate of penetration and results in less harm to the tissue. (59)

Addition Reaction of the Michael Type, 2.2.3.3

Under physiological conditions, the Michael addition reaction is based on the addition of a nucleophile (electron donor) such as amine or thiols to unsaturated carbonyl molecules such as aldehydes and ketones (electron receptor).(60) The gelling period of IHs is significantly influenced by the fraction of electron donor or electron receptor, the concentration of polymer solution, and its molecular weight.

(number 60) Since the in situ production of IHs needs to take place in an alkaline environment and at a high temperature, Michael's addition to amines is not an appropriate method for this process. The Michael addition with thiols is a strong contender for the production of in situ IHs due to the spontaneous nature of the reaction that takes place under physiological conditions. (61) (61) (61) Li et al. synthesized thiol derivatized hyaluronan (HA-SH) as an electron acceptor and maleilated collagen (Col-MA) as an electron donor, and they reported that injecting them into the target location resulted in quick hydrogel synthesis (with a rapid gelation period of about 40 seconds). (62) It has been demonstrated that vinyl sulfones and maleimides have higher cross-linking rates than acrylates, despite the fact that acrylates are the electrophiles that are used for Michael adds the majority of the time. (60, 63) Hubbell et al. designed and fabricated several types of in situ forming hydrogels based on Michael addition. These in situ forming hydrogels are appealing for biomedical applications because they have low toxicity due to rapid formation under physiological conditions without the use of a catalyst and the absence of any byproducts. If you are looking for a unique way to express yourself, you may be interested in this research. (64)

Cross-Linking of Schiff Bases, Section 2.2.4

It is also important to note that the quantity of amines and aldehyde moieties utilized in this process controls the gelation duration and intensity of the IHs that are formed. (65) an It is also worth noting that the basis for Schiff base cross-linking is the interaction of amine and aldehyde moieties. an It is also worth noting that it is the interaction of amine and aldehyde moieties. (57) Condensation reactions between aldehyde and amine groups can lead to the formation of Schiff base linkages such as oximes, imines, and hydrazones. These linkages are also known as hydrazones. (66) (66) (66) Because of its biocompatibility, reversibility, pH sensitivity, and simplicity, Schiff base cross-linking is a strong candidate for the design of intelligent hydrogels for use in biomedical applications. (26, 19) Using Schiff base cross-linking to generate IHs has a number of potential downsides, one of which is that free aldehyde moieties in the polymer's backbone have the potential to react with amine moieties in biomolecules, which can result in toxicity as well as other unwanted side effects. (18, 67)

2.2.5 Reaction Involving Enzymes

Enzymatic cross-linking is a type of chemical cross-linking strategy that makes use of a variety of enzymes (such as transglutaminases, phosphatases, glucose oxidase (GOx), tyrosinase, laccase, and horseradish peroxidase (HRP)) extracted from animal and plant sources in order to facilitate the formation of protein-based intramolecular hydrogen bonds (IHs). In the process of preparing IHs, the enzymes transglutaminases (69, 70), tyrosinases (71), and peroxidases are utilized most frequently. a Transglutaminases are thiol enzymes that assist in the formation of a covalent bond between the free amine moieties of other macromolecules and the g-carboxamide moiety of peptide-bound glutamine. Tyrosinases are enzymes that are made up of copper and play a role in the production of activated quinones through the oxidation of phenols in the presence of oxygen. Through a Michael-type addition process, activated quinones subsequently interact with amino or hydroxyl moieties, which ultimately results in the formation of a macromolecular network. Peroxidases are yet another category of enzymes, and they are distinguished by the fact that H2O2 is their primary substrate. In the presence of hydrogen peroxide, HRP, a type of peroxidase, is responsible for the conjugation of phenol and aniline derivatives. This makes HRP the peroxidase that is most frequently used in the synthesis of IHs. (73)

Inorganic heterocycles (IHs) can be reliably produced by means of an enzymatic technique, which has several advantages over alternative methods, such as high crosslinking efficiency, biocompatibility, and reaction under physiological conditions. In this method, the concentration of the enzyme is an important factor that determines how long the gelation process lasts and how quickly the hydrogel breaks down. (69) There are many different applications for 3 IHs in the treatment of cancer.

The survival rates of cancer patients continue to be extremely low, despite recent advances in the research and development of novel treatment approaches. (74) Due to the diversity, complexity, and heterogeneity of malignancies, as well as the high costs of cancer medication development, many treatments using one or more therapeutic agents or unique processes may be a preferable choice. This may be the case because multiple treatments use one or more therapeutic agents. (75) In comparison to monotherapy, this approach can improve treatment efficacy and reduce the risk of developing medication resistance since it takes a synergistic approach to tackling the pathogenesis route of the disease. (76) The subsequent section will talk about recent advancements in IH-based multimodal synergistic treatment for cancer metastasis and multidrug resistance.

3.1 IHs as Vehicles for the Concomitant Administration of Cancer-Fighting Medications

IHs can play a vital part as a smart drug carrier in the effective cancer therapy method known as controlled co-delivery of anticancer drugs. This strategy aims to treat cancer in the most efficient manner possible. The majority of the research that has been done in this area has concentrated on developing effective ways to achieve synergistic therapeutic effects by combining different drugs and IH systems.

In addition to their capability of transporting therapeutic substances in tandem, IHs frequently possess the capability of transporting pharmaceuticals and genes simultaneously in order to battle the formation of tumors and the spread of metastases. A peritumoral IH combining cyclodextrin (-CD) and a positively charged amphiphilic copolymer called methoxy-poly (ethylene glycol)-b-poly (-caprolactone)-b-poly (ethylene imine) (targeted for folic acid (FA)) was developed by Liu et al. (77). This IH was given the moniker MPEG-PCL-PEI-FA. In this study, the researchers utilized a combination of paclitaxel (PTX) and the Nur77 B-cell lymphoma-2 (Bcl-2) conversion gene in order to limit the development of Bcl-2 overexpressed therapeutically resistant cancers in a targeted manner. While the PTX was loaded into the hydrophobic area of the carrier, electrical interactions led to Nur77 being adsorbed into the cationic region of the carrier. Because of IH's slow biodegradation, the study's findings demonstrated that a peritumoral injection of MPEG-PCL-PEI/-CD supramolecular hydrogel inhibited the growth of tumors in a manner that was maintained over a period of seven days. More intriguingly, the MPEG-PCL-PEI-FA/-CD supramolecular hydrogel with simultaneous Nur77 gene and PTX drug administration via controllable drug and plasmid deoxyribonucleic acid (pDNA) release and targeting ability mediated by FA ligand could extraordinarily inhibit in vivo expression of Bcl-2 protein overexpressed in drug-resistant liver and lung cancer cells as well as subcut the expression of Bcl-2 protein overexpressed in drug (77)

One of the most significant challenges connected with and applicable to the use of biomaterials in the treatment of cancer is the prolonged release of therapeutic chemicals that can be either hydrophilic or hydrophobic from a delivery platform. Because of this limitation, researchers have developed innovative delivery methods, such as in situ IHs, that are capable of transporting medicinal compounds with distinct chemical and physical properties over extended periods of time. These unique delivery methods can be employed to transport both hydrophilic and hydrophobic medicinal compounds. For instance, Shen et al. conceived up and produced a thermosensitive hydrogel that was capable of transporting both hydrophilic cisplatin and hydrophobic paclitaxel (PTX). They were able to construct an aqueous solution with a thermosensitive sol-to-gel transition feature by creating the Bi (mPEG-PLGA) Pt (IV) (PtGel) by attaching the hydrophobic ends of two mPEG-PLGA copolymers on the Pt (IV) as a cisplatin prodrug. In addition to this, the core-corona micelles that formed in the water as a result of the self-assembly of the amphiphilic cisplatin-polymer conjugates served as a reservoir for the PTX to be dissolved in. This was accomplished by the fact that the amphiphilic cisplatin-polymer conjugates were amphiphilic.

As a direct consequence of this, an IH that contains not one but two medications was developed. Surprisingly, in addition to having anticancer effects, the PTX decreased the sol–gel transition temperature of the IH and increased gel strength. Investigations conducted in vitro shown that these medicines may be administered in a regulated fashion over a period of two and a half months, which would result in a synergistic anticancer effect being exerted on ovarian cancer cells. (78) They also stated that injecting a hydrogel comprising the two pharmaceutical mixtures into an SKOV-3 ovarian cancer xenograft mice model resulted in a considerably lower tumor weight after four weeks than either treatment alone. This was the conclusion they reached after comparing the results of the two treatments.

In addition, He et al. (79) developed an IH with the purpose of simultaneously giving cancer patients three drugs, which included sorafenib (SFN), doxorubicin (DOX), and metformin (MET), using three separate administration techniques. In order to accomplish this, a thiolated HA derivative was utilized in the production of the self-crosslinking IH, which is abbreviated as HA-SH. In vitro experiments on this triple drug-loaded IH indicated that it was cytotoxic to breast cancer cells (4T-1, MCF-7, and MDA-MB-231 cells), and that the synergistic effects of the drugs resulted in a higher rate of tumor cell death than single drug-loaded IH. This was the case because the triple drug-loaded IH was more potent than the single drug-loaded IH. Furthermore, an ex vivo histological analysis of the main organs of Balb/c mice revealed that this triple drug-loaded IH (Gel+DOX/SFN/MET) has less cytotoxicity than PBS, Gel, free drug-treated groups, Gel+DOX, and Gel+DOX/SFN groups, with only minor lesions visible in the Gel+DOX/SFN/MET treated groups' kidneys. Additionally, the Gel+DOX/SFN/MET treated group was successful in inhibiting tumor metastasis. This is because of the synergistic effects that these drugs have on one another. Using catechol-Fe (III) coordinative cross-linking, Yavvari et al. (79, 80) developed a CS-catechol (CS-CAT)-based drug-loaded IH (CAT-Gel) to treat murine lung and breast cancer models. The hemolytic and cytotoxic effects of this self-healing injectable polymeric drug carrier were very low. Because of the amphipathic structure of the polymer, it was simple for them to load the hydrophobic docetaxel (DTX) and the hydrophilic DOX hydrochloride into the IH. DOX can be loaded at a rate of 2.5 weight% into the gel, and DTX can be loaded at a rate of 25 weight% separately. When it came to the matter of co-loading, 2.5 weight percent DOX and 12.5 weight percent DTX were used because the greater quantity had a negative impact on the gel-forming ability of the substance. The ability of the material to self-heal was confirmed by rheology studies. The regulated release of the encapsulated anticancer medications DOX and DTX increased the median survival against mouse lung and breast cancer models after subcutaneous injection of the drug-loaded CAT-Gel into mice. This was achieved through synergistic effects. In a similar vein, bioluminescence images demonstrated that animals treated with DOX-DTX-Gel exhibited a significantly lower rate of tumor formation in comparison to the animals in the control group. This strategy has the potential to successfully construct a novel IH for cancer therapy that combines the effects of localized medicine distribution and combination effects. (80)

Xie et al. (81) developed a CS-based IH that was cross-linked with telechelic difunctional poly (ethylene glycol) (DF-PEG-DF) and loaded with DOX, DTX, and iron oxide in order to achieve stimuli-responsive drug release by the use of magnetic nanoparticle-induced hyperthermia. The treatment of triple-negative breast cancer cells (TNBC) with a magnetic hydrogel that was loaded with two different drugs and then subjected to heat produced outstanding results, as well as a significant reduction in the size of the tumor. The magnetic field was able to exert control over the release of anticancer drugs, which led to the development of a treatment method that combined chemotherapy and thermotherapy. Studies conducted in vivo demonstrated that medication co-delivery had a larger therapeutic impact and led to a smaller reduction in the size of the tumor than did administration of a single drug-loaded IH. (81) Davoodi et al. (2) created poly (lactic-co-glycolic acid) (PLGA 50:50) and poly (D, L-lactic acid) core–shell polymeric microparticles containing cisplatin and PTX by using a coaxial electrohydrodynamic atomization technique.

After that, they implanted them in an antibacterial IH that was made of alginate-aldehyde and branched polyethyleneimine (PEI-25k) that was created using Schiff's base reaction for the purpose of local delivery of anticancer drugs to combat TNBC. As a consequence of this, the MDA-MB-231 cell line saw a regulated release for a period of 45 days as well as a synergistic impact, with three processes predominating: the denaturation of DNA strands, the stability of microtubules, and the creation of intracellular reactive oxygen species (ROS). The incorporation of microparticles into this IH resulted in an increase in the sustained release of medicine, a reduction in the first burst release of medication (especially in the case of cisplatin), and a reduction in the substantial toxicity of cisplatin in human patients. In addition to this, the IH showed promise as a promising technology as well as a non-invasive strategy for retaining particles within the tumor cavity. In addition, when compared to treatment groups that received the free drug, microparticles and hydrogel formulations loaded with anti-cancer agents showed better therapeutic outcomes against aggressive tumor cells. These formulations also displayed synergistic anti-cancer activity against TNBC, which indicates the high potential of IHs for multimodal synergistic therapy against cancers. (2)

3.2 IHs for the Treatment of Cancer in Combination

Over the course of the past ten years, treatments such as radiation, chemotherapy, and high-intensity focused ultrasound have each showed significant clinical effectiveness in terms of reducing the size of tumors and increasing the likelihood of patient survival. Other treatment possibilities, including as immunotherapy, photothermal therapy, magnetic hyperthermia, and gene therapy, are still in the early stages of clinical trials; nevertheless, multiple preclinical publications have proved their high efficacy, which speaks well for future clinical translation. Other therapeutic possibilities include: photothermal therapy, magnetic hyperthermia, and gene therapy. Despite this, it has been demonstrated that using a single therapy technique does not successfully slow down the progression of tumors. In this part of the article, we will talk about cancer multitherapies incorporating IHs as well as the therapeutic alternatives that were presented before.

According to Xing et al. (82), biomineralization enhanced the self-assembly of collagen protein by mixing it with chloroauric acid (HAuCl4) in acid solution. They hypothesized that an electrostatic connection between positively charged collagen chains and anionic clusters (AuCl4) resulted in the formation of collagen protein-based hydrogels, and that this interaction was the source of the formation. In the meantime, the incorporation of gold nanoparticles (GNPs) as cross-linkers increased the structural integrity of the structure. This was possible as a result of the chemical reduction of anionic clusters that was used to produce the GNPs. Additionally, the self-healing and shear-thinning capabilities were stimulated by the weak connections that existed between collagen chains and GNPs. They used collagen-based materials containing both GNPs and meso-tetra-(N-methyl-4-pyridyl) porphine tetrachloride (TMPyP) (photosensitizer) as IHs for combined photothermal treatment (PTT) and photodynamic therapy (PDT) in order to reduce the formation of tumors in MCF-7 tumor-bearing mice.

TMPyP endowed the resulting hydrogel with PDT capabilities and demonstrated a sustained release for a period of 120 hours after being injected into the tumor. On the other hand, GNPs that have a high photothermal conversion efficiency may be able to absorb light and convert it to heat, which then provides the resultant hydrogel with the capability to PTT. This IH has the potential to enhance the bioavailability of free TMPyP, which would be a significant benefit given that the clearance rate of free TMPyP following injection is high. After 23 days, hematoxylin and eosin (H & E) staining of tumor sections revealed that there were no cancer cells in the site of the initial tumor in the mice that were given five treatments of laser irradiation at a wavelength of 635 nm and with a power density of 169.85 milliwatts per square centimeter. Xu et al. (83) generated an in situ producing degradable HA hydrogel for combined cancer treatment by using the chemo-photodynamic approach. (82) This method was used to treat cancer. This IH contained doxorubicin (DOX), a chemotherapeutic medication that is used in combination with photodynamic therapy (PDT) to treat cancer, as well as protoporphyrin IX (PpIX), a photosensitizer that provided the hydrogel the ability to undergo PDT. Both of these components were included in the immunohematology mixture. PpIX was chemically bonded to adipic dihydrazide modified HA (HA-ADH) to form HA-ADH-PpIX conjugate, which was then used to make hydrogel precursors. HA-ADH-PpIX conjugate was utilized to make hydrogel precursors. Along with a ROS-cleavable thioketal linker (TK), dialdehyde functionalized thioketal (TKCHO) was synthesised in order to operate as a minute crosslinker. As a result of the formation of dynamic covalent acylhydrazone between the crosslinker and HA-ADH-PpIX, the precursor solution was injected into the tumor site, which led to the formation of the hydrogel (HPTG). During the course of their experiment, exposure to NIR light caused a significant amount of ROS to be produced. The reactive oxygen species (ROS) not only boost the effectiveness of the photodynamic therapy (PDT), but they also kick off a chain reaction consisting of several processes. These processes include the cleavage of a ROS-cleavable small molecule crosslinker, the degradation of IH, and the release of DOX molecules for cascaded treatment. Irradiation from light could be utilized as a method to regulate the release of drugs. After additional research into the biocompatibility of the pH-responsive IH, it was discovered that MCF-7, 4T1, and NIH-3T3 cells retained over 95% of their viability after incubation with IHs in the absence of light irradiation. This result indicates that the pH-responsive IH has outstanding biocompatibility and excellent safety. When exposed to LED light (633 nm, 20 mW cm2), the viability of MCF-7 cells was lowered in a time-dependent irradiation manner, indicating the efficiency of the formulation as a PDT. According to the findings, the proposed IH has the potential to extend the amount of time that the PpIX agent is present in vivo and to reduce the excessive aggregation and quenching effects of the PpIX agent. After 18 days, the combined effect of PDT and chemotherapy caused DOX-loaded HPTG to have the highest inhibition effect on tumor growth (tumor volume and tumor weight). This was in comparison to other groups, such as free DOX, HPTG with and without laser irradiation, DOX-loaded HPTG without laser irradiation, and the control group (saline) with and without laser irradiation. The results of the H & E staining demonstrated unequivocally that the formation of 4T1 tumors was completely thwarted by the administration of DOX-loaded HPTG in conjunction with laser therapy. (83) In situ, producing HPTG in vivo similarly revealed a time-dependent biodegradation pattern (disappearance 35 days after injection),

which was linked to the polysaccharide HA's higher biodegradability. This was due to the fact that the polysaccharide HA was able to break down into smaller and smaller pieces over time.

Gou et al. (84) developed multi-responsive silk fibroin (SF) IHs with the intention of simultaneously activating chemotherapy, PTT therapy, and PDT therapy. In this study, the hydrophilic SF (HSF) that was isolated from the regenerated SF (RSF) was employed to self-assemble into a hydrogel by the formation of sheet structures and interactions based on hydrogen bonding. In addition, the photosensitizer that was used in this triple-therapy approach was a near-infrared (NIR) irradiation absorbing dye called Cy7 that had the potential to convert photons into heat energy. In addition to this, the anticancer drug DOX was encapsulated with Cy7 and included in the HSF-based IH that was manufactured. By creating sheets, HSF enabled the hydrogel to have features such as shear thinning, injectability, and self-healing. In contrast to the RSF solution, the HSF solution became gel-like in just six hours when it was heated to 37 degrees Celsius. The shear-thinning stress and subsequent self-healing that occurred during the resting period were responsible for the clear cyclic morphological variations that were seen in the SEM photos of the freeze-dried samples. These morphological changes occurred between firmly connected mesoscale multilayer structures and loosely linked multilayer structures. There was no impact from the DOX/Cy7 loading on the gelation. After the formation of hydrogel, there was no reduction in the photothermal ability of Cy7, and after 10 minutes of NIR irradiation, the temperature of both the Cy7 solution and the Cy7-hydrogel increased to 55 and 56 degrees Celsius, respectively. These temperatures are significantly higher than the minimum threshold temperature for tumor ablation, which is 43 degrees Celsius. In vitro drug release experiments revealed that the HSF-based IH was sensitive to pH (higher release at low pH), H2O2, and glutathione. Acidity and H2O2 efficiently accelerated the DOX release rate from HSF, reaching an ultimate release of 90% in the presence of H2O2 (1 mm) at pH 6 and after a 6-day incubation period. Glutathione had no effect on the rate of DOX release from HSF. At ten minutes, forty-eight hours, and ninety-eight hours after NIR irradiation, the thermal infrared camera showed that the temperature of tumors that had been treated with either Cy7 solution or Cy7-hydrogel had significantly increased in comparison to the PBS group, which served as a negative control. Irradiating the IH with NIR light at a wavelength of 808 nm was shown to significantly boost DOX release, providing evidence that the IH is light-responsive in its activity. In conclusion, in vivo antitumor experiments conducted over a period of 20 days indicated that the DOX/Cy7-hydrogel exhibited the best inhibition rate and therapeutic efficiency against cancer when exposed to NIR irradiation. This was demonstrated in comparison to single-modal therapy. (84)

According to Jiang and colleagues' research, nanoparticles have also been incorporated into the production of hydrogels. (86) In their research, palladium nanosheets were coupled with thiol-terminated four-arm polyethylene glycol (4arm-PEG-thiol). The palladium nanosheets served as the crosslinker, and an IH was produced as a result of the formation of dynamic PdS bonds between the palladium nanosheets and the 4arm-PEG-thiol. Additionally, the anticancer drug DOX was included into the hydrogel that was described earlier in the sentence.

In addition, the high photothermal conversion efficiency of the Pd nanosheets included within the IH structure made it possible for them to rapidly absorb the irradiated NIR light and transform it into heat. Irradiation with an NIR laser offered a synergistic chemo-photothermal therapy that was effective in combating cancer. This was accomplished by activating the PTT activity of Pd NSs and promoting the release of DOX from the hydrogel. IH has the potential to block nanoparticles from aggregating, which would improve their stability; preventing nanoparticles from diffusing out of IH would reduce the potential toxicity of the particles. The live/dead cell labeling done with 4T1 cells indicated the good combinatorial performance of the Pd cross-linked IH in the treatment of cancer via regulated DOX release and hyperthermia. As a consequence of this, the effectiveness of this IH was evaluated in vivo in mice that were carrying the 4T1 tumor. The results of this test revealed that the DOX-loaded IH could be easily injected into solid tumors, and that NIR irradiation inhibited the growth of tumors as well as their ability to metastasize. This work developed a simple preparation method without surface modification of nanoparticles and used an effective anticancer nanosystem. This method can be used in future studies to engineer photothermal and responsive drugs using other 2D nanostructures as a crosslinker. Because most methods for using nanoparticles as crosslinkers require additional surface modification of nanoparticles, this work developed a simple preparation method without surface modification of nanoparticles. For the purpose of chemo-photothermal cancer treatment, Zhou et al. (87) utilized the HA-based IH's multistage-targeted gold/mesoporous silica core–shell nanocomposites. SEM pictures provided conclusive evidence that nanoparticles had a core–shell structure. The loading of anticancer medications is made easier by the core–shell nanoparticles, which do this by producing suitable holes. DOX was loaded into gold mesoporous silica nanoparticles (Au@MPP), and then DOX-encapsulated nanoparticles were implanted into the HA-based IH (Au@MPPD@HA) through the covalent cross-linking of tyrosine functionalized HA (HA-Tyr) to Au@MPP under the catalysis of HRP. On the surface of Au@MPP, the phenol groups and the triphenylphosphine that performs the mitochondrial targeting activity were connected. It is possible that the HA fragments on these nanoparticles will accurately target the CD44 receptors that are located on the surface of cancer cells. The hyaluronidase (HAase) that was produced by the tumor was what prompted the hydrogel degradation at the tumor site. This led to the release of Au@MPP nanoparticles and their subsequent penetration into the deep tumor. In conclusion, the DOX was transported into cancer cells and their mitochondria in a preferred manner by the nanoparticles that had been produced. The PTT behavior was caused by the au nanoparticles, and the hyperthermia that resulted increased the amount of DOX that was released when the sample was exposed to NIR light. In vitro research showed that the Au@MPPD@HA was sensitive to enzymes, and it was discovered that the presence of HAase resulted in a 60% increase in the amount of DOX that was released. DOX release, on the other hand, was just 7 percent after two days when enzyme wasn't present. After forty-eight hours, NIR irradiation may cause a roughly eighty percent increase in the release of DOX. In addition, in vivo experiments on mice with MGC-803 tumors showed that after Au@MPPD@HA injection and NIR irradiation, the local temperature reached 62 and 75 °C within 5 and 10 minutes, respectively, whereas the temperature in the saline and HA gel treated groups increased to 38 °C, indicating that this system has excellent photothermal conversion capability. These results show that this system has the ability to convert light into heat very effectively. When compared to the other groups, the DOX-loaded

IH coupled with NIR irradiation had the largest inhibitory influence on tumor formation. This finding suggests that tumor targeting, chemotherapy, and PTT can work synergistically to cure cancer. After 21 days, the IH's histocompatibility was determined to be positive. In addition, H & E stained sections taken from tumor tissue indicated considerable damage and necrotic death of the tumor cells in the DOX-loaded IH group following NIR irradiation. On the other hand, H & E stained sections taken from normal organs did not exhibit any evident deleterious consequences of this DOX-loaded IH. (87)

Zheng et al., (88) developed and built an in situ thermogelling CS IH that included MoS2/Bi2S3-PEG (MBP) nanosheets and DOX for the treatment of colon cancer with hyperthermia and chemotherapy. Because of an increase in hydrogen bonding, electrostatic attraction, and hydrophobic interaction between the CS and glycerophosphate (-GP), the solution transitioned from a sol to a gel when the temperature was raised to 37 degrees Celsius. The incorporation of a photothermal agent that is able to absorb NIR in the range of two biological windows, which consists of the first (700–980 nm) and second (1000–1400 nm), has the potential to significantly improve the system's capacity to perform PTT. According to the findings, the presence of DOX had no impact on the NIR absorption of the hydrogel. After thirty seconds and five minutes of exposure to NIR irradiation (808 nm, one watt per square centimeter), the surface temperature of the tumor reached 45.76 and 60.43 degrees Celsius, respectively. Additionally, the NIR light was able to limit the release of DOX by increasing the temperature of the surrounding area. Furthermore, the tumor volume was dramatically reduced after 14 days as a result of the combination of phototherapy and chemotherapy. Antibacterial studies against Escherichia coli (E. coli) revealed the antibacterial behavior of the CS-based IH due to the inherent bacteriostatic activity of CS with a rate of 40.28 percent. This indicates that the suppression of the autoimmune system that can occur as a result of cancer and the use of chemotherapy can increase the risk of bacterial infection. (88) This antibacterial combinatorial smart system shows promise for treating a range of different types of cancer since it demonstrates that the appropriate combination of photothermal nanomaterials and an IH can successfully destroy tumor cells.

Using a host–guest interaction between PEG and cyclodextrin, Liu et al. (89) produced an IH with the goal of improving the photothermal performance, retention time, and stability of a thermosensitive photothermal network IH (PNT-gel). The backbone of the conjugated polymer was grafted with PEG chains, and this resulted in the successful conversion of the irradiation NIR to light, which led to increased photothermal efficiency. Furthermore, in this thermo-sensitive IH with a low critical solution transition (LCST), which is slightly above the physiological temperature, the reversible gel–sol transition may improve drug release in response to NIR light, making it possible to have on-demand drug release. (90)

Jin et al. (90) designed the polypeptide and hollow gold nanoshells (HAuNS) for the purpose of synergistic chemo-photothermal treatment of the HepG2 malignancy. In the experiment that they conducted, positively charged DOX and negatively charged polypeptide PC10A were coated layer by layer on the surface of negatively charged HAuNS to create PC10A/DOX/HAuNS IH. One portion of the DOX was adsorbed on the HAuNS surface, and the other portion was incorporated into the PC10A hydrogel, which resulted in sustained drug release. PC10A/DOX/HAuNS IH could be injected with relative ease using a needle measuring 0.25 millimeters in diameter. The photothermal treatment of this non-toxic hydrogel destroyed the tumor cells, and the DOX release repressed and removed any surviving tumor cells. (number 90) The intensity of IR783 fluorescence in the control group that was injected with free IR783 solution began to rapidly decrease on the first day, and by the sixth day, it had almost completely vanished. A clear fluorescent signal of IR783 was found in the PC10A/IR783 hydrogel group until day 30, showing that IR783 was continually released from the PC10A/IR783 hydrogel in tumors. This was observed till day 30. Similarly, in the control group, no fluorescence signal of free IR783 was seen in the tumor or any of the main organs with the exception of the liver. On the other hand, IR783 in the PC10A hydrogel was primarily seen at the tumor site at day 6 after injection, which indicates the potential of PC10A hydrogel as a preeminent drug carrier for long-term chemotherapy without distribution to other organs.

In a separate line of research, the PC10A polypeptide was combined with PTX and Ag2S quantum dots in order to provide chemo- and phototherapy to treat the ovarian cancer tumor SKOV3. (91) Ultrasonically loading Ag2S quantum dots (QDs) and PTX into polypeptide PC10A nanogels was the first step in the synthesis of PC10A/Ag2S QD/PTX nanogels in this research. Following that, the PC10A/Ag2S/PTX nanogels were dissolved in the PC10A hydrogel, which resulted in the production of an IH that was able to treat multiple types of cancer. IH has the ability to localize nanogel, which in turn increases its residence time. In both in vitro and in vivo testing, it was shown that this IH did not exhibit any hazardous properties. The researchers found that the combination of PC10A/Ag2S/PTX worked significantly better than either single NIR photothermal or chemotherapeutic treatments in inhibiting the proliferation of human ovarian cancer cells (SKOV3 cells). Monitoring the in vivo degradation of IH caused by the optical properties of Ag2S QDs was accomplished through the use of fluorescence and photoacoustic (PA) imaging. A long-term breakdown of the hydrogel was demonstrated in vivo by the fact that the Ag2S QD fluorescence signal was detected for a period of 35 days. In addition, the PA signal at the area of the tumor reduced during the course of time (up until 9 days), which was consistent with the findings of fluorescence imaging. (91)

Other researchers have followed suit by administering chemo-phototherapy by incorporating gold nanostructures and DOX into thermoresponsive ionic hydrogels. (93) He an et al. created a multi-stimulus (pH, enzymes, and near-infrared light)-responsive IH for combined chemo-photothermal cancer therapy based on amphoteric gelatin nanoparticles (Gela NPs) and polydopamine nanoparticles (PDA NPs) loaded with DOX. The hydrogel received its ability to PTT as a result of the incorporation of PDA NPs that has a high photothermal conversion potential. After DOX was loaded into PDA NPs, the Gela NPs and DOX-PDA NPs were mixed at a basic pH (pH 12), and then the system pH was dropped to a value that was less than the Gela NPs' isoelectric point. This resulted in charge reversal and the production of a uniform hydrogel. This apparatus has the potential to be employed as a smart DOX carrier, with the ability to react to an acidic pH, enzyme, and NIR. IH was able to release DOX into the tumor location in a continuous and regulated way thanks to the sensitivity of GEL NPs to the acidic pH of the tumor microenvironment and PDA NPs to NIR laser irradiation. The enhanced DOX release was due to enhanced DOX solubility and the repulsion between positively charged Gela NPs and DOX at acidic pH. (93) various researchers have also sought to use various IH structures in conjunction with photothermal agents, anticancer medications, and X-ray radiation. This was done in an effort to treat cancer. (94) In addition to NIR-triggered hyperthermia, magnetic hyperthermia is another mechanism that can be utilized for the treatment of cancer in combination with other therapies. Using superparamagnetic iron oxide nanoparticles (SPIONs) and the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), Zhang and Song (95) established a new cancer multi-therapy system. They generated injectable, biodegradable, and thermosensitive TRAIL/SPION noncomplex hydrogels (T/S-NHs) for this purpose by means of electrical and hydrophobic interaction between positively charged TRAIL and oleic acid-coated SPIONs and negatively charged poly (organophosphazene). This was done in order to fulfill the requirements of PPZ. This thermosensitive IH changed into hydrogel at body temperature (37 degrees Celsius), and the T/S noncomplex release was improved by magnetic hyperthermia (43 degrees Celsius). (95)

One more advancement in cancer multitherapy is imaging-guided tumor ablation. In order to improve the efficacy of chemotherapy and synergistic hyperthermia, Zhao et al. (96) conceived of and created a phase-changeable alginate-based IH. In order to produce an alginate/MoS2/Bi2S3-poly (ethylene glycol) (MBP)/DOX (AMD) hydrogel, the researchers encapsulated DOX and MBP nanosheets in an alginate/MoS2/Bi2S3-poly (ethylene glycol) (MBP)/DOX (AMD) hydrogel by binding between-L-guluronic blocks of alginate and calcium ions. In addition, in vivo testing demonstrated that MBP nanosheets and DOX may be able to deliver computed tomography or photoacoustic imaging-guided tumor cell targeting through photothermal and chemotherapeutic procedures, respectively. The photothermal conversion efficiency of this alginate-based IH was 42.7%, and after photothermal transformation of the MBP nanosheets, there was an increase in the drug diffusion from the IH. Even more intriguing is the possibility that the encapsulated MBP and DOX will be kept by the one-of-a-kind structure of the IH, which will prevent their release into the circulation. (96)

Irradiation in conjunction with chemotherapy is yet another method that can be utilized in the treatment of a wide variety of cancers. This method makes it possible to provide both radioactive agents and cancer-fighting drugs to the irradiated area simultaneously. This method was utilized by Puente et al. (97) to target glioblastoma (GBM), a cancer that can manifest in a wide variety of ways in the brain. They developed a CS-based IH that was capable of maintaining iodine as a radioactive isotope within its network while simultaneously releasing temozolomide (TMZ) as a chemotherapeutic drug in a manner that was under controllable conditions. According to the findings of the in vitro research, the iodine isotopes could potentially be stored for longer than 42 days. On the other hand, the on-demand content for TMZ was completely delivered within forty-eight hours. According to the findings of this investigation, injectable chemo-radio-hydrogel implants could be valuable tools for improving GBM local chemoradiotherapy. (97)

In addition to study into cancer cell targeting, immunotherapy can be employed in conjunction with photothermal cancer treatment employing immunomodulatory drugs (IHs). A collagen/alginate IH with a shear-thinning feature was created by co-assembly of positively charged collagen and negatively charged alginate. Mei et al. (98) inserted the photothermal medication methylene blue and the immunological drug imiquimod (R837) into the IH. Following intratumoral injection of the collagen/alginate hydrogel, the researchers found that PTT induced immune responses related to tumor-associated antigens (TAA). IH's TAA and R837 reagents were combined to provide a vaccination that successfully reduced cancer metastasis by activating an anticancer immune response. This was accomplished by the combination of the two IH reagents. (98)

4 IHs that can be used in multiple treatments for wound healing

For a very long time, one of the primary focuses of research that is related to biomaterials has been the conception and production of a three-dimensional structure that can regulate the re-epithelialization and dermal regeneration of cutaneous wounds and epithelial tissues. (99) A number of different therapeutic chemicals and delivery systems are now under development in order to treat wounds that are difficult to heal. In the following part, we will examine numerous examples of nanoengineered IHs for combined wound treatment. IHs can be used to provide antibacterial medications and growth factors concurrently to the wound site, resulting in enhanced treatment of chronic wounds that are predisposed to infection. This is an improvement over monotherapy, which is the traditional treatment method.

For instance, Qu et al. (100) created a multifunctional IH for wound healing by oxidizing HA and synthesizing N-carboxyethyl chitosan (CEC). They called this compound OHA. The OHA had an aniline tetramer grafted onto it, making it the OHA-AT. After that, the OHA-AT/CEC was created by first dissolving the CEC polymer in the PBS solution and then adding the OHA-AT. After mixing the CEC solution with the OHA-AT solution and heating the mixture to 37 degrees Celsius, the hydrogel was produced by creating a Schiff base link between the functional groups of the two solutions. During the process of synthesis, antibiotics like amoxicillin were utilized to load other medications into the IHs that were created. The AT was found to increase mechanical qualities and to lengthen the time it took for the gelation to take place. After 48 hours, these IHs were able to release up to 73% of the amoxicillin they contained through a diffusion mechanism, which resulted in a significant amount of antibacterial activity against Staphylococcus aureus (S. aureus) and E. coli. coli. Surprisingly, the HCl-doped OHA-In/CEC hydrogels were effective at scavenging reactive oxygen species (ROS). This was demonstrated by a decrease in,-diphenyl—picrylhydrazyl (DPPH) free radicals, which were scavenged at an AT concentration-dependent rate of around 80%. Gels with a higher AT content in their structure resulted in speedier wound healing than gels with a lower AT content. This may be connected to the antioxidant activity of AT, which transfers electrons to free radicals, as a higher AT content in the structure of IHs results in a higher AT content. It has also been demonstrated that IH has anti-inflammatory effects, conductivity effects, and angiogenesis effects. In addition, the rate at which this IH healed wounds was significantly faster than the rate at which commercial counterparts did, which led to a higher density of fibroblasts as well as enhanced collagen deposition and vascular regeneration. (one hundred) Diabetic wounds are difficult to maintain because of their high susceptibility to microbial infection due to vascular dysfunction. This makes it difficult for wound care professionals to treat diabetic patients. In order to solve this problem, Chen et al. (101) designed an IH that is centered on the AgS coordination link that exists between multi-arm thiolated polyethylene glycol (SH-PEG) and silver nitrate (AgNO3). The antibacterial properties of Ag+ have been associated with accelerated wound healing in diabetic patients. As a consequence of this particular type of cross-linking, the hydrogel has both the capability of self-healing and that of being injectable. An angiogenic substance known as deferoxamine (DFO) was added during the process of cross-linking. The diabetic skin lesion was shown to have been efficiently healed, as well as having improved angiogenic and antibacterial capabilities, according to in vivo studies. In addition, the hydrogel's in vitro antibacterial activity was evaluated by determining whether or not it produced a distinct zone of inhibition (ZOI) when tested against S. aureus, and the antibacterial activity in vivo was evaluated by immunofluorescent labeling with Staphylococcus. aureus antibodies, which suggests that DFO-loaded hydrogel may be able to effectively restrict the development of bacteria. This may be the case since iron chelation and the subsequent amplification of bacterial genes are both caused by the presence of DFO. Neovascularization, also known as vascular endothelial growth factor (VEGF), can be identified by an increase in CD31 expression as well as a significant rise in vascular endothelial growth factor expression. In addition, the capacity for re-epithelialization and in vivo wound healing was greatly improved when DFO-loaded IH was present. Kong et al. (102) used DFO and bioactive glass (BG) as angiogenesis stimulators and successfully cured diabetic chronic skin abnormalities in rats by inserting them into alginate-gluconolactone intradermal hydrogels

(IHs). The combination of BG and DFO revealed superior effects on migration and tube formation of human umbilical vein endothelial cells (HUVECs), in comparison to monotherapy with either BG or DFO. (102)

In order to construct a multifunctional injectable wound dressing that could limit bacterial growth while also stimulating angiogenesis and wound healing, Li et al. (103) developed a biocompatible IH using sodium alginate (SA) and the bioactive hardystonite (HS) bioceramic. This IH was used to build a multifunctional injectable wound dressing. HS was responsible for the release of Ca2+, Zn2+, and Si ions, with Ca2+ and Zn2+ ions serving as crosslinkers for the creation of hydrogel through double ion cross-linking. In addition, Zn2+ ions may act as antibacterial components and offer sustenance for wound repair. On the other hand, Si ions may enhance wound healing by stimulating angiogenesis. Since the rapid interaction between SA and divalent ions is a barrier to injectability, the gelation process of the hydrogel may be controlled by controlling the release of the integrated Ca2+ and Zn2+ ions from HS. This was done in order to improve the hydrogel's ability to be injected. In the antibacterial experiments, the SA/HS composite hydrogel demonstrated a 100% antibacterial rate in both the extract assay and the direct contact assay, but the pure SA hydrogel was unable to produce any antibacterial effects. Investigations conducted in vitro suggested that the IH, in addition to possessing antibacterial properties, may also encourage the proliferation of HDFs and HUVECs and may also facilitate their migration. The results of studies conducted in vivo, on the other hand, showed significant epithelial and blood vessel growth, which suggests that this IH has a wide range of potential therapeutic applications. (103)

Because traditional IHs are incapable of self-healing, they are susceptible to damage from external pressures during clinical therapy; this is especially true for irregular wound sites. This is one of the most significant disadvantages of using traditional IHs for co-delivery into the wound site. (104) If the IHs are damaged when providing wound care, this could lead to a loss of function as well as an increased likelihood of bacterial infection at the wound site. An interaction of aminated gelatin (NGel), oxidized dextran (ODex), and adipic acid dihydrazide was employed by Chen et al. (105) to develop a covalent dynamic IH with the characteristics of self-healing, antibacterial property, and ongoing drug release. This was done in order to address the problems that were being faced (ADH). It is believed that the links between IH's imine and acylhydrazone components are responsible for its self-healing capabilities. Basic fibroblast growth factor (bFGF)@poly (lactic-co-glycolic acid) (PLGA) microspheres and chlorhexidine acetate (CHA) were used in the production of the IHs. After being subjected to swelling, the hydrogel that was created kept its morphological integrity and exhibited a high level of biodegradability. They discovered that the modified IH might potentially improve cell proliferation and the healing of wounds by releasing bFGF gradually over time and releasing CHA in bursts. (105)

IHs can be utilized for the co-delivery of cells and therapeutics in addition to the delivery of drug molecules because to the similarities they have with ECM. (106) For instance, Zhao et al. (107) utilized benzaldehyde-capped PEG (OHC-PEG-CHO), phenylboronic-modified chitosan (CSPBA), and poly (vinyl alcohol) in order to construct pH-and glucose-sensitive IHs by covalent crosslinking of imine linkage and phenylboronate ester (PVA). The fibroblasts and insulin were put into the IHs in the course of the in situ crosslinking procedure. Due to the stability of the imine bond at physiological pH and its instability at acidic pH, the system was able to release required components for wound healing at a moderately acidic pH. This is because the diol moieties of glucose bind strongly to boronic acid derivatives in these modified IHs, forming a reversible boronate ester. According to the researchers, the modification of the IHs by adding imine bonds (benzoicimine bonds) and phenyl boronic acid moieties resulted in dual responsive insulin and fibroblast release at the wound site in a streptozotocin-induced diabetic rat model.

Improvements were seen in collagen deposition, neovascularization, and the overall healing process of diabetic wounds when the insulin/cell-loaded IHs were used. Dong et al. (62) utilized poly (ethylene glycol) (PEG) –gelatin hydrogel in order to improve cutaneous wound healing and stem cell retention. In order to produce the hydrogel, a Michael-type addition method (Gel-SH) was used to combine the acrylate groups of poly (ethylene glycol) diacrylate (polyPEGDA) polymers with the thiolated anions resulting from the thiolation of gelatin. Gelation occurred in a matter of about two minutes as a direct result of the physiological conditions that were present. into the scope of this investigation, adipose-derived stem cells produced from murine fat were encapsulated into the IH. Because of its three-dimensional network structure and its structural similarity to extracellular matrix (ECM), the hydrogel was able to support the survival, proliferation, migration, and retention of cells more effectively than direct cell distribution at the wound site. Bioluminescence imaging showed that the "hydrogel+cells" group produced a significantly greater bioluminescence signal in vivo for up to 14 days than the "cells alone" group did when compared to the "cells alone" group. This was the case when comparing the "hydrogel+cells" group to the "cells alone" group. In addition to its malleable mechanical properties, biodegradability, and biocompatibility, the hydrogel is suitable for use in cell engraftment since it possesses all of these qualities. According to the CD68 immunohistochemical labeling, the cell-loaded IH was able to significantly lower the quantity of macrophages, which was linked to the effective role that IH played in the healing of wounds. In addition, the CD31 immunohistochemistry labeling demonstrated that the combination of cells and IH has the potential to promote angiogenesis. Last but not least, the hydrogel plus cells group saw a wound closure that was significantly faster than the other groups. (62)

## 5 Therapeutic Approaches for Illness-Induced Tissue Regeneration

Insufficient cell motility, loss of cell viability following single-cell suspension injections, stress responses of cells into 2D constructs, and activation of inflammatory responses are still issues with tissue engineering procedures due to the sluggish biodegradation rate of scaffolds. (108). Additionally, their therapeutic applications have been hampered by expensive costs, time-consuming methods, and poor bio-mimicking. (110) On the other hand, long-term tissue remodeling caused by IHs provides a good substrate for encapsulating many different types of pharmacological compounds or cells without causing the molecules or cells to lose their bioactivity. This is done for the purpose of multi-therapy. (111) In point of fact, addressing tissue damage brought on by IHs can benefit by combining tissue similarity with medicine delivery as a viable treatment technique. (112)

### 5.1 Cartilage Regeneration Through Tissue Engineering

IHs are designed to accept a variety of therapeutic substances and cell types, which allows for the regeneration of cartilage tissue to be induced in a coordinated fashion. Sá-Lima et al. (113) created stimuli-responsive chitosan-starch IHs linked with encapsulated adipose-derived stromal cells in order to enhance the regeneration of articular cartilage. According to the researchers, the incorporation of starch into the IHs improved the degradation profile and promoted the chondrogenic differentiation of adipose-derived stromal cells for cartilage regeneration. (113) Chondrocytes and poly (N-isopropylacrylamide)-co-acrylic acid IH containing transforming growth factor 3 (TGF3) were used in another investigation to create neocartilage. This study was funded by the National Institutes of Health. Eight weeks following injection, the modified IHs showed higher chondrogenic differentiation than the control IHs did. This was in comparison to the original IHs. (114)

Using a combination of cells, growth factors, and biomaterial scaffolds, Arora et al. (115) were able to show that articular cartilage defects could be corrected. In order to transfer TGF-1, fat pad derived MSCs, and articular chondrocytes (ACs) to a cartilage defect location and stimulate TGF-1 mediated chondrogenesis, they created an IH out of carboxymethyl cellulose (CMC), sulfated carboxymethyl cellulose (sCMC), and gelatin. This IH was crosslinked in situ using HRP enzyme. TGF-loaded hydrogels resulted in increased cell survival, greater sulfated glycosaminoglycans (sGAGs), and greater collagen deposition when compared to control hydrogels. In addition, the incorporation of TGF-1 into the hydrogels resulted in an increase in the expression and deposition of hyaline cartilage marker while simultaneously resulting in a decrease in the deposition of fibrocartilage and hypertrophic marker. The research conducted by the experts revealed that hydrogels composed of cellulose can be utilized to produce cartilage tissue engineering materials at an affordable price. (115)

### 5.2 Regenerative Medicine for the Heart

In spite of the fact that numerous research organizations have demonstrated that conventional tissue engineering treatments (direct injection of multiple cell types into the tissue of the heart) might improve cardiac function after a myocardial infarction (MI), it has been shown that cell survival after transplantation is poor. (116) When compared to the practice of injecting human embryonic stem cell-derived cardiomyocytes directly into the infarcted region, the combination of cell therapy and in situ tissue engineering can be considered an ideal solution for protecting the cell-graft from inflammation in the ischemic environment of an infarction and resulting in better functional outcomes. This is because the combination of these two practices allows the cell-graft to heal more effectively. (117) Song et al. (118) created acrylated HA IHs combining stem cell homing factor (SDF-1) and angiogenic peptides (Ac-SDKP) to increase the recruitment of stem cells to the site of damage while also enhancing the expression of angiogenic genes. This was done in a chronic heart failure model in rats. It was found that IHs with only SDF-1 or Ac-SDKP were unable to induce cardiac regeneration, but that IHs with both factors were able to improve mature vessel formation and cardiac function. (118)

In spite of these developments, there are still a number of downsides to using cells as a treatment for MI. These drawbacks include a low cell transit efficiency, limited cell retention in the site of damage, and poor survival of retained cells in a ROS-rich environment. In a rat model of myocardial infarction, Hao et al. (119) used IHs formed by a mild gelation technique and ionic cross-linking between alginate and divalent cations (Ca2+) in the presence of fullerenol nanoparticles to transfer stem cells to the site of injury. These IHs were created by ionic cross-linking between alginate and fullerenol nanoparticles. The hydrogel was produced by using a method of mild gelation and ionic cross-linking between alginate and divalent cations (Ca2+) while it was in the presence of fullerenol nanoparticles. The incorporation of fullerenol nanoparticles, which sequester reactive oxygen species (ROS) free radicals, boosts the antioxidant activity of the hydrogel. In addition to this, the hydrogel has the potential to offer the left ventricle some structural support. This hydrogel showed only a low level of toxicity in brown adipose derived stem cells (BADSCs), and it reduced the amount of oxidative stress they were under. Even in the presence of ROS, it stimulated angiogenesis and led to increased survival, cardiomyogenic differentiation, and proliferation of BADSCs. This was accomplished through activation of the extracellular signal-regulated kinase (ERK) and p38 pathways, as well as inhibition of the c-Jun N-terminal kinase (JNK) pathway. (119)

These defects allow hydrogels to be damaged by external forces and prevent them from being utilized for a long period with a stable function for cell healing. Injectable hydrogels for cardiac regeneration have substantial limits in terms of self-healing and conductivity. (120) Injectable hydrogels for cardiac regeneration have considerable limitations in terms of self-healing and conductivity. In point of fact, because of the feature of contraction that the heart possesses, the cell delivery vehicles need to be able to bear a substantial mechanical force when they are injected, which elevates the risk of injury to the IH. (121)

The application of conductive polymers in self-healing ionic hydrogels has the potential to facilitate the proliferation and differentiation of electrically sensitive cells, such as cardiac and myoblast cells. Dong et al. (123) exploited the dynamic covalent Schiff base reaction between benzaldehyde moieties of dibenzaldehyde-terminated PEG and amine moieties of chitosan-graft-aniline tetramer to construct conductive IHs with self-healing properties. This reaction was used to make conductive IHs with self-healing properties. The presence of aniline tetramer in the structure of IHs was hypothesized by the study's authors to be responsible for the remarkable similarity between the conductivity of IHs and that of native myocardium (range from 2.29 103 to 2.42 103 S cm1). This was one of the findings of the study. This IH exhibited remarkable cell transportation carrier features that promoted cell survival and helped ensure their viability. (123)

### 5.3 Tissue Engineering for Bone Defects and Related Abnormalities

Oliviera et al. (125) evaluated the possibility of electrospun poly (lactic acid) (PLA) fiber-based membranes incorporating calcium phosphate (CaP) ormoglass particles to enhance angiogenesis in order to overcome this limitation. Poor angiogenesis inside tissue-engineered grafts is one of the key drawbacks of bone tissue engineering, which may restrict its clinical use for the healing of extensive bone lesions. (124). An IH containing CaP ormoglasses was produced by dispersing the CaP ormoglasses over a matrix composed of (hydroxypropyl) methylcellulose (HPMC). This composite has the ability to regulate calcium release in a constant and sustained manner, which results in the inner part of the bone tissue mending at a slower and longer rate. This is because the calcium release is regulated in a steady and prolonged manner. Both the synthesis of calcium ions by bone marrow progenitor cells and the ongoing production of proangiogenic cytokines contributed to the acceleration of bone development and angiogenesis. [Ca]lcium ions were produced by bone marrow progenitor cells. However, in order for ionic hydrogels to successfully regenerate bone, a formulation that possesses the desired self-healing and antibacterial characteristics is required. In order to satisfy these prerequisites, adhesive liposomes (A-LIP) loaded with bone morphogenetic protein 2 (BMP-2) were combined with PEG hydrogel to produce adhesive lipo-hydrogel (A-LIP-PEG). The formation of the hydrogel occurred as a result of coordination cross-linking between thiolated PEG (SH-PEG) and Ag in the presence of A-LIP. The coordinated cross-linking that took place between SH-PEG and Ag contributed to improvements in the hydrogel's self-healing and injectability. In addition to this, the incorporation of Ag into the formulation led to the production of an antibacterial effect against E. coli and Staphylococcus aureus have been isolated. After the formulation was injected into the target area, A-LIP was released from the hydrogel and linked to the tissue, which resulted in a local drug depot that was both efficacious and able to last for a significant amount of time. A-LIP-PEG with tissue adhesion ability revealed stronger in vitro osteogenic differentiation and improved bone restoration (LIP-PEG) in comparison to conventional lipo-hydrogels. As a consequence of this, the A-LIP-PEG group had a greater number of calcium nodules after 14 and 21 days of incubation in osteoblastic induction media compared to the LIP-PEG group and the control group. This method showed a lot of promise in mending a bone cavity that had been damaged in a specific area. (126)

The A-LIP that was released by A-LIPPEG, on the other hand, significantly increased the relative fluorescence intensity (100 20%), which served as an indicator of osteocalcin (OCN) expression (green). In comparison, the LIP-PEG and control groups had significantly lower fluorescence intensity (46 8% and 4%, respectively), which suggests that A-LIPPEG has a high potential for enhancing BMSC osteogenic differentiation. The A-LIP-PEG therapy group had much greater mineralization and fracture repair than the control group and the LIP-PEG group, as demonstrated by micro-CT scans of bone healing.

In order to enhance angiogenesis toward bone repair and regeneration, Kocak et al. (21) constructed pH-and temperature-sensitive IHs based on CS and hydroxyapatite (HA) composite materials loaded with heparin (Hep). Hydrogel precursor solutions with different concentrations of Hep were created by the use of the sol–gel technique. The researchers were able to evaluate the process of angiogenesis by injecting different injectable solutions onto the chorioallantoic membrane (CAM) of ex-ovo chicks. Histological examination provided proof that inducing microvascularity in the CAM test was successful. In a similar manner, the efficiency of the pro-angiogenic response was improved by reducing the amount of Hep that was included in the IHs. The overall survival rates of CAM studies were between 45 and 50 percent before sample implantation and between 70 and 80 percent after sample implantation, respectively. (21) a

Rheumatoid arthritis (RA) is a disease that has a complex pathogenesis; therefore, treatment systems should act through many mechanisms that are concentrated on anti-inflammatory and osteogenic processes. Traditional methods often have unintended consequences and only address one or two of the underlying mechanisms, while disregarding the others. Pan et al. (127) investigated a novel platform for the treatment of RA that comprised black phosphorus nanosheets (BPNs) with platelet-rich plasma (PRP)-CS thermoresponsive IH. This platform was used to treat rheumatoid arthritis. BPNs that have a high photothermal conversion efficiency and ROS generation could be employed in conjunction with NIR illumination to eradicate hyperplastic synovial tissues. In addition, platelet-rich plasma (PRP) has the potential to support the adhesion and proliferation of mesenchymal stem cells (MSCs), in addition to the mechanical stability and biodegradability of the CS hydrogel. In addition to lubrication and the preservation of cartilage, CS thermosensitive hydrogel with exceptional rheological properties has the potential to manage medication release thanks to its thermosensitivity and biodegradability. Furthermore, the breakdown products of BPNs have the potential to be changed in situ into P-based agents, which enhance the osteogenesis process through calcium-extracted biomineralization brought about by BPNs driven in situ by phosphorus. Both in vitro and in vivo testing demonstrated that the BPNs/CS/PRP thermoresponsive hydrogel has high promise for treating RA. Additionally, the hydrogel's multimodal mode of action opened the route toward mending this challenging condition. (127)

In a different piece of research, Parameswaran-Thankam et al. (128) utilized the graft polymerization method to create an injectable thermoresponsive hydroxypropyl guar-graft-poly (N-vinyl caprolactam) (HPG-g-PNVCL) copolymer. This copolymer was then modified with nano-hydroxyapatite (n-HA) by in situ covalent cross-linking using the divinyl Ciprofloxacin, a common antibiotic, was included in the composite by the researchers so that it would have a higher level of antibacterial activity. According to the results of several in vitro testing, the hydrogel has the potential to release pharmaceutical molecules over a protracted period of time. In vitro biomineralization studies using simulated body fluid (SBF) for 14 days revealed that an apatite-like structure was deposited on the surface of the HPG-g-PNVCL/n-HA/DVS scaffold. This was confirmed by scanning electron microscopy (SEM), and the Ca/P ratio increased from 0.83 to 2.00 within 7 days, which is comparable to the ratio found in the human body. Because of its ability to create calcium-rich apatite, its high bioactivity, and its effective encouragement of osteoblast cell development, this system was a huge success for tissue regeneration. As a result of these factors, the process was exceedingly effective. (128)

### 5.4 The Application of Tissue Engineering in Dentistry

Masticatory efficiency and facial beauty are both significantly impacted by periodontal disease, also known as gum disease, as well as tooth lesion and tooth loss. It is possible to hasten the process of dental regeneration with the use of combination treatments that involve injectable biomaterials. (129) Xu et al. (130) developed a thermosensitive IH that was composed of CS, b-sodium glycerophosphate (b-GP), and gelatin. The purpose of this IH was to stimulate periodontal regeneration by the regulated release of erythropoietin (EPO) and aspirin. IHs released aspirin and EPO continuously for at least 21 days without producing any harm in either vitro or in vivo testing conditions. According to micro-CT and immunohistochemical staining, CS/b-GP/gelatin IHs were able to stop the inflammation and restore the height of the alveolar bone. This was accomplished by down-regulating the proteins cyclooxygenase-2 (COX-2) and matrix metalloproteinase-9 (MMP-9). (130)

By co-assembling the hydrogelator NapFFY with the growth factors BMP-2 and SDF-1, Tan et al. (131) were able to develop a biocompatible supramolecular hydrogel of SDF-1/BMP-2/NapFFY for the regeneration of periodontal tissue. Because of the modest G′ and G″ values that hydrogels have (approximately 1–30 Pa), it has been demonstrated that hydrogels are injectable and are able to fill irregular periodontal bone defects. They found that the area of the tissue defect was filled with a hydrogel that contained SDF-1 and BMP-2, and that the sustained release of periodontal tissue reconstruction stimulators (SDF-1 and BMP-2) resulted in the beginning of the process of periodontal bone regeneration. Both of these findings were made possible by the fact that the periodontal tissue reconstruction stimulators were released continuously. (131) However, due to the complicated structure of the root canal system and the short apical access, poor revascularization ability is a major barrier in the field of tissue engineering. This is especially true in endodontic regeneration treatments. In their research, Silva et al. employed HA-based hydrogels that were injectable as well as viscoelastic for the purpose of releasing chemotactic and angiogenic growth factors (GFs).

In order to create the HA hydrogels (PL), cellulose nanocrystals (CNCs) and platelet lysate were added. The incorporation of CNC resulted in the HA hydrogel exhibiting increased mechanical strength as well as resistance to enzymatic degradation. Platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) were both produced by PL in addition to chemotactic and proangiogenic growth factors. These IHs permit the controlled release of PDGF and VEGF, which are growth factors that promote angiogenesis and chemotaxis, respectively. Because it contained PL (hDPCs), the hydrogel improved the viability of the human dental pulp cells that were enclosed in it. The dental pulp-origin cells were drawn to an in vitro study by the GFs that were released from the hydrogel, and an ex vivo examination showed that these GFs encouraged cell sprouting. This technique has a lot of potential for use in vascularized tissue engineering applications such as regenerative dentistry due to its ability to function as a GFs controlled delivery system as well as a supportive matrix for cell culture, recruitment, and induction of revascularization. (132)

### 5.5 Neural Engineering and Regeneration

IHs have the potential to be utilized as carriers for neural stem cells and growth factors in the treatment of nerve injuries (133). For example, Zhao et al. (134) developed a thermosensitive IH that included nerve growth factor (NGF) and heparin-poloxamer (HP) for the treatment of spinal cord injuries (SCI). They first synthesized HP using the EDC/NHS strategy, and then they employed the cold approach to create NGF–HP in situ hydrogels. Initially, they synthesized HP using the EDC/NHS approach. The NGF–HP hydrogels exhibited very high levels of bioactivity. The NGF–HP hydrogels enhanced neuron functioning and tissue shape more than the free HP hydrogel and NGF therapy groups, according to in vivo research conducted on a rat model of spinal cord injury (SCI). These studies also showed that the NGF–HP hydrogels reduced the development of glial scars. There is a possibility that the neuroprotective qualities of NGF and the anti-inflammatory properties of heparin are responsible for the synergistic benefits that NGF–HP hydrogels have on SCI regeneration. (134) In the same line of research that was conducted in 2017, the researchers employed a cold method to generate GDNF-HP hydrogels. They found that injecting these hydrogels into the lesion epicenter after SCI had a greater influence on neural stem cell proliferation and axonal regeneration than the treatment groups that were given free HP hydrogel and GDNF. (135, 135) For the purpose of peripheral nerve regeneration, bFGF and NGF were incorporated into thermosensitive HP hydrogels and administered to diabetic rats by Li et al. (136). It is possible for the HP hydrogels to have significant amounts of growth factors (GFs) injected into them, which would then allow for their regulated release. Injection of GFs-HP hydrogels into the lesion site resulted in increased schwann cell proliferation, axonal regeneration, and remyelination as compared to injection of HP hydrogel alone or direct GFs. (136) These findings were published in the journal Experimental Neurology.

IHs can also be utilized to rebuild damaged nerves following an ischemic stroke by simultaneously sending stem cells and growth factors to the area. This process is known as neuroregeneration. Moshayedi et al. (137) created a modified HA hydrogel with heparin-bound growth factors and MMP degradable motifs in order to synchronize the distribution of human neural progenitor cells (iPS-NPCs) and growth factors for nerve regeneration after an ischemic stroke. A MMP-degradable peptide cross-linker was introduced to the gel precursor solution after growth factors and heparin had already been incorporated into the solution. According to the findings, increased astrocytic differentiation of iPS-NPCs within the stroke cavity was caused by the up-regulation of GFAP and S100b markers by cells encapsulated in the IHs. This resulted in enhanced astrocytic differentiation. (137)

Additional Applications for Combination Therapy Involving Inhibitory Hormones (IHs)

The researchers investigated the effectiveness of IHs in the co-delivery of therapies in order to offer many treatments simultaneously. This is one of the fascinating qualities and capabilities of IHs. Tuladhar et al. (23) concentrated on co-delivering medicines to the brain, which is a challenging task due to the blood-brain barrier (BBB) and off-target effects generated by systemic administration. However, they were successful in this quest. A number of the drugs, including erythropoietin (EPO) and cyclosporine A (CsA), are known to have potential adverse effects. On the other hand, the administration of these medicines locally has the potential to minimize the severity of their side effects. As a consequence of this, they devised a method of IH in order to circumvent the BBB and, for the very first time, co-deliver CsA and EPO in a manner that was both regulated and carried out locally. They encapsulated the drugs in poly (lactide-co-glycolide) (PLGA) particles and then distributed them in a hyaluronan and methylcellulose (HAMC) gel so that they could construct a delivery system that could be modularized. scientists implanted the composite into the surface of the rat brain four days after the injury to limit the amount of tissue damage caused by intracranial implants. To do this, scientists first enclosed the composite in a polycarbonate shell and then sealed it with dental cement to prevent drug leakage into the cerebrospinal fluid (CSF). Additionally, they implanted the composite into the surface of the brain. According to the findings, both drugs have the potential to diffuse into the sub-cortical neural stem and progenitor cell (NSPC) niche, where they may remain for around 32 days. The CsA was discovered to promote striatal plasticity, whereas the EPO was effective in raising the number of endogenous NSPCs. Both of these effects were observed. Furthermore, these outcomes were only feasible due to the local and constant co-delivery of both drugs, which promoted tissue repair to the extent that the lesion volume in the CsA+EPO treated group was greatly reduced at day 46 compared to day 4 ($p$ 0.05). This was a statistically significant finding. On the other hand, this significant difference was not observed in the groups that were treated with a single medication. In comparison, the volume of the lesion fell by 27% in the EPO-alone group whereas it decreased by about 23% in the CsA-treated group. Because of this issue, it was shown that CsA and EPO had an additive impact as well as independent processes on stroke lesion. This was proved by the fact that the lesion volume was reduced by 50% in the treatment group that received both CsA and EPO. (23)

Sequestering or attaching pro-angiogenic growth factors to nanoparticles and integrating them into IHs has been proven to induce prolonged activation of cell-surface receptors and higher efficacy for the treatment of various diseases in contrast to the administration of exogenous (unbound) growth factors. This is the case when compared to the administration of growth factors that are not bound. (138) Nih et al. (139) developed in situ gelling HA hydrogels for the co-delivery of nanoparticle-clustered VEGF and heparin nanoparticles in order to facilitate the recovery of brain tissue following a stroke. They found that heparin nanoparticle-clustered VEGF in the brain had stronger effects on normal vascular development, reducing microglia activation, promoting axonal ingrowth, and migration of immature neurons from the subventricular zone to the infarcted region. This was in comparison to traditional VEGF delivery in the brain, which they found to have weaker effects. It was discovered that the anti-inflammatory properties of naked heparin particles might counterbalance the inflammatory activity caused by VEGF, which would then result in the development of an environment that is conducive to repair in the infarcted area. (139)

Copper ions and ibuprofen were both given at the same time by Boffito et al. (140), which resulted in the formation of an IH. In order to accomplish this, they initially produced nano and microparticles made of copper-substituted bioactive mesoporous glasses (Cu-MBGs). These particles were then loaded with ibuprofen through the application of the incipient wetness methodology. The thermosensitive IH made from amphiphilic polyurethane was then disseminated with this composite. According to the statement, the loaded medication and ions did not have any effect on the gelation behavior of this IH. The findings demonstrated that this approach was capable of coordinating the continuous delivery of Cu+2 and ibuprofen, with the released copper ions driving the chemical breakdown of polyurethane and managing the gel's residence time at the pathological site. This work showed that the IH, when combined with MBGs, may be successfully employed to provide regulated and local co-delivery of therapeutic ions and medicines, which is something that is much wanted in the field of biomedicine (140).

Fan et al. used Schiff's base reaction to create an IH from natural polysaccharides for medication and cell scaffold co-delivery.(142-143) CMC and oxidized chondroitin sulfate (OCS) were used to cross-like the IH during the manufacturing process, with the mechanism being a reaction between amino and aldehyde groups. For the purpose of co-delivery, bovine serum albumin (BSA) was packaged inside of CS-based microspheres before being implanted into the CMC-OCS IH. The mechanical and bioactive properties of the IH may be improved with the use of the CS microspheres. Acute myocardial infarction was successfully treated with GF medication by Rufaihah et al. (143). They produced an IH out of polyethylene glycol-fibrinogen (PF), and it was utilized to distribute VEGF and angiopoietin-1 (ANG-1) in a regulated and coordinated manner (PF-VEGF-ANG1). This was done with the intention of enhancing myocardial repair and function. Both VEGF and ANG-1 were secreted in a managed fashion throughout the course of a period of thirty days. The integrity of the heart muscle was preserved as a direct result of the collaborative efforts of VEGF and ANG-1.

The group that was treated with 1 percent PF-VEGF-ANG1 had the maximum capillary density in the infarct and peri-infarct areas when compared to the group that was treated with saline and the group that was treated with 1 percent PF. In addition, there is a possibility that the PF-VEGF-ANG-1 hydrogel can perform the role of a mechanical support in order to aid in the prevention of adverse cardiac remodeling. To summarize, it is possible that combining treatment with the co-delivery of medications through an IH will assist minimize post-MI cardiac dysfunction. (143)

In the study by Zhang et al. (144), the authors focused on drug delivery and 3D cell cultivation of L929 cells using an IH. This IH was synthesized by mixing glycol CS and a dibenzaldehyde terminated copolymer poly (N-isopropyl acrylamide)-co-poly (acrylic acid) (DF poly (NIPAM-co-AA)) solution, as well as dynamic imine bonds formation between benzal According to the researchers, this IH was sensitive to both pH and temperature, and it had the ability to discharge the drug in a manner that was in accordance with the pH and temperature of its surroundings. This non-cytotoxic IH was successfully employed for 3D cell culture of L929 cells, which resulted in outstanding viability (i.e., 90%) after 24 hours of incubation with hydrogel. This indicates that hydrogel is a suitable cell carrier choice since it provides a 3D environment for cells to develop in. This optimistic discovery may pave the way for IHs to explore more work in multimodal treatment, such as simultaneously delivering medication and cell therapy to address the condition. (144)

Pentlavalli et al. (145) created an in situ producing biocompatible IH (TEMED) by performing a simple free-radical polymerization of N-isopropyl acrylamide (NIPAAm) on the alginate backbone. They also employed ammonium persulfate (APS) and N, N, N′, N′-tetramethylethylenediamine. The resultant hydrogel exhibited thermoresponsive activity when subjected to an LCST of 32 degrees Celsius, which is relatively near to the average temperature of the human body. Because the hydrogel was biocompatible and biodegradable, and because after eight weeks it had deteriorated by around 70 percent due to surface degradation, it was an excellent candidate for long-term drug delivery. At a pH of 7.4 and a temperature of 37 degrees Celsius, it was found that the large protein molecule BSA was released from the hydrogel at a slower rate than NaF due to contact with the polymeric network. This was discovered in relation to the delivery behavior. In addition, the viscosity of the alginate can potentially change the mechanical and structural properties of the P (Alg-g-NIPAAm). This newly developed thermosensitive IH was also utilized in the local and sustained co-delivery of human osteosarcoma (MG63) cells and pig bone marrow-derived mesenchymal stem cells (pBMSCs) (pBMSCs). The pBMSCs were dispersed evenly throughout the IH before being encased in it. The osteogenic and chondrogenic potential of pBMSCs encapsulated in the P (Alg-g-NIPAAm) hydrogel were evaluated by incubating the cells in osteogenic and chondrogenic media. After a two-week culture period in both osteogenic and chondrogenic conditions, the viability of the cells increased from an initial value of 60 percent to more than 80 percent. According to the findings of the histological examination, the collagen and sGAGs staining was significantly greater in hydrogels that were incubated in chondrogenic conditions as opposed to osteogenic settings.

At the same time, it was shown that hydrogel that was incubated under osteogenic conditions produced significantly more mineralization. In addition, the hydrogel that had been cultured in chondrogenic circumstances showed a high DNA content, which was linked to the proliferative effect of TGF-3 in the media that it was grown in (145).

Linh et al. (146) developed an in situ forming IH through the in situ enzymatic crosslinking of tyramine-conjugated gelatin and hydroxyl phenyl acetamide CS in the presence of HRP as a catalyst and hydrogen peroxidase as an antioxidant with the intention of simultaneously delivering human adipose-derived stem cells (hADSC) and platelet-derived growth factor (PDGF). This was done According to the findings of histological research, the biocompatible scaffold equipped with a one-of-a-kind branching network and channels may stimulate cell infiltration and vascularization. (146)

7 Concluding Remarks

When several different therapeutic treatments are utilized in conjunction with one another, they usually produce higher benefits, counteract downsides, and improve treatment outcomes in comparison to when only one treatment is employed. Injectable biomaterials, whether they are natural or synthetic, have the potential to form degradable networks in situ. This has the dual benefit of alleviating patient suffering and cutting healthcare costs, while also opening up new and exciting possibilities for minimally invasive surgery. The ability of biomaterials to design and manufacture injectable systems is highly impacted by the physicochemical and mechanical properties of the biomaterials (147-274).

Because they need to ensure drug/biomolecule/material bioactivity as well as cell survival and retention, the design and fabrication of injectable systems that contain cells, therapeutic molecules, particles, and biomolecules and that can be injected into geometrically complex regions of the body tissues present a significant challenge. These systems can be injected into areas of the body that are geometrically complex. Because of their enormous potential for the manipulation, encapsulation, and co-delivery of pharmaceutical substances, cells, biomolecules, and nanomaterials, hydrogels are an excellent solution in this scenario. The method of cross-linking and the chemical make-up of hydrogels can be altered to produce desired changes in the material's mechanical and degradation properties. This ability is one of the many advantages of hydrogels. Because of the ability of IHs to have their mechanical strength altered, it is possible to in situ co-encapsulate medicinal compounds, cells, nanomaterials, and growth factors within the matrix. This makes it possible to treat many conditions at once using a synergistic combination of different treatment modalities.

In the future, a number of obstacles and scientific challenges that have not yet been solved will need to be tackled and cleared away in order to increase the likelihood that IHs will be used in conventional medical settings. To get started, any future research that includes the use of IHs in multimodal synergistic therapy ought to be carried out in large animal models such as monkeys and dogs, or even ex vivo human tissue models to be more specific. In addition, the length of time spent conducting in vivo evaluations ought to be increased from a few weeks to a few months in order to collect accurate and trustworthy data that may be carried over into clinical trials.

The toxicity of certain of the crosslinking agents that are employed in the manufacture of IH is the next thing that needs to be taken into consideration, and as a result, the residues will create unwelcome reactions in vivo. On the other side, toxic crosslinkers may interact with therapeutic molecules/biomolecules or nanomaterials that are trapped in the matrix of hydrogels, which results in the loss of the bioactivity of the therapeutic molecules or nanomaterials. In a similar vein, the sol–gel transition of IHs is an important topic that calls for a significant amount of research. When the precursor solutions undergo a rapid sol–gel transition, there is a possibility that the fluid may become caught in the needle. On the other hand, when the precursor solutions have a high viscosity, the injection force must be increased, which causes hand fatigue for the physicians and an annoyance for the patients. In addition to these factors, clinical translation of IHs must also take into account quick drug release and rate of degradation. When it comes to controlling the release of therapeutic chemicals and the regeneration of tissue, the rate at which degradation occurs is of the utmost importance. A rapid breakdown of the hydrogel may result in an initial inflammatory reaction due to the breakdown products, whereas a delayed degradation may result in inadequate drug release for therapeutic purposes. As a consequence of this, the rate at which polymers break down can be tailored by making adjustments to their composition, structure, and crystallinity. If knowledgeable researchers have a better understanding of the physiochemical properties of polymers, they will be better able to address the challenges posed by these problems. In general, the design of future IH should place a higher emphasis on the construction of straightforward and clearly defined three-dimensional networks that have a low level of toxicity, a high rate of biodegradation, and acceptable functioning.

References


1. P. Mehta, D. F. McAuley, M. Brown, E. Sanchez, R. S. Tattersall, J. J. Manson, Lancet 2020, 395, 1033.
2. P. Davoodi, W. C. Ng, M. P. Srinivasan, C. H. Wang, Biotechnol. Bioeng. 2017, 114, 2931.
3. Gu, S. Zhu, L. Yan, F. Zhao, Y. Zhao, Adv. Mater. 2019, 31, 1800662.
4. G. Tian, X. Zhang, Z. Gu, Y. Zhao, Adv. Mater. 2015, 27, 13566;
5. W. Fan, W. Bu, J. Shi, Adv. Mater. 2016, 28, 3987.
6. M. Motwani, T. M. Delohery, G. K. Schwartz, Clin. Cancer Res. 1999, 5, 1876.
7. Y. Akiyama, Y. Kimura, R. Enatsu, T. Mikami, M. Wanibuchi, N. Mikuni, World Neurosurg. 2018, 113, e508
8. Abdelhamid, H. N., M. Dowaidar, M. Hällbrink, and Ü. Langel. 2019. Cell Penetrating Peptides-Hierarchical Porous Zeolitic Imidazolate Frameworks Nanoparticles: An Efficient Gene Delivery Platform. SSRN Electron. J. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3435895.
9. Abdelhamid, Hani Nasser, Moataz Dowaidar, Mattias Hällbrink, and Ülo Langel. 2020. Gene Delivery Using Cell Penetrating Peptides-Zeolitic Imidazolate Frameworks. Microporous and Mesoporous Materials: The Official Journal of the International Zeolite Association 300 (June): 110173. https://doi.org/10.1016/j.micromeso.2020.110173.
10. Abdelhamid, Hani Nasser, Moataz Dowaidar, and Ülo Langel. 2020. Carbonized Chitosan Encapsulated Hierarchical Porous Zeolitic Imidazolate Frameworks Nanoparticles for Gene Delivery. Microporous and Mesoporous Materials: The Official Journal of the International Zeolite Association 302 (August): 110200. https://doi.org/10.1016/j.micromeso.2020.110200.
11. Ahmad, Almeman, Khalaf Hassan, Rasool Semaab, Moataz Dowaidar, and Al Orainy Mohammad. 2013. The Impact of CYP2C19 Polymorphism on Platelet Reactivity for Guiding Clopidogrel Treatment and Cost Analysis. Journal of the Saudi Heart Association 25 (2): 107. https://doi.org/10.1016/j.jsha.2013.03.005.

12. Algahsham, Abdullah, Ahmad A. A. Settin, Ahmad Ali, and Hisham Ismail. n.d. Association of MTHFR C677T and A1298C Polymorphisms with Hypertension among Saudi Subjects from Qassim Region. International Journal of Health Sciences 6 (1). Accessed June 18, 2021. http://ijhs.org.sa/index.php/journal/article/view/312.
13. Algasham, Abdullah, Hisham Ismail, Moataz Dowaidar, and Ahmad A. Settin. 2011. Methylenetetrahydrofolate Reductase (MTHFR) and Angiotensin Converting Enzyme (ACE) Gene Polymorphisms among Saudi Population from Qassim Region. International Journal of Health Sciences 5 (2 Suppl 1): 3–4. https://www.ncbi.nlm.nih.gov/pubmed/23284552.
14. Alghasham, Abdullah, Ahmad Ali, Hisham Ismail, Moataz Dowaidar, and Ahmad A. Settin. 2012. CYP2J2 -50 G/T and ADRB2 G46A Gene Polymorphisms in Saudi Subjects with Hypertension. Genetic Testing and Molecular Biomarkers 16 (9): 1027–31. https://doi.org/10.1089/gtmb.2012.0006.
15. Alghasham, Abdullah, Ahmad A. Settin, Ahmad Ali, Moataz Dowaidar, and Hisham Ismail. 2012a. Association of MTHFR C677T and A1298C Gene Polymorphisms with Hypertension. International Journal of Health Sciences 6 (1): 3–11. https://doi.org/10.12816/0005968.
16. Moataz Dowaidar. 2012b. Association of MTHFR C677T and A1298C Gene Polymorphisms with Hypertension. International Journal of Health Sciences 6 (1): 3–11. https://doi.org/10.12816/0005968.
17. Ali, Ahmad, Abdullah Alghasham, Hisham Ismail, Moataz Dowaidar, and Ahmad Settin. 2013. ACE I/D and eNOS E298D Gene Polymorphisms in Saudi Subjects with Hypertension. Journal of the Renin-Angiotensin-Aldosterone System: JRAAS 14 (4): 348–53. https://doi.org/10.1177/1470320312459976.
18. Ali, Ahmed A. A., Nahla M. Wassim, Moataz M. Dowaidar, and Ahmed E. Yaseen. 2013. Genetic Polymorphism of CYP2D6 Gene among Egyptian Hypertensive Cases. The Journal of Basic & Applied Zoology 66 (4): 228–33. https://doi.org/10.1016/j.jobaz.2012.12.002.
19. Ali, Ahmed A. A., Nahla M. Wassim, Moataz Dowaidar, and Ahmed E. Yaseen. 2013b. Association of eNOS (E298D) and CYP2J2 (−50G/T) Gene Polymorphisms with Hypertension among Egyptian Cases. The Journal of Basic & Applied Zoology 66 (4): 234–41. https://doi.org/10.1016/j.jobaz.2012.12.001.
20. Moataz Dowaidar. 2013. Association of eNOS (E298D) and CYP2J2 (−50G/T) Gene Polymorphisms with Hypertension among Egyptian Cases. The Journal of Basic & Applied Zoology 66 (4): 234–41. https://doi.org/10.1016/j.jobaz.2012.12.001.
21. Aljarallah, Badr, Ahmed Ali, Moataz Dowaidar, and Ahmad Settin. 2011. Prevalence of α-1-Antitrypsin Gene Mutations in Saudi Arabia. Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association 17 (4): 256–60. https://doi.org/10.4103/1319-3767.82580.
22. Dowaidar, M., J. Regberg, D. A. Dobchev, and T. Lehto. 2017. Refinement of a Quantitative Structure–activity Relationship Model for Prediction of Cell-Penetrating Peptide Based Transfection Systems. International Journal of. https://link.springer.com/content/pdf/10.1007/s10989-016-9542-8.pdf.
23. Dowaidar, Moataz. 2017. In-Silico Design of Peptide-Based Transfection Systems, in-Vitro Validation, and up-Take Pathways Investigation. Department of Neurochemistry, Stockholm University.
24. Moataz Dowaidar. 2018. Chimeric Gene Delivery Vectors : Design, Synthesis, and Mechanisms from Transcriptomics Analysis. Department of Biochemistry and Biophysics, Stockholm University. https://www.diva-portal.org/smash/record.jsf?pid=diva2:1242000.
25. Moataz Dowaidar. Cardiometabolic Conditions Could Be Related to Vitamin D Deficiency. The Genetic Determinants That Affect Vitamin D Pathways May Be Solved with Nanomedicines. https://doi.org/10.31219/osf.io/nqewr.
26. Moataz Dowaidar. Different Insulin Resistance and Inflammation Pathways Are Influenced by Genetic Factors in Metabolic Syndrome. Gene Therapy Enables Early Recognition and Treatment of the Genetic Factors. https://doi.org/10.31219/osf.io/gqwj2.
27. Moataz Dowaidar. Gene Therapy Has Been Shown to Be Valuable for Understanding Complex Disease Pathophysiologies. The Medical Profession as a Whole Will Have to Invest in Specialized Investigations. https://doi.org/10.31219/osf.io/8fg9y.
28. Moataz Dowaidar. Genetic and Epigenetic Discoveries Hold Promising Avenues in Cardiovascular Prevention and Management (CVDs). Key Nucleic Acids Are Being Researched and Developed for Medicinal Use. https://doi.org/10.31219/osf.io/hk7pe.
29. Moataz Dowaidar. Genome Editing Can Now Be Carried out in an Isogenic Setting. It Can Be Effectively Transmitted to Somatic Tissues in Mice, but Not to Humans. Despite These Doubts, CRIS Has Great Potential as a Medical Promise. https://doi.org/10.31219/osf.io/4rn3v.
30. Moataz Dowaidar. Genome-Wide Association Experiments Have Uncovered a Slew of Cardiometabolic Trait-Associated Variants. This Information Can Be Useful in the Implementation of New Diagnostic and Treatment Strategies. https://doi.org/10.31219/osf.io/4vws8.
31. Moataz Dowaidar. Genome-Wide Association Studies (GWAS) Have Revolutionized Our View of Human Health and Disease Genetics and Offered Novel Gene Therapy Targets. https://doi.org/10.31219/osf.io/rvm3z.

32. Moataz Dowaidar. Metabolic Syndrome_ the Presence of Inflammatory Mechanisms in Abdominal Obesity Is Undeniable, Gene Therapy Using Nanoparticles and Adenoviruses Technologies Is Promising. https://doi.org/10.31219/osf.io/2j5xt.
33. Moataz Dowaidar. miRNAs May Be Used as Preventive Agents for Metabolic Diseases in the near Future. Understanding the Interplay between pro-Adipogenic_ and Anti-Ad Pipogenic miRNA' Could Lead to New Biomarkers. https://doi.org/10.31219/osf.io/3dr8c.
34. Moataz Dowaidar. Nanomedicine Has Elegantly Attempted to Cure Multiple Gene Polymorphisms and Mutations in Cardiovascular Diseases Using Gene Therapy Techniques. https://doi.org/10.31219/osf.io/d3x8g.
35. Moataz Dowaidar. Thrombosis Pathways and Therapeutic Strategies. https://doi.org/10.31219/osf.io/57vyz.
36. Moataz Dowaidar. What Genomic Research Has Told Us about the Obesity and Its Possible Gene Therapy Targets. https://doi.org/10.31219/osf.io/ym49s.
37. Moataz Dowaidar. Exosomes Can Make the Use of Circulating miRNA as a Biomarker More Feasible. The Aim of Gene Therapy Should Be to Learn Everything There Is to Know about miRNA Activity. https://doi.org/10.31219/osf.io/edkua.
38. Moataz Dowaidar. Anti-Sense Pathways Have Been Generated Using siRNA. The Liver and Other Often Used Organs Will Now Be Targeted. https://doi.org/10.31219/osf.io/m6xvp.
39. Moataz Dowaidar. CrisPR/CRIS Systems Are Highly Effective and Useful for Genomic Manipulation. Despite This, Cardiac Treatment Remains Difficult due to Existing Genome Editing and Delivery Processes. https://doi.org/10.31219/osf.io/3nwzd.
40. Moataz Dowaidar. Discoveries in Gene-Environment Interactions That Influence CVD, Lipid Traits, Obesity, Diabetes, and Hypertension Appear to Be Able to Influence Gene Therapy. https://doi.org/10.31219/osf.io/cr5af.
41. Moataz Dowaidar. Genome Editing's Potential Target Diseases in the Cardiovascular Field. https://doi.org/10.31219/osf.io/gc23p.
42. Moataz Dowaidar. Key Genetic Factors in the Metabolic Syndrome Predisposition Which May Be a Therapeutic Options by Gene Therapy. https://doi.org/10.31219/osf.io/f38sk.
43. Moataz Dowaidar. miRNA Can Be a Part of Both the Onset and Cure of Coronary Heart Disease. https://doi.org/10.31219/osf.io/teqh8.
44. Moataz Dowaidar. Preclinical Studies and Clinical Trials Have Sparked Interest in Certain Biological Medications for Atherosclerotic Coronary Heart Disease. https://doi.org/10.31219/osf.io/ts8mh.
45. Moataz Dowaidar. Researchers Would Be Able to Develop a Detailed Picture of Chromatin in Disease, Which Would Be Useful for Gene Therapy. https://doi.org/10.31219/osf.io/m9z48.
46. Moataz Dowaidar. The Cardiometabolic-Based Chronic Disease Model Lays the Foundations for Accurate, Evidence-Based Preventive Targeting and Gene Therapy. https://doi.org/10.31219/osf.io/up9z4.
47. Moataz Dowaidar. 2D MOFs Have Unique Features for Biological Applications. They Can Be Utilized for Gene Therapy, Bioimaging, Biosensing, Photodynamic Therapy, and Tissue Engineering. https://doi.org/10.31219/osf.io/4q9ct.
48. Moataz Dowaidar. 3D Bioprinting for Enhanced Vascularization, and Gene Editing to Provide a More Favorable Immunological Response Are Just Some of the Potential Uses of Carbon Materials. https://doi.org/10.31219/osf.io/v2xy8.
49. Moataz Dowaidar. Anderson–Fabry Disease Can Be a Target for Gene Therapy. https://doi.org/10.31219/osf.io/tcgka.
50. Moataz Dowaidar. Antisense Oligonucleotides (ASOs) and CRISPR Systems Are Promising Gene Therapy Treatments for Alzheimer's Disease. https://doi.org/10.31219/osf.io/ws796.
51. Moataz Dowaidar. Any Alteration in PPAR Genomic Sequence, Splicing Pattern, or PTM Is Likely to Cause Major Alterations in Its Function. In Personalized Medicine, Such Data Becomes More Significant in Gene Therapy Design. https://doi.org/10.31219/osf.io/y8n79.
52. Moataz Dowaidar. Applying Genome-Wide Association Technology to Brain Diseases Enables the Discovery of lncRNas Targets for Gene Therapy. https://doi.org/10.31219/osf.io/hm4eu.
53. Moataz Dowaidar. Autophagy and Proteostasis Adjustment Role in Normal Brain Function and Neurodegenerative Disorders. https://doi.org/10.31219/osf.io/m4yra.
54. Moataz Dowaidar. Basal Ganglia-Cerebellar and Brainstem-Cerebellar Circuits May Interact Improperly with Dystonia. Linking Network Disruptions to Cell Failure Will Enable Understanding Pathophysiology and Designing Gene Therapy Methods. https://doi.org/10.31219/osf.io/8w35s.
55. Moataz Dowaidar. Blood Products Are Used to Treat a Multitude of Diseases, so the Blood Transfusion System Needs to Be Enhanced. CRISPR/Cas9 Has Made It Viable to Make HLA Class I-Deleted Blood Products to Avoid Rejection. https://doi.org/10.31219/osf.io/egr3n.
56. Moataz Dowaidar. Calixarenes (CAs) Are Promising in Biomedicine, Biosensing, Bioimaging and Gene Delivery Systems. https://doi.org/10.31219/osf.io/n9vjy.

57. Moataz Dowaidar. CAR T Cell Research Has Quickly Advanced from the Bench to the Clinic and Back. The Results of the Trials Have Revealed New Mechanisms. https://doi.org/10.31219/osf.io/f9wm7.
58. Moataz Dowaidar. CAR T-Cell Treatment Remains Clinically Challenging. Therapeutic Strategies May Be Designed to Cut off Immunotherapy Utilizing Safety Switches. https://doi.org/10.31219/osf.io/s7x4y.
59. Moataz Dowaidar. Central Nervous System Gene Therapy Has Entered a New Development Paradigm. New Techniques Are Being Employed for a Wide Range of Illness Indications and Pathways. https://doi.org/10.31219/osf.io/j49wz.
60. Moataz Dowaidar. Chronic Obstructive Pulmonary Condition (COPD) Is a Prevalent, Preventable, and Curable Illness with Persistent Respiratory Symptoms and Airflow Limitation. https://doi.org/10.31219/osf.io/vkdut.
61. Moataz Dowaidar. CircRNAs Have the Potential to Aid in the Diagnosis and Treatment of Lipid Diseases. https://doi.org/10.31219/osf.io/y3hp4.
62. Moataz Dowaidar. Clinical Symptoms, Underlying Pathogenesis, and the Prospect of Tailored Therapies Have All Benefited from Genetic Discoveries in Parkinson's Disease. https://doi.org/10.31219/osf.io/pdzqb.
63. Moataz Dowaidar. Code Distribution of siRNA for Cancer Genes such as p53 and Bcl2 Family Genes Has Demonstrated Efficacy in Killing Cancer Cells. Nanoparticles Can Produce a Surface Where Numerous Drugs May Be Coupled, Allowing Combinatory Treatment. https://doi.org/10.31219/osf.io/hvcse.
64. Moataz Dowaidar. Cognitive Deficiencies Pathophysiology Are Mainly an Unknown Area. Curing the Neurological Conditions Could Be an Objective for Gene Therapy. https://doi.org/10.31219/osf.io/23xf8.
65. Moataz Dowaidar. CRISPR-Based Gene Editing Is Presently Being Tried in Many Clinical Trials. https://doi.org/10.31219/osf.io/qbngx.
66. Moataz Dowaidar. CRISPR–Cas9 Gene Editing as a Tool for Developing Immunotherapy for Cancer. https://doi.org/10.31219/osf.io/dvr4t.
67. Moataz Dowaidar. CRISPR/Cas System Research Has Advanced Significantly in Biological sciences.There Are Still Many Challenges to Effective Delivery before Efficient Gene Editing May Be Achieved. https://doi.org/10.31219/osf.io/mc26v.
68. Moataz Dowaidar. CRISPR/Cas9 Genome Editing Technology Applications in Biological and Biomedical Fields. https://doi.org/10.31219/osf.io/ctqbe.
69. Moataz Dowaidar. Critical Limb Ischemia Potential Gene Therapy Strategies. https://doi.org/10.31219/osf.io/aqcpt.
70. Moataz Dowaidar. Deep Learning Algorithms for scRNAseq Analysis Have Yielded Positive Results, but There Are Still More Promising Ways That Need to Be Developed for Regenerative Medicine. https://doi.org/10.31219/osf.io/dh2pt.
71. Moataz Dowaidar. Depression May Be Epigenetically Controlled by miRNAs Making It a Diagnostic or Gene Therapy Target. https://doi.org/10.31219/osf.io/fw65m.
72. Moataz Dowaidar. Dermatophytes: Role of Host Genetics in the Development of Illness. https://doi.org/10.31219/osf.io/mf3bu.
73. Moataz Dowaidar. Developments in Biomedical Technology Will Increase the Importance of mRNA in Treating Brain Tumors, as Well as Other Malignancies. https://doi.org/10.31219/osf.io/tvj5x.
74. Moataz Dowaidar. Downstream Processing of Virus, Virus-like Particles and Nanoparticulate Inclusion Bodies to Be Used as Gene Delivery Vehicles for Human Gene Therapy Applications. https://doi.org/10.31219/osf.io/exa3q.
75. Moataz Dowaidar. Dravet Syndrome Is a Severe Developmental and Epileptic Encephalopathy. Fenfluramine and Gene Therapy Are Promising. https://doi.org/10.31219/osf.io/zvq8y.
76. Moataz Dowaidar. Exosomes' Function in Cardiovascular Protection and Neovascularization Implies That They Might Be Used to Treat Ischemia and Atherosclerotic Cardiovascular Diseases. https://doi.org/10.31219/osf.io/2h8c7.
77. Moataz Dowaidar. Ferropsis Cell Death Can Cause Complications That May Be Difficult to Detect and Quantify: Autophagy Role and Possible Therapeutics. https://doi.org/10.31219/osf.io/zd2jg.
78. Moataz Dowaidar. Following the Discovery of Anti-MDA5 Ab, the Clinical Understanding of Dermatomyositis Has Been Improved. https://doi.org/10.31219/osf.io/j2t5f.
79. Moataz Dowaidar. For the Treatment of Cystic Fibrosis, RNA Medicines, Gene Transfer Therapies, and Gene Editing Treatments Have Potential. https://doi.org/10.31219/osf.io/6afzm.
80. Moataz Dowaidar. Frontotemporal Dementia Is a Complex Disorder with a Wide Spectrum of Clinical Symptoms. Personalized Medicine and Gene Therapy Are Promising Strategies for Treatment. https://doi.org/10.31219/osf.io/gh4x7.
81. Moataz Dowaidar. G6PD Deficiency Is a Common Genetic Trait That Can Protect Heterozygotes from Dying from Malaria. https://doi.org/10.31219/osf.io/g2kza.
82. Moataz Dowaidar. Gastric Cancer Is the World's Second-Largest Death Cause. Peptides Can Be Used to Deliver Radiation or Other Fatal Chemicals to Tumors. https://doi.org/10.31219/osf.io/eu5mj.

83. Moataz Dowaidar. Gene Doping May Be Possible for Lifestyle Enhancement. https://doi.org/10.31219/osf.io/8xkm5.
84. Moataz Dowaidar. Gene Expression Assays Gather Evidence That They Can Provide Useful Therapeutic Information in Young Women. https://doi.org/10.31219/osf.io/d372s.
85. Moataz Dowaidar. Gene Therapy and Genome-Editing Treatments That Can Protect Patients from Coronary Artery Disease Are under Investigation. https://doi.org/10.31219/osf.io/xqgf8.
86. Moataz Dowaidar. Gene Therapy Approaches for Hemophilia A and B. https://doi.org/10.31219/osf.io/ufc4g.
87. Moataz Dowaidar. Gene Therapy for the Central Nervous System Has Been Initiated. This Expansion Will Require Some Degree of Simplicity in Delivery Processes. https://doi.org/10.31219/osf.io/hdy5q.
88. Moataz Dowaidar. Gene Therapy for the Treatment of Spinal Muscular Atrophy. https://doi.org/10.31219/osf.io/kpz5f.
89. Moataz Dowaidar. Gene Therapy May Benefit Inherited Ichthyoses with Concurrent Fungal Infections and Severe Ich Thyroidoses. https://doi.org/10.31219/osf.io/zxmun.
90. Moataz Dowaidar. Gene Therapy May Target APOE for Alzheimer's Disease. https://doi.org/10.31219/osf.io/3y52k.
91. Moataz Dowaidar. Gene Therapy Promises Accurate, Targeted Administration and Overcoming Drug Resistance in Diverse Cancer Cells. https://doi.org/10.31219/osf.io/j34n6.
92. Moataz Dowaidar. Gene Therapy Targeting FVIII, FIX for Haemophilia Treatment. https://doi.org/10.31219/osf.io/qcbwp.
93. Moataz Dowaidar. Gene Therapy Targeting PRMT5 May Be Useful in Immunotherapy. https://doi.org/10.31219/osf.io/gkw8j.
94. Moataz Dowaidar. Gene Therapy Using Extracellular Vesicles Loaded with miRNA Derived from Bone Marrow Mesenchymal Stem Cells Is a Cell-Free Medication Delivery Method Used in a Variety of Diseases. https://doi.org/10.31219/osf.io/3znvw.
95. Moataz Dowaidar. Genetic Engineered MSCs Are Attractive Possibilities for Regenerative Stem-Cell Therapy to Treat Several Liver Diseases. https://doi.org/10.31219/osf.io/4cfrd.
96. Moataz Dowaidar. Genetic Variants Shared between Alzheimer's Disease and Parkinson's Disease Have Been Discovered in Blood and Brain Samples. Somatic Mosaicism Might Function as an Accelerator. https://doi.org/10.31219/osf.io/tr58n.
97. Moataz Dowaidar. Genome-Wide Association Studies Promise to Discover Novel Indicators of Hypertension. Endothelin-Related SNPs Are Currently in Clinical Trials. https://doi.org/10.31219/osf.io/2n4wa.
98. Moataz Dowaidar. Gingival and Intraventricular Haemorrhages Are Severe Newborn Diseases Causing Damage to White Matter and Neurological Dysfunction in Surviving Newborns Who Can Benefit from Gene Therapy. https://doi.org/10.31219/osf.io/qb84p.
99. Moataz Dowaidar. Glioblastoma Therapeutic Approaches Were Established Utilizing Contemporary Discoveries in Delivering Medicines to the Brain as Smart Nanoparticles for Focused Therapy. https://doi.org/10.31219/osf.io/db4f6.
100. Moataz Dowaidar. Haemophilia Gene Therapy Is in Clinical Studies, Making Continuous Safety and Efficacy Testing a Key Emphasis. https://doi.org/10.31219/osf.io/sa8ny.
101. Moataz Dowaidar. Hematopoietic Stem Cell Transplantation and Gene Therapy Are the Sole Treatments for Sickle Cell Disease and Other Hemoglobinopathies. https://doi.org/10.31219/osf.io/v8xqc.
102. Moataz Dowaidar. Huntington's Disease Gene Therapy and Nanomedicines May Be Available Shortly. https://doi.org/10.31219/osf.io/rxvgd.
103. Moataz Dowaidar. Hybrid Gene Therapy Designed to Fully Understand the Underlying Molecular Cancer Process May Be a Feasible Option. https://doi.org/10.31219/osf.io/ajyfd.
104. Moataz Dowaidar. Hydrogels Are Promising Considering Their Incredible Capacity to Modify, Encapsulate and Co-Deliver Medicinal Compounds, Cells, Biomolecules, and Nanomaterials. https://doi.org/10.31219/osf.io/px3qy.
105. Moataz Dowaidar. Immune Evasion Is Linked to Histone Variation Malfunction. Gene Therapy Could Provide Tools for Targeting Histone Variant Deposition as a Critical Part of Its Pharmacology. https://doi.org/10.31219/osf.io/kjm76.
106. Moataz Dowaidar. Implementing the Human Artificial Chromosome Gene Therapy Platform Remains Challenging, but Continuous Animal Model Research Will Advance the Platform Closer to Clinical Trials. https://doi.org/10.31219/osf.io/a53f7.
107. Moataz Dowaidar. Inflammatory Breast Cancer Remains the Most Aggressive Form of Breast Cancer. A Multimodality Therapeutic Plan Has Shown Improved Survival Results. https://doi.org/10.31219/osf.io/cr935.

108. Moataz Dowaidar. Inherited Immunohematological and Metabolic Diseases Have the Potential to Improve Significantly, or Be Cured, Using Haematopoietic Stem Cell Transplantation Gene Therapy. https://doi.org/10.31219/osf.io/ukbnm.
109. Moataz Dowaidar. Insulin and IGF-1 Receptors Mutations Can Lead to Targets for Gene Therapy in Diabetes, Obesity, and Metabolic Syndrome. https://doi.org/10.31219/osf.io/s86x5.
110. Moataz Dowaidar. Integrating High-Throughput Genetics and Neuroimaging Technologies Promises Greater Information on Neurobiological Anomalies in Neurodegenerative Diseases. https://doi.org/10.31219/osf.io/hpgyz.
111. Moataz Dowaidar. Intravitreal and Subretinal Injections Currently Deliver Most Gene Therapy, Including siRNA for Eye Illnesses. Non-Viral Vectors May Provide Targeting. https://doi.org/10.31219/osf.io/rjkhy.
112. Moataz Dowaidar. LncRNA Regulating Reprogramming Glucose Metabolism Has Become One of the Most Tempting Antineoplastic Targets for Gene Therapy. https://doi.org/10.31219/osf.io/hqma5.
113. Moataz Dowaidar. lncRNAs Are Upregulated and Downregulated in OS Cells. Angiogenesis, Metastasis, Cell Signaling, Autophagy, and Death Are among Biological Processes That RNAs Play a Role in. https://doi.org/10.31219/osf.io/48n7q.
114. Moataz Dowaidar. Magnetic Nanoparticles Are Widely Used in Drug Delivery, Imaging, Diagnosis, and Targeting. It Has Promises for the Treatment of Inflammatory Disorders such as Rheumatoid Arthritis. https://doi.org/10.31219/osf.io/p2gme.
115. Moataz Dowaidar. Many miRNAs Participate in Inflammatory Regulation and Bone Metabolism. Overexpression of miR21 and miR155 Releases Proinflammatory Cytokines. https://doi.org/10.31219/osf.io/2wuvp.
116. Moataz Dowaidar. MiR490's Diagnostic Capacity Was Demonstrated in Various Cancer Kinds and Diseases, Adding to Its Clinical Value. https://doi.org/10.31219/osf.io/wysre.
117. Moataz Dowaidar. miRNAs Have an Impact on Xeno-Infectious Diseases by Influencing Host And/or Infection Factors. https://doi.org/10.31219/osf.io/7qewx.
118. Moataz Dowaidar. Mutations in MED12 Lead to Mental Retardation, Including Opitz–Kaveggia Syndrome, Ohdo Syndrome, Lujan–Fryns Syndrome, and Psychosis. It's a Target for Gene Therapy. https://doi.org/10.31219/osf.io/cyns8.
119. Moataz Dowaidar. Nanocarriers Can Be Used to Control the Activity of Genome Editing in a Spatiotemporal Way by Using Stimulusresponsive Nanocarriers. https://doi.org/10.31219/osf.io/nua89.
120. Moataz Dowaidar. Nanomaterials Were Formed into Various Shapes, with Functionalization Aimed at Various Internalization Processes. Their Nanoscale Size Allows Drugs to Reach Cells or Extracellular Environments. https://doi.org/10.31219/osf.io/p2ajv.
121. Moataz Dowaidar. Nanomedicine Is Offering Promising Strategies for Tumor Blockade Treatment. https://doi.org/10.31219/osf.io/yzxuq.
122. Moataz Dowaidar. Network Medicine Might Lead to New Treatments for Dyslipidemia. It Will Be a Challenging Method to Implement in a Clinical Context. https://doi.org/10.31219/osf.io/nksbw.
123. Moataz Dowaidar. Neuroinflammation Caused by Activated Microglia and Astrocytes Can Contribute to the Progression of Pathogenic Damage to Substantia Nigra Neurons, Playing a Role in Parkinson's Disease Progression. https://doi.org/10.31219/osf.io/ac896.
124. Moataz Dowaidar. Neurologists Rarely Perform Genetic Testing for Parkinson's Disease. Evidence Suggests That Many Patients with Major Genetic Variants Go Undiagnosed. https://doi.org/10.31219/osf.io/ykpb2.
125. Moataz Dowaidar. Neuronal Intranuclear Hyaline Inclusion Disease Is a Neurodegenerative Condition Which Can Be a Target for Gene Therapy. https://doi.org/10.31219/osf.io/upgqd.
126. Moataz Dowaidar. New Therapies Aim at Restoring the Molecular, Morphological, and Functional Integrity of Parkinson's Specific Brain Circuits. https://doi.org/10.31219/osf.io/dvyxc.
127. Moataz Dowaidar. Not All lncMIRHGs Are 'Junk Transcripts,'. LncM IRHG Loci May Make Both Functional miRNAs and lncRNAs, Which Can Work Together or Separately. https://doi.org/10.31219/osf.io/a567w.
128. Moataz Dowaidar. Nrf2 Signaling Pathways Are Part of a Wider Network of Signaling Pathways Regulating Thymoquinone Therapeutic Actions Which Need Innovative Formulations and Delivery Methods. https://doi.org/10.31219/osf.io/u2fa7.
129. Moataz Dowaidar. Omics Should Be Integrated with Genomics to Uncover Molecular Networks and Tissue and Single-Cell Epigenetic Changes. With These Findings, Targeted Pseudoexfoliation Syndrome and Glaucoma Gene Therapy Procedures May Be Viable. https://doi.org/10.31219/osf.io/48fj5.
130. Moataz Dowaidar. Ophthalmic Gene and Cell Therapies. https://doi.org/10.31219/osf.io/n84m9.
131. Moataz Dowaidar. P21 Is a Flexible, Multi-Functional Protein. It Governs Various Tumor Cell Activities, Including Autophagy. p21 Is a Possible Radiotherapy Target. https://doi.org/10.31219/osf.io/ydkca.
132. Moataz Dowaidar. Parkinson's Disease Simulating Complexity via Improving the Identification of Significant Genetic Alterations and Environmental Contaminants Should Be a Priority. https://doi.org/10.31219/osf.io/pmcu9.

133. Moataz Dowaidar. Patient-Specific Microphysiology Systems Are Likely to Become a Crucial Aspect of Translational Research and Precision Medicine. https://doi.org/10.31219/osf.io/bc8fr.
134. Moataz Dowaidar. Patients with PMD Who Are Thoroughly Screened by Genomic Medicine Have a Considerable Chance of Benefiting Greatly from Whole-Genome Sequencing. https://doi.org/10.31219/osf.io/dajft.
135. Moataz Dowaidar. Polydopamine Nanoparticles' Activity and Long-Term Stability Should Be Fully Studied for Gene Therapy Applications. https://doi.org/10.31219/osf.io/x4nej.
136. Moataz Dowaidar. Potential Therapeutics for Primary Mitochondrial Disorders. https://doi.org/10.31219/osf.io/6pz5k.
137. Moataz Dowaidar. Potentials of Medicinal Nanostructured Diamond Particles and Coatings. https://doi.org/10.31219/osf.io/h68xz.
138. Moataz Dowaidar. Preclinical Investigations Revealed Possibilities for Salmonella Tumor Treatment. Bacteria Can Also Be Coupled to Nanomaterials Enabling Drug-Loading, Photocatalytic And/or Magnetic Properties, Using the Bacteria's Net Negative Charge. https://doi.org/10.31219/osf.io/embqk.
139. Moataz Dowaidar. Research into P2X Purinergic Receptor Function in Tumor Growth Has Made Substantial Progress with Potential Gene Therapy Targeting. https://doi.org/10.31219/osf.io/r34fs.
140. Moataz Dowaidar. RNA Therapies Hold Great Promise for Treating Cancer. High-Throughput Screening Techniques Have Facilitated the Development of RNA Treatments. https://doi.org/10.31219/osf.io/9vxrb.
141. Moataz Dowaidar. RNAi Treatment Has Been Shown to Successfully Modify Human-Related Target Gene Expression, Including Cancer. It Has the Capacity to Control Non-Standard Oncogenes, such as Oncogenic lncRNAs. https://doi.org/10.31219/osf.io/bwqep.
142. Moataz Dowaidar. RNAs Hold a Lot of Potential When It Comes to Druggable Molecular Targets. https://doi.org/10.31219/osf.io/2dtxg.
143. Moataz Dowaidar. Shadow Enhancers' Objective Seems to Be to Establish Robust Growth Patterns Independent of Genetic or Environmental Stress. https://doi.org/10.31219/osf.io/qfnkp.
144. Moataz Dowaidar. Sickle Cell Disease Hematopoietic Stem Cell Gene Therapy with Globin Gene Addition Is Promising. https://doi.org/10.31219/osf.io/j5fkb.
145. Moataz Dowaidar. Single-Gene Mutations in mtDNA-Associated Proteins Are Unlikely to Be the Main Cause of Sporadic Parkinson's Disease. Cumulative Genetic Variation in Numerous Genes May Be Important in Neurodegeneration and PD Risk. https://doi.org/10.31219/osf.io/89qte.
146. Moataz Dowaidar. Small Nuclear Ribonucleoproteins (snRNPs) Based Gene Therapy. https://doi.org/10.31219/osf.io/c43r9.
147. Moataz Dowaidar. Studying the Pathologic Mechanisms of Osteoporosis and the Bone Microenvironment May Help Researchers Better Know the Etiology of Rheumatoid Arthritis, Periodontitis, and Multiple Myeloma, as Well as Other Inflammatory and Autoimmune Disorders. https://doi.org/10.31219/osf.io/t3z6y.
148. Moataz Dowaidar. Suicide Gene Therapy May Be Effective in the Treatment of Malignant Glioma. https://doi.org/10.31219/osf.io/vdkst.
149. Moataz Dowaidar. Synuclein Is a Protein That Is Expressed in Brain Tissue. The Specific Missense Mutation (SNCA) Found in a Family with Parkinson's Disease Is the Cause. Other Diseases Include Alzheimer's Disease and REM Sleep Behavior Disorder. https://doi.org/10.31219/osf.io/bs8rc.
150. Moataz Dowaidar. Systems Biology Is a Method for Analyzing Massive Amounts of Multidimensional Data Generated by Omics Technologies. Cross-Validation of the Various Technological Platforms Is Critical. https://doi.org/10.31219/osf.io/p8vkd.
151. Moataz Dowaidar. Targeting Mitochondria and Especially Taz Gene Mutation Induces CL May Give Novel Therapeutic Alternatives for Treating Barth Syndrome. https://doi.org/10.31219/osf.io/unfpy.
152. Moataz Dowaidar. The Ability to Combine Multiple mRNA Antigens Targeting Multiple Pathogens Simultaneously, and the Robust Immune Responses Are Confirmed in Several Clinical Studies. https://doi.org/10.31219/osf.io/6qksx.
153. Moataz Dowaidar. The Cubic Polyhedral Oligomeric Silsesquioxanes Based Hybrid Materials Have a Wide Variety of Applications, Including Drug Administration, Gene Therapy, Biological Imaging, and Bone Regeneration. https://doi.org/10.31219/osf.io/9peq8.
154. Moataz Dowaidar. The Development of Tissue Replacement Therapies and Drug Discovery Was a Critical Milestone in Advancing Regenerative Medicine. https://doi.org/10.31219/osf.io/w9bsm.
155. Moataz Dowaidar. The Epidemic of COVID-19 Prompted Widespread Use of mRNA Vaccinations. https://doi.org/10.31219/osf.io/jqws5.
156. Moataz Dowaidar. The Most Useful and Commonly Available Acute Rejection Surveillance Strategies Are Routine Monitoring of Myocardial Function and Donor-Specific Anti-HLA Abs Monitoring. https://doi.org/10.31219/osf.io/ebw68.

157. Moataz Dowaidar. The Protease MBTPS2 Is an Important Regulator of Several Cellular Processes, Especially in Health and Sickness. https://doi.org/10.31219/osf.io/qyn6h.
158. Moataz Dowaidar. The Sigma 1 Receptor (S1R) Is a Potential Therapeutic Target for the Treatment of Huntington's Disease. https://doi.org/10.31219/osf.io/mcefx.
159. Moataz Dowaidar. The Use of a Network Medicine Approach Might Result in Innovative Strategies for Lowering Coronary Heart Disease and CV Risks. https://doi.org/10.31219/osf.io/eakg8.
160. Moataz Dowaidar. The Vasoconstrictor Endothelin System Involvement in Chronic Kidney Diseases Pathogenesis Is Now the Most Often Employed Treatment Method. https://doi.org/10.31219/osf.io/cnkqy.
161. Moataz Dowaidar. The VPS35-D620N Mutation Is Associated with Parkinson's Disease and Can Be a Target for Gene Therapy. https://doi.org/10.31219/osf.io/83sxr.
162. Moataz Dowaidar. Therapeutics Including Gene Therapy for Osteoarthritis as a Concept. https://doi.org/10.31219/osf.io/7zsqy.
163. Moataz Dowaidar. Tissue Hypoxia Has Been Established as a Master Regulator for Alternative Splicing, with Substantial Clinical Consequences and Possibilities for Gene Therapy Targeting. https://doi.org/10.31219/osf.io/5pbw4.
164. Moataz Dowaidar. To Rectify Alzheimer's Disease Etiology, Excessive Mitochondrial Division Might Be Stopped or Mitophagy Might Be Promoted. https://doi.org/10.31219/osf.io/6kdxw.
165. Moataz Dowaidar. Transcriptomics Is a Rapidly Growing Field That Generates New Data That May Be Used on Its Own or in Combination with Existing Clinical Data for Development of New Therapeutics, Including Gene Therapy. https://doi.org/10.31219/osf.io/kfr6a.
166. Moataz Dowaidar. Tumor Microenvironment Has Clinical Significance in Terms of Prognosis and Therapy Prediction. https://doi.org/10.31219/osf.io/4dz8q.
167. Moataz Dowaidar. Using AAV as a Gene Delivery Vector in the Neural System Is Effective in Several Animals, such as Nonhuman Primates. https://doi.org/10.31219/osf.io/ut4fa.
168. Moataz Dowaidar. Using Pre-Existing Datasets to Combine Published Information with New Metrics Would Help Researchers Construct a Broader Picture of Chromatin in Disease. https://doi.org/10.31219/osf.io/gsqv5.
169. Moataz Dowaidar. Virus-like Particles Are Good Nanocarriers for Liquid Biopsy Probes, Imaging Contrast Agents, and Anticancer Medications. https://doi.org/10.31219/osf.io/xbtka.
170. Moataz Dowaidar. ZEB1 Controls the Expression of ICAM1, Promoting Monocyte-Macrophage Adhesion and Hence the Formation of Atherosclerotic Lesions. https://doi.org/10.31219/osf.io/kzjqg.
171. Moataz Dowaidar. Gene Therapy Development and Legislation. https://doi.org/10.31219/osf.io/mwb2n.
172. Moataz Dowaidar. Next-Generation Sequencing Is Now Utilized to Identify Genetic Abnormalities and Develop Gene Therapy. https://doi.org/10.31219/osf.io/em7xp.
173. Moataz Dowaidar. Nucleic Acid Designs, Artificial Intelligence for Screening Nanomaterials, and Enhanced Characterization Methods Are Needed to Make Nanomedicine More Successful. https://doi.org/10.31219/osf.io/2w5aq.
174. Moataz Dowaidar. Potential Strategies for Cancer Gene Therapy. https://doi.org/10.31219/osf.io/atcqz.
175. Moataz Dowaidar. Quantitative Groups Will Be Critical to the Success of Future Gene Therapy Programs. https://doi.org/10.31219/osf.io/v97ht.
176. Moataz Dowaidar. The Treatment of Major Human Illnesses with Recombinant Adeno-Associated Virus (rAAV) Has Shown Tremendous Promises. https://doi.org/10.31219/osf.io/uwa4e.
177. Moataz Dowaidar. Carbon Nanotubes Have Enormous Potential in Gene Therapy. https://doi.org/10.31219/osf.io/9bcxk.
178. Moataz Dowaidar. Charge-Alteration-Based Approaches Can Address the Evolving Needs of Nucleic Acid-Based Gene Therapy, Charge Reversal Techniques Are Also Promising. https://doi.org/10.31219/osf.io/zwq5h.
179. Moataz Dowaidar. Chromosome X, the Most Explored Genome-Editing Chromosome, Presents Possibilities for Hemophilia A Treatments. https://doi.org/10.31219/osf.io/6vsdz.
180. Moataz Dowaidar. Clinical Investigations Show That siRNA May Be Used to Treat a Variety of Disorders, Including Cancer. https://doi.org/10.31219/osf.io/fcsgq.
181. Moataz Dowaidar. Cyclodextrins as Potential Gene Therapy Vectors. https://doi.org/10.31219/osf.io/zhtsc.
182. Moataz Dowaidar. Development of Specialized Carriers Capable of Delivering Effective RNAi and siRNA Gene Therapy. https://doi.org/10.31219/osf.io/3ykwm.
183. Moataz Dowaidar. Gene Therapy Can Target Mutations such as BRAF, Which Have Been Shown to Make Tumors More Susceptible to Autophagy Suppression. https://doi.org/10.31219/osf.io/3gwra.
184. Moataz Dowaidar. Gene Therapy Vectors Should Enable CRISPR Systems to Accumulate at Disease Sites and Successfully Penetrate Nuclei. https://doi.org/10.31219/osf.io/xzmnc.
185. Moataz Dowaidar. Nanoformulations Can Be Utilized to Deliver Effective siRNA to Tumor Cells to Decrease Gene Expression. https://doi.org/10.31219/osf.io/zvukc.

186. Moataz Dowaidar. Neuronal Ceroid Lipofuscinosis Therapeutics. https://doi.org/10.31219/osf.io/75vcp.
187. Moataz Dowaidar. Nonviral Gene Delivery Vectors for Transfection of the CAR Gene for CAR-T Cell Therapy. https://doi.org/10.31219/osf.io/ckxh5.
188. Moataz Dowaidar. Potential HIV Gene Therapy Strategies. https://doi.org/10.31219/osf.io/e5hm2.
189. Moataz Dowaidar. Research on Cell Sources for Brain Cell Replacement Methods Has Gained Major Importance. Cell and Gene Therapy Are Potentially Intriguing New Domains of Regenerative Medicine. https://doi.org/10.31219/osf.io/g835b.
190. Moataz Dowaidar. RNAi-Based Gene Therapy Provides a Wide Variety of Applications. Safe, Biodegradable Nano Delivery Vectors Are Still Needed. https://doi.org/10.31219/osf.io/s2zhn.
191. Moataz Dowaidar. Strategies for Treating Multiple Sclerosis with Gene Therapy. https://doi.org/10.31219/osf.io/sycn6.
192. Moataz Dowaidar. The Combination of Unique Biomolecules and Nanoparticles Has Shown Successful Gene Therapy Treatment Approaches for Non-Small Cell Lung Cancer Treatment. https://doi.org/10.31219/osf.io/yeq5z.
193. Moataz Dowaidar. Understanding Why the Same Gene Delivery Vector Behaves Differently in Different Cell Types Is Essential for Developing More Adaptable Transfection Systems. https://doi.org/10.31219/osf.io/6q8af.
194. Moataz Dowaidar. AAV9 Is Considered the Most Efficient AAV Serotype Targeting Blood-Brain Barriers. To Enhance Effective Gene Therapy for CNS Illnesses, Testing Novel Vectors with More Efficient Crossing Capabilities Is Vital. https://doi.org/10.31219/osf.io/7bf5s.
195. Moataz Dowaidar. Artificial miRNAs Are Potential Gene Therapy Tools, Especially for Incurable Monogenic Disorders. https://doi.org/10.31219/osf.io/d5rnm.
196. Moataz Dowaidar. Breakthroughs in mRNA Modification and Nanoparticle-Based Delivery Vehicles Facilitate Gene Therapy Strategies. https://doi.org/10.31219/osf.io/ky7dt.
197. Moataz Dowaidar. CRISPR/Cas9-Mediated Genome Editing Has Demonstrated Significant Promise for Genetic Correction in Autologous Hematopoietic Stem/progenitor Cells (HSPCs) and Induced Pluripotent Stem Cells (iPSCs). https://doi.org/10.31219/osf.io/xk54r.
198. Moataz Dowaidar. Gene Therapy Vectors for Targeting the Heart. https://doi.org/10.31219/osf.io/gcbhf.
199. Moataz Dowaidar. Liposomes Can Minimize Cardiotoxicity, Address Drug Resistance, and Improve Overall Drug Release Profiles in Breast Cancer. https://doi.org/10.31219/osf.io/tn56d.
200. Moataz Dowaidar. Liposomes with Cerasome-Forming Lipids as Gene Therapy Vectors. https://doi.org/10.31219/osf.io/zjn6v.
201. Moataz Dowaidar. Nanomaterials Combine Multiple Therapeutic Approaches for Cancer Cell Multidrug Resistance, Ferroptotic Cell Death Is Promising in Various Cancers. https://doi.org/10.31219/osf.io/7bg9t.
202. Moataz Dowaidar. Nanomedicines for Enhanced Permeability and Retention (EPR)-Stratified Patients Have the Potential to Improve Treatment Outcomes. https://doi.org/10.31219/osf.io/xrcb2.
203. Moataz Dowaidar. RNA-Based Gene Therapy for Manipulating the Neuroinflammatory Cascade Closely Linked to Neurodegeneration Can Help Reduce Disease Development. https://doi.org/10.31219/osf.io/2hswv.
204. Moataz Dowaidar. Targeted Chemical Nucleases Have a Wide Range of Untapped Applications in Biological Fields, Including Gene Therapy. https://doi.org/10.31219/osf.io/6bexs.
205. Moataz Dowaidar. Bacterial Nanoparticles Can Deliver Proteins, Medications, Enzymes, and Genes to Diagnose and Cure Numerous Illnesses. https://doi.org/10.31219/osf.io/7gyna.
206. Moataz Dowaidar. Exosomal miRNA Diagnostic and Gene Therapy Tools. https://doi.org/10.31219/osf.io/aknrc.
207. Moataz Dowaidar. Gene Modification Research Has Potential, from Diagnostic to Therapeutic Levels. The Most Promising Metabolic Pathways Include the TGF-1 Signaling System, Inflammation and Protein Transport. https://doi.org/10.31219/osf.io/5ert4.
208. Moataz Dowaidar. Gene Therapy Using MnO2 Nanoparticles. https://doi.org/10.31219/osf.io/xmwjs.
209. Moataz Dowaidar. Gene-Regulatory Elements May Change the Amount, Timing, or Location of Gene Expression, Cis-Regulation Therapy Platforms Might Become a Gene Therapy to Treat Many Genetic Diseases. https://doi.org/10.31219/osf.io/xc5a2.
210. Moataz Dowaidar. Hemophilia Therapeutics. https://doi.org/10.31219/osf.io/gu74x.
211. Moataz Dowaidar. Mesenchymal Stem Cells Strategies in Cancer Immunotherapy. https://doi.org/10.31219/osf.io/dkv6w.
212. Moataz Dowaidar. Nanomaterials Can Inhibit Planktonic and Biofilm Bacteria and Can Be Used as Topical Therapy for Mouth and Wound-Related Infections. https://doi.org/10.31219/osf.io/aqd2e.
213. Moataz Dowaidar. New Technologies to Improve CAR T Cell Generation and Biomanufacturing Will Lead to Safer, More Therapeutically Effective Cells. https://doi.org/10.31219/osf.io/un8gp.
214. Moataz Dowaidar. Ocular Gene Therapy Strategies. https://doi.org/10.31219/osf.io/7en3k.

215. Moataz Dowaidar. Peripheral Nerve Injury Therapeutics, Including Electrical Stimulation, Stem Cell Treatments, and Synthetic Neural Scaffolds, Have Shown Promising Preclinical and Even Clinical Results with Potential Regenerative Treatment. https://doi.org/10.31219/osf.io/m8cs9.
216. Moataz Dowaidar. Photothermal and Photodynamic Photoactivation of Nanomaterials-Based Prodrugs Are Two Key Methods for NIR Light-Mediated Photoactivation. https://doi.org/10.31219/osf.io/2bh3r.
217. Moataz Dowaidar. Quantum Dots Have the Potential to Be Used in Gene Therapy. https://doi.org/10.31219/osf.io/bdeg6.
218. Moataz Dowaidar. Sickle Cell Disease Has Emerged as a Public Health Concern. Some Drugs May Conflict with Curative Therapies, yet They May Be Useful as a Bridge to HSCT and Gene Therapy. https://doi.org/10.31219/osf.io/6kufh.
219. Moataz Dowaidar. Stimulator of Interferon Genes (STING)-Activating Nanoparticles Can Be Employed as a Tool for Controlled Immune Activation. https://doi.org/10.31219/osf.io/2ez7a.
220. Moataz Dowaidar. CRISPR/Cas9 Has Introduced New Gene Therapy Possibilities for Muscular Dystrophies. https://doi.org/10.31219/osf.io/ug8v4.
221. Moataz Dowaidar. Degradable Branched Polycationic Systems Are Promising Gene Therapy Vectors. https://doi.org/10.31219/osf.io/utypf.
222. Moataz Dowaidar. Developing Nanotechnology Platforms for Peptide-Based Combinatory Cancer Gene Therapy Will Likely Have a Significant Influence on the Development of Personalized Cancer Medicines. https://doi.org/10.31219/osf.io/zbrkj.
223. Moataz Dowaidar. Exosomes May Prevent Cardiac Attacks, Heart Failure, and Cardiomyopathy. https://doi.org/10.31219/osf.io/agm3k.
224. Moataz Dowaidar. 2021gr. Exosomes Potential Therapeutics. https://doi.org/10.31219/osf.io/mhwt3.
225. Moataz Dowaidar. Gene Therapy Using miRNA Treatment Suppresses the Expression of Bone-Forming Defective Genes and Raises the Expression of Genes That Become Dormant during Bone Building. https://doi.org/10.31219/osf.io/tcka3.
226. Moataz Dowaidar. Genome-Editing Is Promising for Producing Therapeutically Relevant Animal Models for Possible Therapies for Rare Human Diseases. https://doi.org/10.31219/osf.io/dehr9.
227. Moataz Dowaidar. Human Corneal Endothelial Cells Grafts to Replace Cadaveric Donor Corneas. https://doi.org/10.31219/osf.io/p9x7e.
228. Moataz Dowaidar. Hybrid Nanotechnology and Peptide Nucleic Acid Could Improve the Effectiveness of Gene Therapy by Increasing Its Cell Permeability. https://doi.org/10.31219/osf.io/d8wzt.
229. Moataz Dowaidar. In Prenatal Stem Cell Transplantation and in Utero Gene Therapy, a Wide Spectrum of Genetic Diseases Can Be Diagnosed and Treated before Birth. https://doi.org/10.31219/osf.io/sa3vz.
230. Moataz Dowaidar. Magnetic Iron Oxide Nanoparticles Have Potential on Gene Therapy Effectiveness and Biocompatibility. https://doi.org/10.31219/osf.io/f3hm4.
231. Moataz Dowaidar. Neurotrophin Gene Therapy May Be Able to Treat Individuals with Noise-Induced Hearing Loss or Neural Presbyacusis. https://doi.org/10.31219/osf.io/spkxh.
232. Moataz Dowaidar. Plant Viral Nanoparticles Can Be Used in Biological Systems for Loading and Transporting Cargo. https://doi.org/10.31219/osf.io/txdka.
233. Moataz Dowaidar. Polydopamine May Be Easily Functionalized with a Range of Nanomaterials for Synergistic Cancer Therapy, in Addition to Its Exceptional Photothermal Effects. https://doi.org/10.31219/osf.io/cq942.
234. Moataz Dowaidar. Tumor-Targeted Drug Delivery Systems for Anticancer Therapies Can Selectively Provide an Appropriate Cytotoxic Payload to Cancer Cells, Reducing the Side Effects of Chemo. https://doi.org/10.31219/osf.io/683nj.
235. Dowaidar, Moataz, Hani Nasser Abdelhamid, Mattias Hällbrink, Krista Freimann, Kaido Kurrikoff, Xiaodong Zou, and Ülo Langel. 2017. Magnetic Nanoparticle Assisted Self-Assembly of Cell Penetrating Peptides-Oligonucleotides Complexes for Gene Delivery. Scientific Reports 7 (1): 9159. https://doi.org/10.1038/s41598-017-09803-z.
236. Dowaidar, Moataz, Hani Nasser Abdelhamid, Mattias Hällbrink, Ülo Langel, and Xiaodong Zou. 2018. Supplemental Material for Chitosan Enhances Gene Delivery of Oligonucleotide Complexes with Magnetic Nanoparticles–cell-Penetrating Peptide. SAGE Journals. https://doi.org/10.25384/SAGE.7105436.V1.
237. Dowaidar, Moataz, Hani Nasser Abdelhamid, Mattias Hällbrink, Xiaodong Zou, and Ülo Langel. 2017. Graphene Oxide Nanosheets in Complex with Cell Penetrating Peptides for Oligonucleotides Delivery General Subjects. Biochimica et Biophysica Acta, General Subjects. https://pubag.nal.usda.gov/catalog/5734174.
238. Moataz Dowaidar. 2017. Graphene Oxide Nanosheets in Complex with Cell Penetrating Peptides for Oligonucleotides Delivery. Biochimica et Biophysica Acta, General Subjects 1861 (9): 2334–41. https://doi.org/10.1016/j.bbagen.2017.07.002.

239. Dowaidar, Moataz, and Moataz Dowaidar. 2018. Chimeric Gene Delivery Vectors : Design, Synthesis, and Mechanisms from Transcriptomics Analysis.
240. Moataz Dowaidar. Addiction Biology Research on miRNAs, and Their Role in the Pathophysiology of Addiction Is Enabling Gene Therapy Opportunities. https://doi.org/10.31219/osf.io/z5wyt.
241. Moataz Dowaidar. Aptamers Targeting Vascular Endothelial Growth Factor Molecular Regulation as Potential Therapists. https://doi.org/10.31219/osf.io/a8qpr.
242. Moataz Dowaidar. Arrhythmogenic Cardiomyopathy Is a Set of Hereditary Cardiac Muscle Disorders Where Various Etiologies Converge. Most ACM Patients Do Not Have a Genetic Diagnosis. https://doi.org/10.31219/osf.io/pztv3.
243. Moataz Dowaidar. Autophagy, Immunological Response, and Inflammation All Rely on the TRIM Family Proteins. TRIM-Based Therapeutics for Inflammatory Illnesses Including Diabetes and Diabetic Comorbidities Are Promising. https://doi.org/10.31219/osf.io/y4g6e.
244. Moataz Dowaidar. Biogenic Particles Can Be Multiantigenic, Immunostimulative and Activate Innate Immunity While Suppressing Tumor Development. https://doi.org/10.31219/osf.io/q2kby.
245. Moataz Dowaidar. Biological Medications for Interventional Pain Have a Lot of Clinical Data behind Them. It Is Fair to Assume They Will Replace Steroid-Based Interventional Techniques, Providing Patients with Longer Relief. https://doi.org/10.31219/osf.io/4y5fm.
246. Moataz Dowaidar. Carbon Nanofibers Assist in the Manufacture of Prosthetic Joints, Promote Tissue, Organ, Nerve Regeneration and Development, and Improve Anticancer Therapy Impact and Chemosensitization for a Range of Tumor Types. https://doi.org/10.31219/osf.io/z3ucn.
247. Moataz Dowaidar. Emerging Therapy Options May Help Patients with RAG Deficiency, Especially Those with Severe Immune Dysregulation. https://doi.org/10.31219/osf.io/v5tjg.
248. Moataz Dowaidar. Exosomes as Promising Gene Therapy Tools Still Need to Be Researched and Manufactured More Efficiently. https://doi.org/10.31219/osf.io/nw4z7.
249. Moataz Dowaidar. Focus on Exosomes Could Help Make the Use of Circulating miRNA as Biomarkers More Practical. A Detailed Understanding of miRNA Behavior Should Be a Subject of Gene Therapy. https://doi.org/10.31219/osf.io/uan6x.
250. Moataz Dowaidar. Gene-Free Viral-like Particles (VLPs) Offer a Safer Alternative to Inactivating or Weakening Viral Strains for Traditional Vaccines. VLP-Based Vaccinations without Adjuvants Have Been Found to Promote Humoral and Cellular Immunity. https://doi.org/10.31219/osf.io/9dvut.
251. Moataz Dowaidar. Given the Importance of mTOR Signaling in a Number of Illnesses, It Looks Suitable to Use miR 99 Family Members as a Therapeutic Intervention to Deal with These Illnesses by Using Gene Therapy Tools. https://doi.org/10.31219/osf.io/8cwgh.
252. Moataz Dowaidar. HMGB1 Has Sparked a Lot of Attention as a Model DAMP Molecule Involved in Inflammation, Inflammatory Diseases, and Cancer. https://doi.org/10.31219/osf.io/5qx36.
253. Moataz Dowaidar. Nucleic Acid Nanocarriers Can Be Programmable, Spatially Adjustable and Biocompatible, Minimizing Systemic Toxicity and Improving Pharmacodynamics. https://doi.org/10.31219/osf.io/wr237.
254. Moataz Dowaidar. Osteoporosis Is a Prominent Source of Morbidity and Mortality in the Elderly, Particularly in Postmenopausal Women. Long Noncoding RNAs (lncRNAs) Have Been Found to Be Important Regulators and Possible Gene Therapy Targets. https://doi.org/10.31219/osf.io/ghfpt.
255. Moataz Dowaidar. Polycomb Genes Role in Cancer Pathophysiology Is Offering Targets for Therapeutics Including Gene Therapy. https://doi.org/10.31219/osf.io/sfvej.
256. Moataz Dowaidar. RNA Sequencing and Microarray Analysis Are Helpful Techniques to Detect Obesity-Related lncRNAs. LncRNA Can Alter Cholesterol Metabolism and Can Be a Target for Gene Therapy. https://doi.org/10.31219/osf.io/3fb6w.
257. Moataz Dowaidar. Sepsis-Associated Acute Kidney Damage Is a Disease That Affects the Patient's Quality of Life. It Should Be a Target for Gene Therapy. https://doi.org/10.31219/osf.io/49k7q.
258. Moataz Dowaidar. The Gene Expression Profiling Gives an in-Depth Insight of Breast Cancer Heterogeneity, Better than a Single Protein or Gene Expression. It Is Time to Include It in the Daily Routine. https://doi.org/10.31219/osf.io/xhyd7.
259. Moataz Dowaidar. The Nanomedicine System Has Successfully Inhibited Tumor Neovascularization Using Gene Silencing, Chemotherapy, Photothermal Therapy, and Other Therapies. https://doi.org/10.31219/osf.io/rk2bf.
260. Moataz Dowaidar. The Therapeutic Application of a Nucleic Acid Sequence to Patients' Diseased Organs Is Currently Available. https://doi.org/10.31219/osf.io/pqsbf.
261. Moataz Dowaidar. Triple-Negative Breast Cancer, Which Lacks the Expression of Hormone Receptors and HER2, Has a Worse Prognosis. Massive Parallel Sequencing Is Capable of Reliably Breaking down the Intra-Tumor and Inter-Tumor Heterogeneity. https://doi.org/10.31219/osf.io/pvk7u.

262. Dowaidar, Moataz, H. A. Ismail, A. A. Alghasham, M. M. Dowaidar, and A. A. Settin. 2011. Polymorophisms in MTHF and Ace Genes and the Association with Hypertension among Saudi Population from Qassim Region. Egyptian Journal of Biochemistry and Molecular Biology 29 (1). https://doi.org/10.4314/ejbmb.v29i1.67382.
263. Dowaidar, Moataz, Hani Nasser Abdelhamid, Mattias Hällbrink, Ülo Langel, and Xiaodong Zou. 2018. Chitosan Enhances Gene Delivery of Oligonucleotide Complexes with Magnetic Nanoparticles-Cell-Penetrating Peptide. Journal of Biomaterials Applications 33 (3): 392–401. https://doi.org/10.1177/0885328218796623.
264. Dowaidar, Moataz, and Ahmad Settin. 2010. Risk of Myocardial Infarction Related to Factor V Leiden Mutation: A Meta-Analysis. Genetic Testing and Molecular Biomarkers 14 (4): 493–98. https://doi.org/10.1089/gtmb.2010.0017.
265. Gestin, Maxime, Moataz Dowaidar, and Ülo Langel. 2017. Uptake Mechanism of Cell-Penetrating Peptides. Advances in Experimental Medicine and Biology 1030: 255–64. https://doi.org/10.1007/978-3-319-66095-0_11.
266. Ismail, H. A., A. A. Alghasham, M. M. Dowaidar, and A. A. Settin. 2011. Polymorophisms in MTHF and Ace Genes and the Association with Hypertension among Saudi Population from Qassim Region. Egyptian Journal of Biochemistry and Molecular Biology 29 (1). https://doi.org/10.4314/ejbmb.v29i1.67382.
267. Settin, Ahmad A., Abdullah Algasham, Moataz Dowaidar, and Hisham Ismail. 2009. Methylene Tetrahydrofolate Reductase and Angiotensin Converting Enzyme Gene Polymorphisms Related to Overweight/obesity among Saudi Subjects from Qassim Region. Disease Markers 27 (2): 97–102. https://doi.org/10.3233/DMA-2009-0660.
268. Settin, Ahmad A., Abdullah Alghasham, Ahmad Ali, Moataz Dowaidar, and Hisham Ismail. 2012. Frequency of Thrombophilic Genetic Polymorphisms among Saudi Subjects Compared with Other Populations. Hematology 17 (3): 176–82. https://doi.org/10.1179/102453312X13376952196575.
269. Settin, Ahmad, Ibrahem S. Abu-Saif, Rizk El-Baz, Moataz Dowaidar, Rabab Abu-Al Kasim, and Shaimaa Shabana. 2007a. Diagnosis of Sex Chromosome Disorders and Prenatal Diagnosis of Down Syndrome Using Interphase Fluorescent In-Situ Hyperidization Technique. International Journal of Health Sciences 1 (2): 203–9. https://www.ncbi.nlm.nih.gov/pubmed/21475429.
270. Settin, Ahmad, Abdullah Algasham, Moataz Dowaidar, and Hisham Ismail. 2011. Methylene Tetrahydrofolate Reductase (MTHFR) and Angiotensinogen Converting Enzyme (ACE) Gene Polymorphisms Related to Overweight and Obesity among Saudi Patients in Al Qassim. International Journal of Health Sciences 5 (2 Suppl 1): 24–25. https://www.ncbi.nlm.nih.gov/pubmed/23284565.
271. Settin, Ahmad, Hala Almarsafawy, Ahmad Alhussieny, and Moataz Dowaidar. 2008a. Dysmorphic Features, Consanguinity and Cytogenetic Pattern of Congenital Heart Diseases: A Pilot Study from Mansoura Locality, Egypt. International Journal of Health Sciences 2 (2): 101–11. https://www.ncbi.nlm.nih.gov/pubmed/21475491.
272. Settin, Ahmad, Moataz Dowaidar, Rizk El-Baz, Ayman Abd-Al-Samad, Ibrahim El-Sayed, and Mahmoud Nasr. 2008. Frequency of Factor V Leiden Mutation in Egyptian Cases with Myocardial Infarction. Hematology 13 (3): 170–74. https://doi.org/10.1179/102453308X316158.
273. Venit, Tomas, Moataz Dowaidar, Maxime Gestin, Syed Raza Mahmood, Ülo Langel, and Piergiorgio Percipalle. 2020. Transcriptional Profiling Reveals Ribosome Biogenesis, Microtubule Dynamics and Expression of Specific lncRNAs to Be Part of a Common Response to Cell-Penetrating Peptides. Biomolecules 10 (11): 1567. https://doi.org/10.3390/biom10111567.