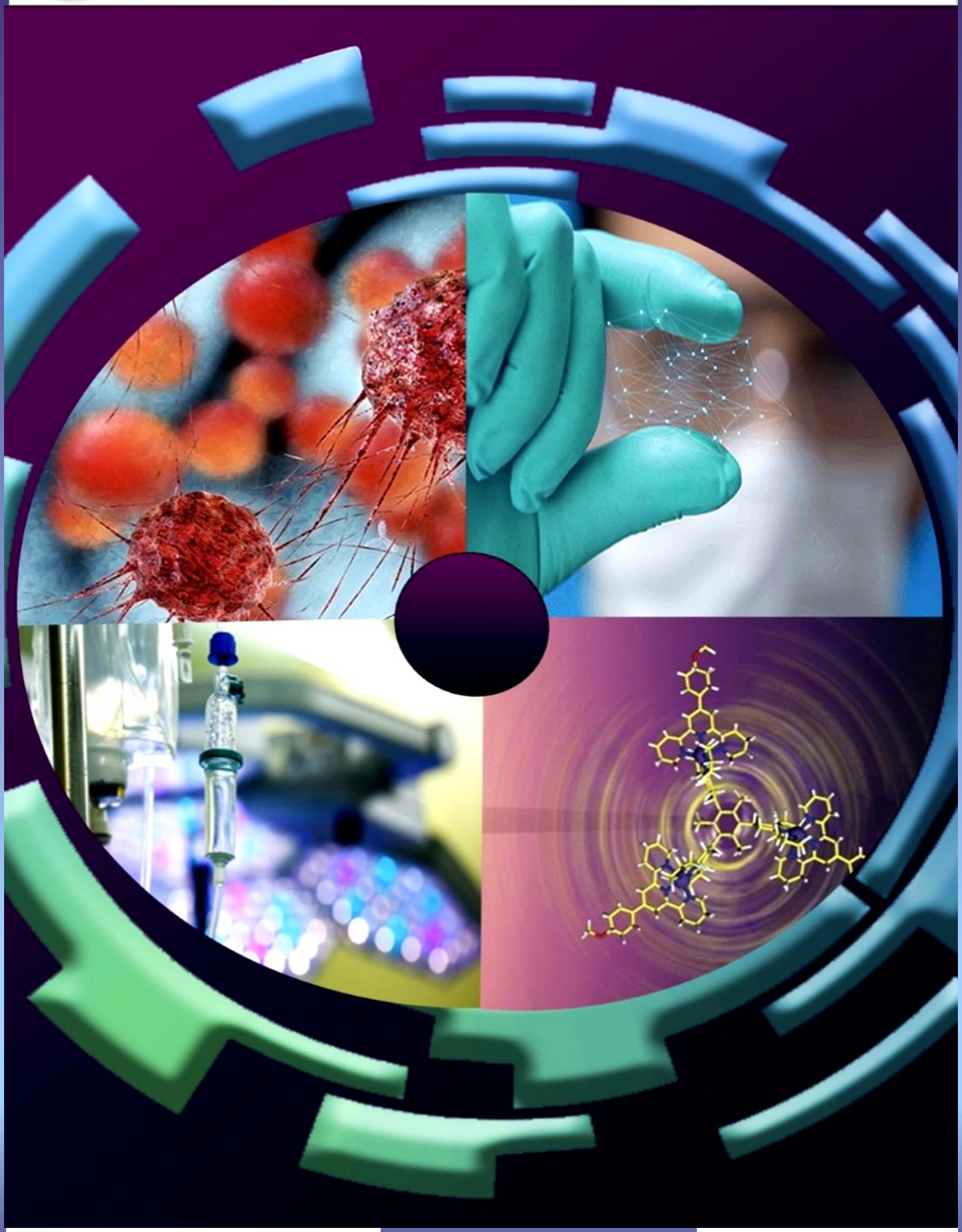
Kuwait Pharmacy Bulletin

DRUG INFORMATION FOR THE HEALTH PROFESSIONAL



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Therapeutic and diagnostic applications of dendrimers for cancer treatment

Dendrimers are hyper-branched nanoparticles with a tree like structure. They can be loaded with active materials and their unique structure can help to bind them to their target for delivery. There are many applications for dendrimers in several fields including drug delivery, gene delivery and imaging. Dendrimers can be used as drug-carrier systems for anti-cancer therapy. The advantages of the developed nanocarriers include enhanced efficiency and decreased systemic side effects of anticancer therapy. However, there are several barriers that hinder their use in cancer therapy such as toxicity of the cells, which is of most concern in positively charged dendrimers, neurotoxicity, haemolytic toxicity, haematological toxicity, degradation and cost.

Architecture and composition of dendrimers

Dendrimers are highly branched, synthetic, symmetrical nanoparticles composed of multiple branched monomers that regenerate radially from a central core resembling a tree [1, 2]. Dendrimers' generation is defined by the number of branch points that meet while moving outward from the core to the periphery (Fig 1). As dendrimers' generation increases, they become more branched, larger and have more peripheral groups. Dendrimers have a unique molecular weight, which doubles with each generation.

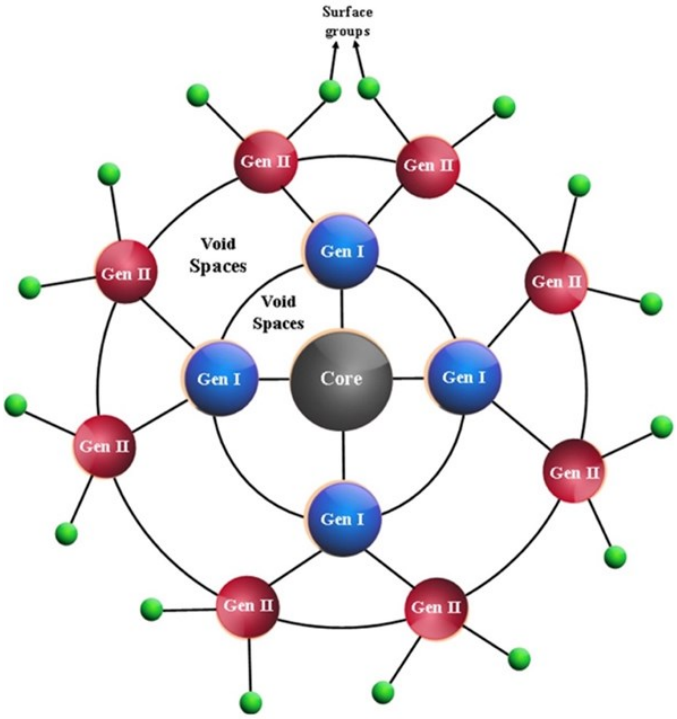

Fig 1. Simplified representation of dendrimer (Gen = generation). Taken from [3].

The peripheral groups can be adjusted to obtain charge and hydrophobic or hydrophilic functions for the required drug delivery and biological application [1, 4].

Types of dendrimers with different functionalities and properties

Polyamidoamine (PAMAM) dendrimers

These were introduced by Tomalia and co-workers in the mid1980s [6], the first to be used commercially and therefore the most studied and widely used in the biomedical field [5].

For each generation, the molecular weight and the terminal primary amine group exponentially increases while the radius roughly increases (Fig 2); the lower generations have almost linear geometries whereas higher generations have more globular-like shapes. For encapsulating and absorbing biomolecules, the intrinsically present cavities in the globular shapes of high PAMAM generations are more suitable (fig 2b). The positively charged PAMAM dendrimers exhibit significant toxicity when compared to negatively charged or neutral ones. One strategy to decrease toxicity is to modify the surface with PEG (polyethylene glycol) [7]. PAMAM dendrimers can be applied for gene delivery, oral and pulmonary drug delivery, odontology, immunodiagnostics and magnetic resonance imaging with contrast agents [5, 7].

Polypropylene imine (PPI) dendrimers

PPI dendrimers are cationic dendrimers

In this issue

(Fig 2a) introduced by Vögtle [8].

These have a subclass called polyethylenimine, which is composed of diaminoethane or diaminopropane as a functional group [3]. Similar to PAMAM dendrimers, the main problem with this type is its toxicity which can be reduced by chemical modifications of their surfaces in order to neutralize the cationic charged [9].

PPI dendrimers accumulate more in liver than in blood [10]. They have been used as antibiotic enhancers with amoxicillin [9], and for gene delivery, for example, in conjugation with dexamethasone [11].

Polyester dendrimers

This type has many applications in treatment for cancer, inflammatory and other infectious diseases. It is attractive because of its biodegradability, biocompatibility and low toxicity. The internal void in the polyester dendrimer is used to encapsulate small molecules of drugs, metals or imaging moieties. This encapsulation increases drug half-life by controlling its release and decreases drug toxicity by decreasing the drug exposure on healthy tissues. It has high solubility and miscibility as well as high reactivity because it has surface hydroxyl groups. Due to labile ester functionalities, the entrapped or covalently bonded drugs can be released by steady *in vivo* hydrolisation [12].

Phosphorhydrazone (PPH) dendrimers

There are two water-soluble families of phosphorus-containing or PPH dendrimers. One of them has positive charges from the ammonium end groups

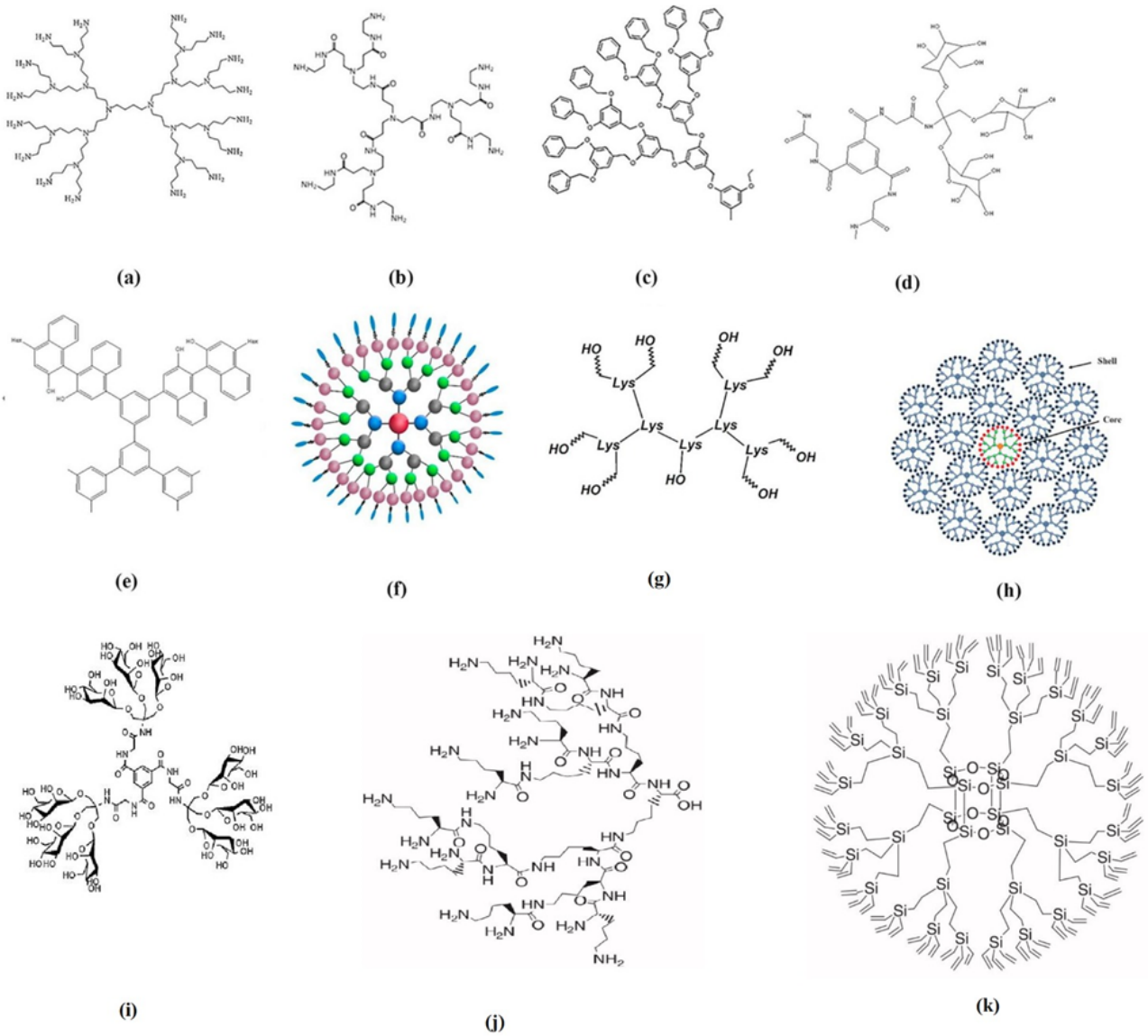

Figure 2. Structures of (a) PPI dendrimer, (b) PAMAM dendrimer, (c) Frechet-type dendrimers, (d) Glycodendrimers, (e) Chiral dendrimer, (f) Liquid crystalline dendrimers, (f) MAP dendrimers, (h) Core-shell tecto dendrimers, (i) Carbohydrate containing glycodendrimers, (j) MAP Dendron, and (k) CBD (Adapted from [3, 13, 15]).

and the other has negative charges from the phosphonate end groups. The two families have different properties; the positively charged type are efficient transgenic agents and effective carrier for siRNA delivery [10].

Frechet-type dendrimers

This type has hyper branches of poly-benzyl ether and carboxylic acid groups as the terminal groups which provides a good branching point to modify the terminal group functionalities. Additionally, the existence of these polar groups help to enhance their solubility in hydrophilic media (Fig 2c) [3].

Core-shell tecto dendrimers

This type is made up of a core dendrimer that may or may not carry the therapeutic agent in it, and surrounding dendrimers. These surrounding dendrimers have several types, with each developed to achieve a function that is essential to a smart therapeutic nano-device (Fig 2h).

Chiral dendrimers

In this type, the chirality is based upon the establishment of chemically similar yet constitutionally different branches to the chiral core. An interesting subclass is the chiral, non-racemic dendrimers with well-defined stereo-chemistry, as it may be applied in asymmetric chiral molecular recognition and catalysis [13].

Carbosilane dendrimers (CBD)

The strength of CBD is linked to the adequate energy and polarity of the C-Si bond (Fig 2k). These properties can be improved by functionalisa-tion of the end groups with polar moieties to increase their hydrophilicity. CBDs have been used successfully as non-viral carriers for the transfection of different types of nucleic acid in diseases such as AIDS and cancer [14].

Peptide dendrimers

Peptide dendrimers are defined as both traditional dendrimers with peptides on the surface and den-drimers incorporating amino acids as core or branching units. This type has several important applications in cancer, antiviral, antimicrobial, analgesics, central nervous system, asthma, allergy and Ca^{2+} metabolism, because of the biological and therapeutic relevance of peptide molecules. The advantage of using peptides is their ability to be taken up by cells making them very valuable in drug delivery. Furthermore, peptide dendrimers can also be applied as contract agents for sero-diagnosis, fluorogenic imaging, magnetic resonance imaging (MRI) and magnetic resonance angiography [13].

MAP dendrimers

MAP dendrimers are formed using polylysine skeleton and the monomer unit of alkyl amino-chain of lysine to place the branching points in the dendrimers' configuration (Fig 2j). This type of dendrimers have been studied broadly in biomedical research involving diagnostic and vaccine research [3].

Glycodendrimers

In order to describe the incorporation of carbohydrates in the structure of this type of dendrimers, the term "glycodendrimers" is used (Fig 2i). Classification of glycodendrimers is carbohydrate-coated, carbohydrate centered and fully carbohydrate based. Glycodendrimers have been useful in studying protein-carbohydrate interactions in many intercellular recognition events using the glycodendrimers with surface carbohydrate units; an important consideration is the accessibility of the sugars. Other applications where glycodendrimers are more likely to be useful are formation of gels, targeting MRI contrast agents and in gene and drug delivery systems.

Attractive features of dendrimers

Dendrimers are a unique class of nano-carriers of highly branched biocompatible macromolecules with a well-defined monodisperse framework [16, 17]. They have many attractive features that distinguish them from other nano-carriers.

Structure and chemistry

Dendrimer molecular structure is composed of a central core of one or more atoms. Growing from this central core by different chemical reactions are dendrons, which are the branches of other atoms. Dendrimers are water-soluble making them a highly desirable choice for drug delivery. They have a high drug encapsulation rate because the surface groups are facing outward. The preparation of dendrimers can be done with control leads to monodisperse global macromolecules with great number of peripheral groups. This distinctive structure gives dendrimers unique opportunities for host-guest chemistry and permitting them to be involved in multivalent interactions. Therefore, dendrimers were applied as container compounds due to the

bounding of small substrates within the internal voids of dendrimers. The physiochemical properties are mostly influenced by the surface end groups, where they can be either hydrophilic or hydrophobic [16, 17]. Dendrimers may be functional with several drugs, ligands or chromophores at their interiors and/or periphery. Moreover, the use of dendrons can accurately extend the drug-loading capacity of carriers including antibodies and biocompatible polymers such as PEG [2].

High ligand capacity

As the dendrimers' generation escalates, the multivalent ligand density at the dendrimers' surface increases, leading to a possible increase in the ligand-receptor binding as well as enhancing the targeting of attached components [2].

Covalent conjugation strategies

Over three decades, experimental strategies have been developed to enhance dendrimers' pharmacological properties by coupling small molecules to polymeric scaffolds via covalent linkages. In majority of cases, the conjugated dendritic combination works as a pro-drug in which the conjugate must be free in order to activate the drug by internalisation into the target cell [16].

Polyvalency and Electrostatic interactions

One of the important features of dendrimers is poly-valency which confers versatile functionalisation. This feature enables many interactions by coordinating with active materials. It is very significant for the production of multiple interactions with receptors of biological sites, such as in antiviral therapeutic design [16]. Moreover, the outward presentation of reactive groups on the exterior is enabled by dendrimer poly-valency [13]. On the other hand, when a large number of usually identical end-groups are charged, a polyelectrolyte dendrimers' surface may form which will likely electrostatically attract molecules with opposite charges enabling the formed complex to show adequate solubility in water [3].

pH-dependent dendrimers

An interesting feature of dendrimers terminating with amine groups, particularly PAMAM and PPI dendrimers, is pH-dependent drug release. For example, at alkaline pH, the tertiary amine groups in the amine-terminated dendrimers are deprotonated, causing the dendrimer to collapse on itself. As a result, drug molecules can be trapped in the core of dendrimers in large amounts leading to dendrimers with a compact architecture. However, at acidic pH, the interior tertiary amine groups are protonated resulting in charge repulsion leading to an 'extended conformation' resulting in an apparent dendrimer swelling that will cause the trapped drug to be released in a slow and sustained manner. For tumour delivery, it must be pointed out that as tumours have

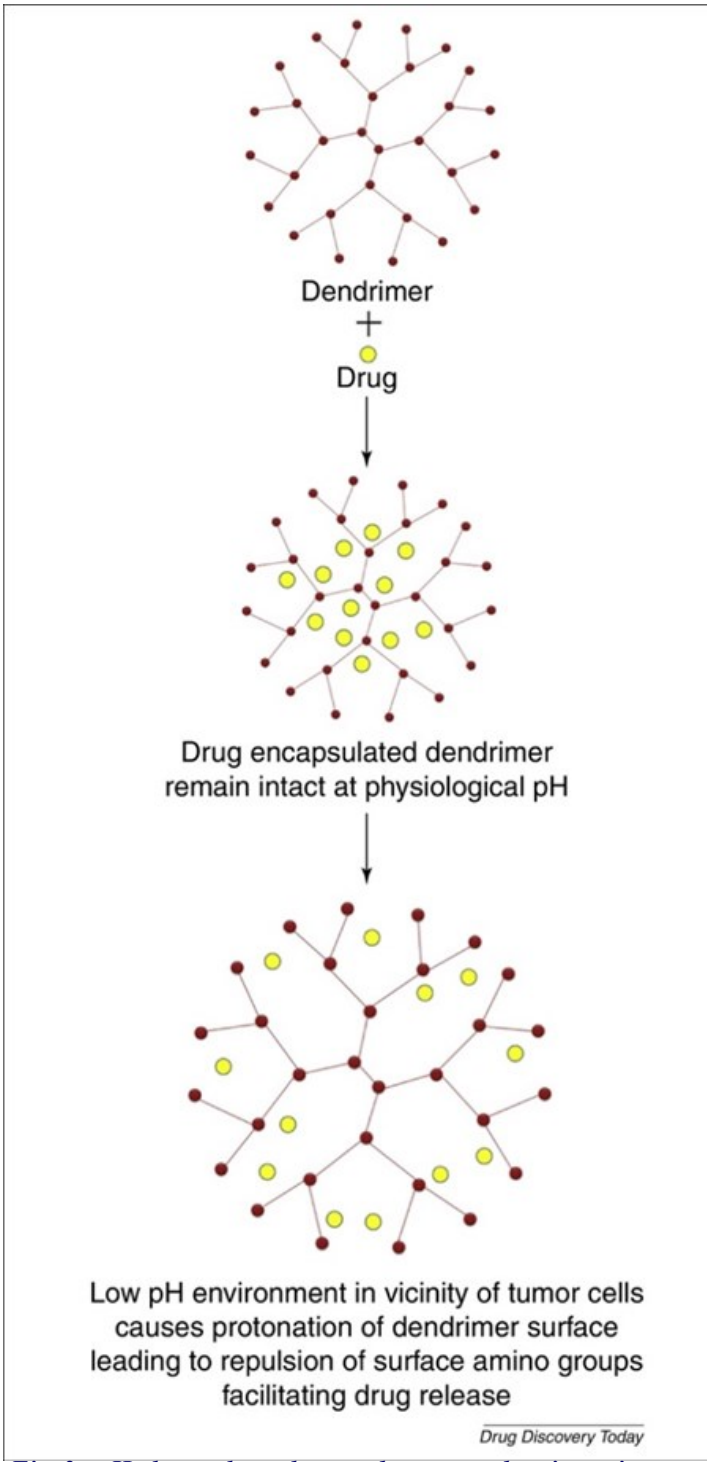

Fig 3. pH-dependent drug release mechanism via dendritic platform (Taken from [18]).

a slightly acidic microenvironment, dendrimer delivery systems can be designed as sustained release for the target tumour tissues for long-term cancer therapy (Fig 3) [18].

Pharmacokinetics and bio-distribution properties

For dendrimers to be considered for biomedical applications such as drug delivery, photodynamic therapy, neutron capture therapy and imaging, one of the most important features to be considered is their pharmacokinetics properties. These as well as biodistribution properties can be controlled by modifying the dendrimer size and configuration which can be precisely achieved by altering dendrimer generation number or the formation of a dendrimer-polymer hybrid [2].

After parenteral and non-parenteral administration of dendrimers, the *in vivo* deposition is dependent critically on dendrimer size and surface, including hydrophilicity and notable charge. Generally, after parenteral administration, the extended circulatory half-lives may be attained with dendrimers that are uncharged, PEGylated and have molecular weights above 20-25 kDa. Similarly, the absorption from interstitial injection sites are dependent upon the charge, size, and hydrophilicity as well.

The *in vitro* demonstration of dendrimers' ability to cross other epithelial barriers provides some confidence in their potential use via these routes; however, *in vivo* absorption data is more limited.

After parenteral administration, the dispositional behaviour of dendrimers is mostly influenced by small changes in the scaffold structure, shape and flexibility.

Cationic dendrimers have high tendency to bind to tissues and the vasculature, and they usually display rapid clearance from the blood.

On the other hand, weakly anionic dendrimers display similar dispositional properties to systems with no overall charge while in some cases, as the negative charge increases, dendrimers are opsonized and their uptake by reticuloendothelial system (RES) is enhanced. Moreover, uncharged dendrimers that are small (<25kDa) are usually rapidly cleared from the blood by urinary excretion. However, uncharged dendrimers that are larger typically avoid renal filtration, display extended blood resistance times, and the clearance mechanisms of dendrimers usually is shifted to non-renal clearance processes whereas a continued but slower renal clearance may persist. Furthermore, PEGylation increases the hydrophilicity and size of dendrimers leading to increase in circulatory time and limits their uptake by the RES; conversely, the increase of dendrimer structural or surface hydrophobicity leads to increased uptake [19].

Contribution of dendrimers as a versatile platform in drug delivery

Dendrimers can deliver drugs by controlling their properties such as size, structure, solubility, mono-disparity and type of functional end groups. They interact with drugs in different ways, either encapsulation to the interior or chemical attachment or physical adsorption on the surface [20, 21]. The physical interactions depend on drug entrapment in the core of dendrimers by non-covalent interactions including hydrogen, electrostatic or hydrophobic bonds. These interactions can increase drug solubility in aqueous media but it may not necessarily suggest an improved efficiency. In *in-vivo* experiments, these interactions were shown to be very weak, excluding a multivalent non-covalent interaction, which is associated specifically between positively charged dendrimers and negatively charged targets including DNA, RNA or siRNA. On the other hand, chemical interactions are the covalent conjugation of drugs and functional end-group of dendrimers, which are more stable than physical interactions. When dendrimers interact with a drug through stable bonds, the drug efficiency might be lost. If this chemical interaction is through cleavable bonds, the cleavage should be induced at the suitable time and place. An example of cleavable bonds are ester bonds which are cleaved under acidic conditions making them useful to deliver anti-cancer drugs [21, 22].

Dendrimers as a versatile platform for anti-cancer drugs

Developing an ideal cancer chemotherapy delivery system is very challenging. This may be due to some limitations including poor pharmacokinetic profiles, decreased hydrophilicity, rapid clearance, an insufficient membrane permeability, a narrow therapeutic index and serious toxicity concerns. These limitations lead to insufficient therapeutic response and increase adverse effects of anti-cancer drugs [18]. Therefore, engineering unique nano-sized drug delivery systems for anticancer drugs is a clever strategy as they passively and/or actively target cancer cells and deliver the conjugated drugs or gene cargoes. A suitable choice is dendrimers since they have a proper nano-size, expectable releasing profile, elevated loading capacity, favourable pharmacoki-

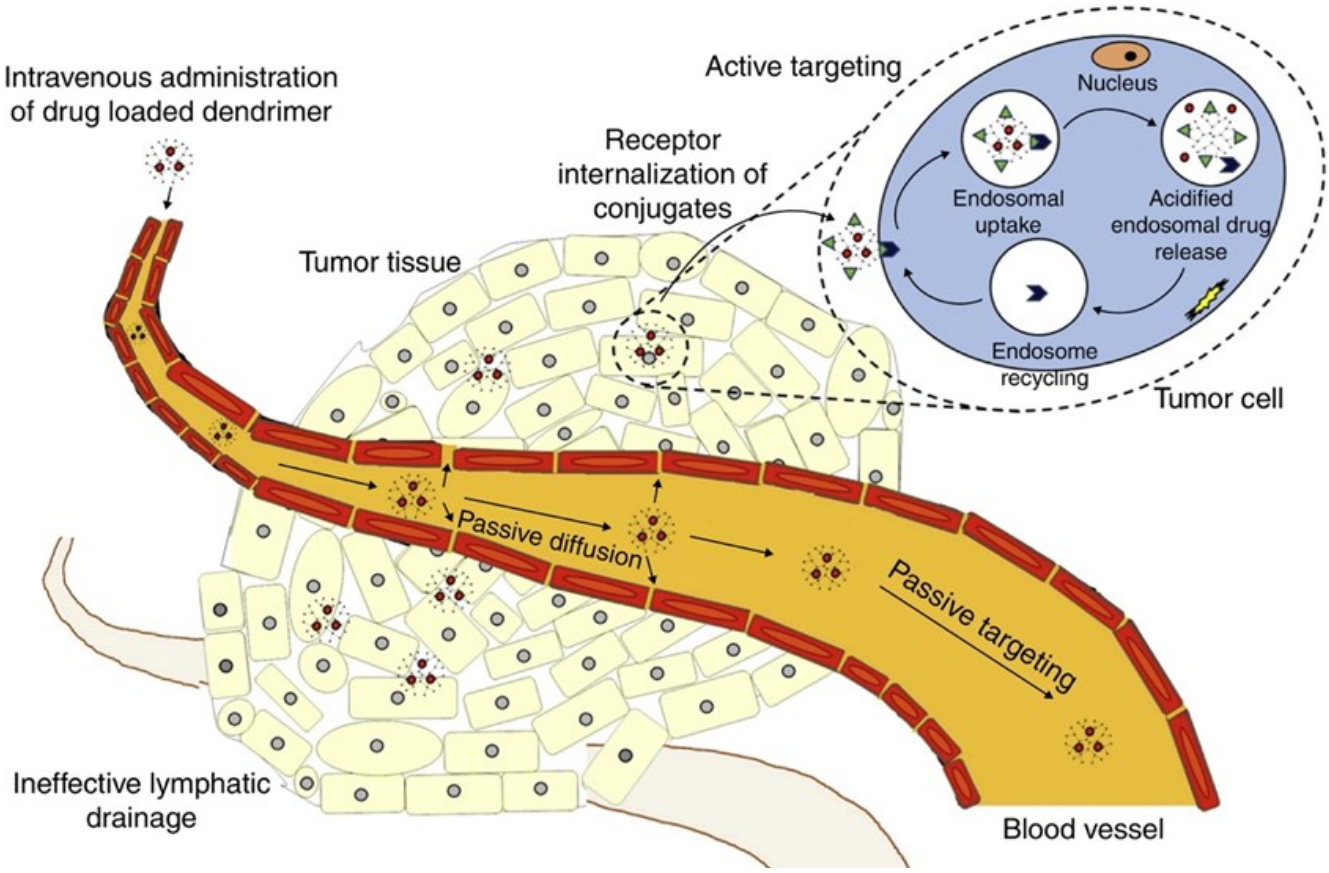

Fig 4. Dendrimer-mediated passive and active targeting strategies (Taken from [18]).

netics and targeting potentiality. The identification of passive targeting strategy here is that upon the exposure to intrinsic pathophysiological, physicochemical or pharmacological factors at a specific site, drug or drug-delivery system will accumulate. In contrast, the active targeting strategy is recognized by a particular modification with active 'homing' ligands to drug or gene carriers. These ligands have increased affinity for specific cell type, tissue or organ binding (Fig 4) [18].

Dendrimers as a versatile platform for gene transfection

There are two types of gene transfection carriers, viral and non-viral carrier. Viral systems may be immunogenic, toxic and oncogenic. For this reason, the use of dendrimers as an effective non-viral medicated gene carrier is increasing. Several publications have described amino-terminated PAMAM or PPI dendrimers to enhance DNA transfection by endocytosis into the nucleus of the cell as non-viral gene transfection agents (Fig 5). At physiological pH, the amine functionalities can effectively cohere to nucleic acid because of their polycationic nature. In order to reach a maximum transfection efficacy, a net positive charge on dendrimer and DNA complexes is obtained involving an excess of primary amines over phosphates of DNA. It is worth mentioning that dendrimers with a highly flexible structure especially high generation of degradable dendrimers may be more suitable for certain gene delivery applications compared to a high generation of intact symmetrical dendrimers. The reason for this could be that these dendrimers have enhanced flexibility which enable them to form compact complexes with DNA [7, 20].

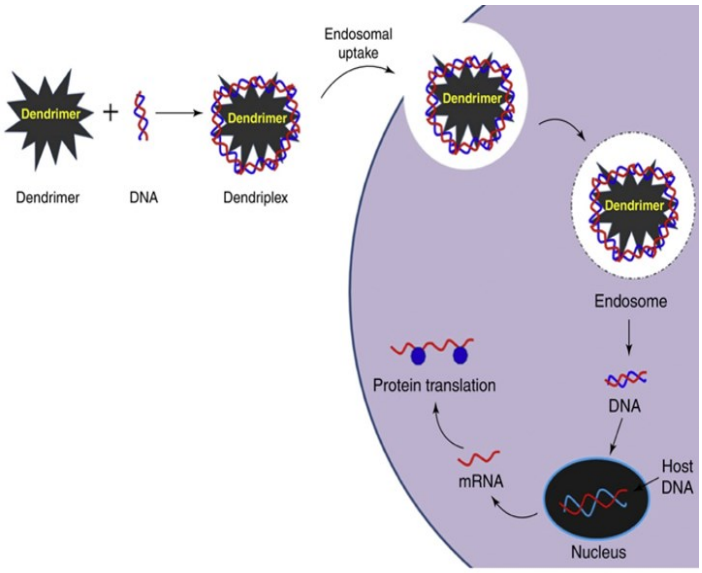

Figure 5. Simplified presentation of dendriplex-assisted gene delivery (Taken from [18]).

Dendrimers as a versatile platform for imaging

In vivo imaging is a helpful tools in biomedicine since it is a non-invasive technique that provides plenty of information about the native state of various types of tissues.

In the field of medical imaging, dendrimers have been developed as contrast agent carriers. Their earliest *in vivo* use as carriers is for magnetic resonance imaging contrast agents [2]. Additionally, for certain types of dendrimers, the external primary amine groups can be functionalised to permit the attachment of contrast agents for MRI, computed tomography, optical imaging and nuclear medicine.

In addition to contrast agents, targeting ligands, including antibodies, can be linked to these groups. There are two developed dendrimer classes having MRI potentialities. One class includes dendrimers that contain paramagnetic iron oxide particles known as magnetic dendrimers. The other class involves dendrimers that incorporate high numbers of gadolinium-chelates and they are simpler and smaller than most typical dendrimers of the same generation.

Moreover, targeting ligands, including monoclonal antibodies, can be integrated to provide a high potential specificity for the imaging agents as well as the targeted drug carrier vehicles, or even both types of "payload" which are incorporated in dual-purpose dendrimers. The pharmacokinetic and pharmacodynamic characteristics of dendrimers are affected by the increasing generation size leading to alteration of dendrimer permeability across the vascular wall, excretion route, and their uptake and recognition by the RES. Dendrimers with smaller diameter may be used for renal imaging since they are excreted primarily by the kidneys while larger dendrimers are preferred for imaging the liver and spleen because they are primarily sequestered by the RES [23].

Barriers that hinder considering dendrimers as ideal drug-carriers for cancer therapy

To use dendrimers as biological carriers they should have certain characteristics in order to fulfill specific biological demands. These characteristics include targeting specific structures, staying in the circulation during the time needed to give a clinical effect, and not having toxic nor immunogenic effects. Additionally, being bio-permeable or having the ability to cross bio-barriers, for instance the blood-tissue barriers, cell membranes etc. [13]. The barriers that hinder the use of dendrimers can be summarised as:

* Cytotoxicity
* Neurotoxicity
* Hemolytic and hematological toxicity
* Degradation
* Cost

Cytotoxicity

Dendrimers can potentially cause cytotoxicity because they have a non-selective uptake feature [24].

The nature of the various end groups present in the dendrimers dictate whether the dendrimers show toxicity or not. For instance, cationic dendrimers PAMAM and PPI show generally concentration-dependent toxicity and hemolysis, whereas neutral or anionic dendrimers show much less toxicity and hemolysis. So by partial or complete modification of the peripheral groups in amino-terminated dendrimers with negatively charged or neutral groups, the cytotoxicity can be decreased.

Moreover, cationic PAMAM dendrimer toxicity increases with each generation, whereas the cationic PPI dendrimers do not [2].

A study was conducted to investigate the cytotoxicity of plain G5 PPI dendrimers, amino-protected PPI dendrimers, and carbohydrate-coated PPI dendrimers in HepG2 and COS-7 cell lines and to observe the effect of the following on the cytotoxicity; terminal functional group, concentration and incubation time. It was found that cell viability decreased with increase in concentration and incubation time. For G5 PPI dendrimers, the cytotoxicity was concentration and time-dependent, associated with the presence of free primary amine groups in these dendrimers and their positive charge. Additionally, it was observed that by masking peripheral amines with different protecting groups, the cytotoxicity could be reduced [25].

Neurotoxicity

Dendrimers express several neurotoxic reactions inside the body. These reactions are dependent on the physiochemical properties of dendrimers, involving size, surface charge and surface chemistry. Using human neural progenitor cells and exposing them to PAMAM dendrimers, the effects on a 3D neurosphere system were evaluated. Higher concentrations induced serious cell proliferation and migration inhibition. Moreover, in zebrafish embryos and larvae, different generations of

dendrimers were used to evaluate the related toxic effects. In the embryos, an innate immune response was noted which suggests a concentration and time -dependent toxicity. Furthermore, for the assessment of neurotoxic effects on human neural progenitor cells, different generations of dendrimers with various surface groups were used. Results indicated that higher generations of cationic dendrimers affected mitochondrial activity, gene expression, apoptosis and neuronal differentiation in relation to oxidative stress and DNA damage. In addition, results demonstrated that more important features to impact on the cytotoxicity of cationic dendrimers are the number of particles and the density of surface groups [26].

Haemolytic and heamatological toxicity

In poly cationic dendrimers, the free cationic peripheral groups interact with RBCs leading to haemolysis. Available reports suggest that dendrimers with higher generations may have increased haemolytic toxicity, as this may be attributed to the higher overall cationic charge. Additionally, uncoated dendrimers with poly cationic nature may have an effect on the haematological parameters. Reports have concluded that cationic dendrimers may show considerable impairment in haematological parameters including a significant rise in WBCs, drop in RBCs count, Hb, HCT and MCV values. This emphasises the need for a strategy to make them more biocompatible [24].

Degradability

The use of biodegradable dendrimers can prevent their bioaccumulation and possibly toxic effects. In PAMAM dendrimers, their amide backbones are the reason that only under harsh conditions are they hydrolytically degradable, and at physiological temperatures the hydrolysis continues slowly. The use of dendrimers based on polyester backbones is more promising regarding hydrolytic degradability. In one example, polyester dendrimers were carefully developed to produce non-toxic and natural metabolites after ester hydrolysis. Another example is dendrons and dendrimers that have thiol-reactive disulfides in their branches as they may potentially cleave under reducing conditions experienced inside cells. Additionally, a recent type of degradable dendrimers has been reported in which they are described as self-immolative, geometrically disassembling, or cascade-release dendrimers (Fig 6). In this type of dendrimers, a single chemical reaction at their core or periphery establishes complete depolymerisation resulting in small units that are structurally identical [2].

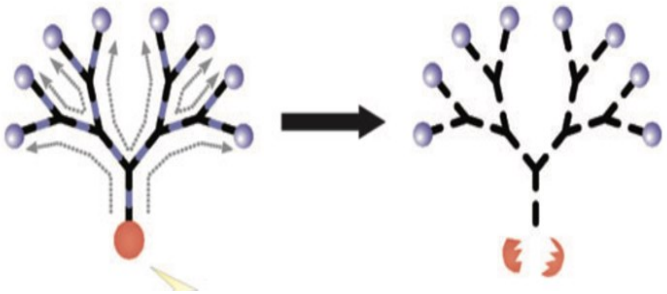

Fig 6. Self-immolative dendrimers. In consequent to chemical reaction at the dendron core, the whole dendrimer is broken down into similar low molecular weight fragments, which will ultimately result in the release of all peripheral groups. (From [2]).

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TEST YOUR KNOWLEDGE

1) Which of the following dendrimers was the first to be introduced commercially?

a) PPI dendrimers
b) Polyester dendrimers
c) PPH dendrimers
d) PAMAM dendrimers

2) The incorrect statement regarding the effect of PEGylation on dendrimers is:

a) Decreases hydrophilicity
b) Increases circulatory time
c) Increases size
d) Limits uptake by RES

3) Which of the following is not a barrier to the use of dendrimers?

a) Cost
b) Degradation
c) Nephrotoxicity
d) Cytotoxicity

Answers on back page

Is there a problem?
A patient is given the prescription for his mild allergic symptoms.
Is there any *major* error with the prescription?

MDB HOSPITAL

Patient Name: Mark Antony Age: 35 years
Address: Street No: 57

Rx

Loratadine 10mg tablet
1 tablet two times a day x 5 days

Dr. Smith
Signature Date: 10/9/19

Answer (Prescription Exercise)
The dose is wrong.
For allergic symptoms the dose should be 10mg once daily.

Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Appetite control drug for clinical obesity

According to new research, a drug that targets the appetite control system in the brain could bring about significant weight loss in people with clinical obesity. On average, people lost 5kg (11lbs) over a 12 week period after receiving weekly doses of ***semaglutide.*** Most of the weight loss came from a reduction in body fat, researchers at the University of Leeds found after reviewing its effectiveness. The drug reduced food cravings. People chose to eat smaller meals and decreased their preferences for foods with a higher fat content.

The study also added to the scientific understanding of how drug therapy can be used to tackle obesity. For the first time, scientists saw the benefit of very specific targeting of receptors or sensors that could affect multiple components of the brain's appetite control system. The striking feature of the drug was the potency of the drug's action. Results were seen in 12 weeks which may take as long as six months with other anti-obesity medication. The drug reduced not only hunger but also cravings for food and the sensation of wanting to eat. The research has been published in the journal *Diabetes, Obesity and Metabolism*.

Semaglutide is a new drug being developed by the Danish pharmaceutical company Novo Nordisk as a treatment for diabetes. Semaglutide is in the advanced stages of development but is not yet on the market. Its chemical structure is very similar to the naturally-occurring hormone GLP-1 which is believed to act on

the appetite control center in the hypothalamus in the brain to reduce feelings of hunger. Given the close similarity between semaglutide and the body's own appetite-control chemical, the study set out to examine whether the drug could also be used to tackle obesity by acting on the brain's appetite control receptors. The potency of the drug is probably due to the action of the GLP-1 protein receptors on broad aspects of the appetite control system including hunger, craving and rewarding aspects of food.

In the study, the drug was given to 28 people with a body mass index (BMI) range of 30 to 45 kg/m2, which meant that they were very overweight with a lot of body fat. The participants were split in two groups, where half got semaglutide and the other half a placebo (dummy) substance for 12 weeks. They did not know what they were getting. At the end of the 12 weeks, they were invited into a testing center and offered a lunch and evening meal and told to consume as much as they needed to feel 'pleasantly full'. What they were eating was recorded, along with food preferences and their sensations of liking and wanting food. Body weight and body composition, which represents the percentage of body fat, were also recorded. They then repeated the process, with participants who got semaglutide, getting the placebo and vice versa. The results were then compared. The research team found that on average the daily energy intake, a measure of the amount of food consumed, was 24 per cent lower with semaglutide.

A further feature of the study was that measured energy expenditure from metabolic processes (the Resting Metabolic Rate) remained roughly the same throughout the experiment suggesting the weight loss could not be due to metabolism becoming more active. Consequently the fat loss produced by the drug could be attributed to better control over appetite. A drug that decreases daily food intake by about a quarter, with an additional substantial reduction in body fat, will help some people to feel more in control of their lives and will help to prevent the onset of poor health that often arises from obesity.

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Is a vegetarian diet more healthy than eating meat?

Over recent years, increasing numbers of people have decided to reduce the amount of meat in their diet. Vegetarians, vegans and pescatarians (people who eat fish but not meat) are a growing demographic. Following any one of these meat-free diets is nothing new, but due to the spike in popularity, researchers are keen to understand the possible health implications.

A recent study, which features in BMJ, looks specifically at plant-based diets and their effect on the risk of stroke and ischemic heart disease (IHD). IHD refers to any problems that occur due to a narrowing of the arteries to the heart. Without treatment, it can lead to a heart attack. The authors of this large, long term study concluded that pescatarians and vegetarianism have an association with a reduced risk of ischemic heart disease, but they note that vegetarians have a slightly higher risk of stroke.

Earlier studies have concluded that vegetarians have a lower risk of obesity and IHD, but as a review of relevant research explains, there is a need for more long term studies involving larger numbers of people. As for stroke risk, only a few studies have looked into the relationship between a plant-based diet and stroke risk. According to the authors of the current study, these "*found no*

significant differences in risk of total stroke deaths between vegetarians and non-vegetarians."

The latest study aimed to fill in some of these gaps. In all, the scientists took data from 48,188 people whom they followed for an average of 18.1 years.

The participants, who had an average age of 45 years at the start of the study, had no history of IHD or stroke.

The researchers assigned each participant to one of three groups:

* Meat eaters: people who reported eating meat
* Fish eaters: those who ate fish but no meat
* Vegetarians and vegans: people who did not eat meat or fish

The team combined vegans with vegetarians for the main analysis due to the small number of vegans in the dataset. Using food questionnaires, the researchers could also assess overall food intake and nutrient levels. Aside from dietary information, they collected information about factors such as body mass index (BMI), height, and blood pressure.

During the 18.1 years of follow-up, there were 2,820 cases of IHD and 1,072 cases of stroke. After adjusting for sociodemographic and lifestyle factors, the analysis revealed both positive and negative relationships between cardiovascular health and reduced meat intake.

The rate of IHD among pescatarians was 13% lower than that of meat-eaters, while vegetarians had a rate that was 22% lower. According to the authors, this positive association appears to be, at least partly, due to lower rates of hypertension and diabetes, as well as lower BMI and cholesterol levels. However, even after the scientists had adjusted the data to account for these factors, the effect was still "marginally significant." Conversely, vegetarians had 20% higher rates of stroke than meat-eaters.

No previous studies have shown this type of relationship between vegetarianism and stroke risk. The authors believe that this might be because earlier work reported stroke mortality rather than incidence. Strokes are only fatal in 10–20% of cases, so many cases would not count toward the reported total.

Why the scientists saw this increase in stroke risk is for debate. The authors believe that it might be due to lower levels of other circulating nutrients in the blood of vegetarians. These might include essential amino acids and vitamins B-12 and D.

The study has several strengths; first and foremost, the researchers used a large sample size and a long follow-up period. They also linked participants to their medical records to ensure the accurate collection of health outcomes. Also, the researchers checked the participants' eating habits at two-time points that were years apart, finding that adherence was good overall.

There were certain limitations. For instance, the participants self-reported their diet, which leaves room for error and misreporting. Diet can also fluctuate over days, weeks, and years. Also, researchers did not have access to the use of drugs, including statins, among participants. As the study is observational, it is not possible to conclude that the effect is causal. In other words, the changes in risk could be due to other factors that the scientists did not measure. Lastly, because the participants were predominantly European and white, the findings may not be widely applicable.

However, these results are sure to open debate and spark more research. That vegetarianism protects against IHD is not surprising given past findings. However, the fact that giving up meat might slightly increase stroke risk is unexpected. More work and more debate is sure to follow.

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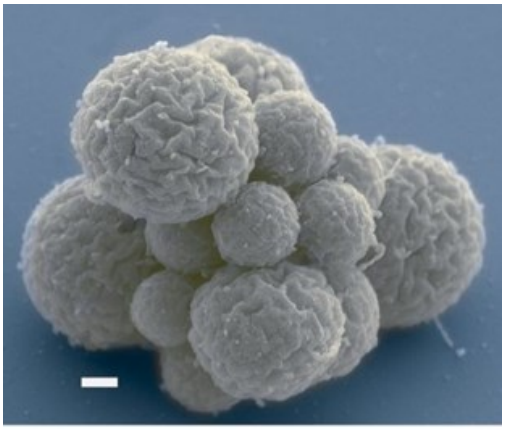
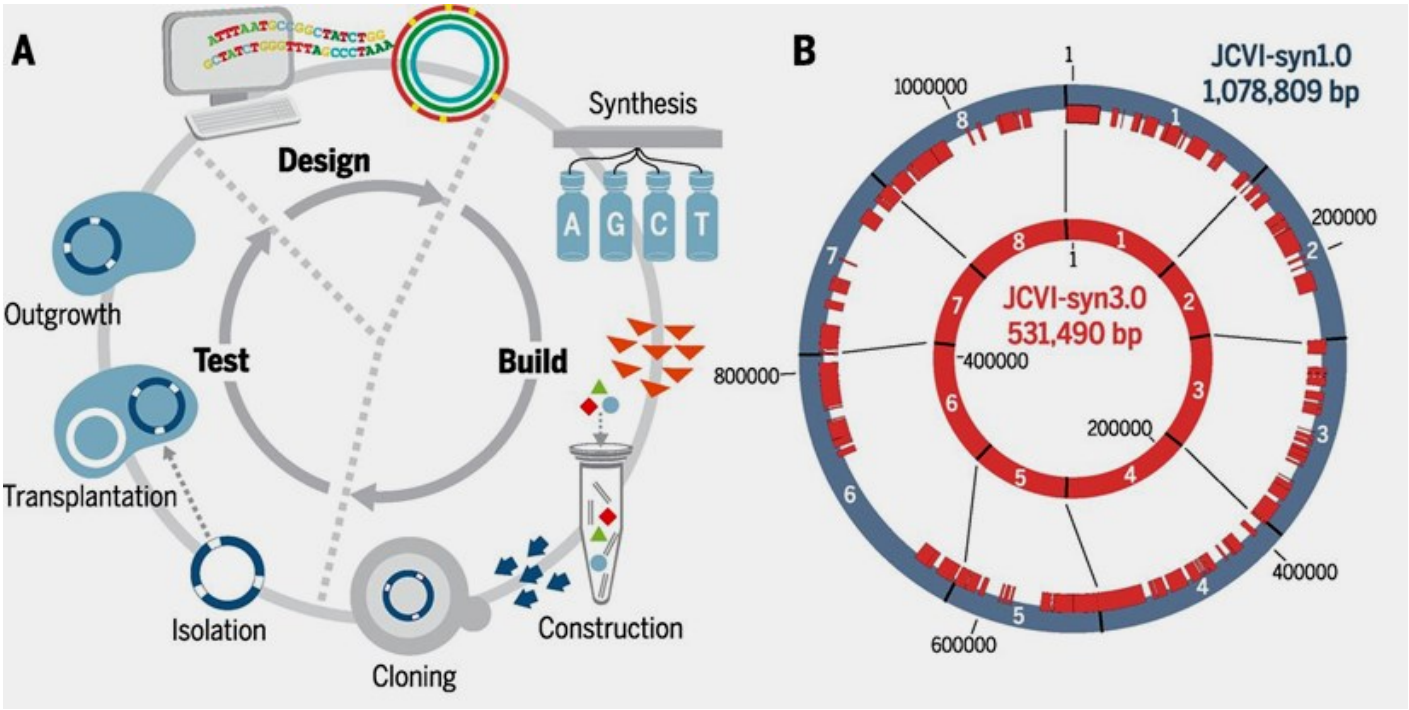
Creation of a living cellular organism using the smallest genome

By stripping down the genome of a mycoplasma bacterium to the minimal genes required for life, scientists at Craig Venter Institute (JCVI) in San Diego created a new organism with the smallest genome of any known cellular life form. This is the closest anyone has come to creating a cell in which every gene and protein can potentially be fully understood.

The lead author of the new study explained the motivation behind the study was to understand at a mechanistic level how a living cell grows and divides. Possession of such fundamental knowledge would put researchers in a better position to engineer cells to make specific products, like pharmaceuticals.

The team's starting point was the bacterium Mycoplasma genitalium, which has the smallest known genome of any living cell with just 525 genes.





However, it also has a very slow growth rate, making it difficult to work with. To practice synthesizing genomes and building new organisms, the team therefore turned to M. mycoides and M. capricolum, which have bigger genomes and faster growth rates. In 2010, the JCVI team successfully synthesized a version of the M. mycoides genome (JCVI-syn1.0) and placed it into the cell of a M. capricolum that had had its own genome removed. This was the first cell to contain a ***fully synthetic genome*** capable of supporting replicative life.

With the genome synthesis and transfer skills mastered, the next step was to make the genome smaller. One approach would be to delete the genes one by one and see which the cells could live without. Using JCVI-syn1.0 as their starting material, the researchers initially designed a minimal genome based on information from the literature and from mutagenesis studies that suggested which genes were likely essential. They divided this genome into eight overlapping segments and tested each one in combination with the complementary seven-eighths of the standard JCVI-syn1.0 genome. All but one of the designed segments failed to sustain viable cells.

The team then decided to perform mutagenesis experiments on JCVI-syn1.0 to determine, categorically, which genes were required for life. Their experiments showed that the genes fell into three groups: essential, non-essential, and quasi-essential-those that aren't strictly required, but without which growth is severely impaired. The failure to include these quasi-essential genes in the initial design explained in large part why it had failed.

The team then re-designed, synthesized, and tested new genome segments retaining the quasi-essential genes. Three iterative cycles of testing later, the team had a genome that successfully supported life, a pioneering step in the use of synthetic biology.

Ultimately, the team removed 428 genes from the JCVI-syn1.0 genome to create JCVI-syn3.0 with 473 genes (438 protein-coding genes and 35 RNA genes) -considerably fewer than the 525 genes of M. genitalium. Interestingly, the functions of around one-third of the genes (149) remain unknown. Some of these appear to be conserved in higher eukaryotes. Those, in a way, are the most exciting, as they might represent some new undescribed function that has spread through other life forms.

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Anti-inflammatory drug 'cuts heart attack risk'

A recent report on 10,000 patients suggests that anti-inflammatory drugs could cut the risk of heart attacks and strokes. Heart attack patients are routinely given cholesterol-lowering statins and blood-thinning drugs to help reduce the risk of repeat attacks.

In this study, 10,000 patients who had previously had a heart attack were treated with the anti-

inflammatory drug canakinumab once every three months. Canakinumab was initially developed by pharmaceutical firm Novartis, which paid for the trial, to treat rheumatoid arthritis.

The trial, held in almost 40 countries, monitored the individuals for up to four years.

It found what researchers said were reductions in risk "above and beyond" those seen in patients who only took statins.

However, the study also found a "significantly higher incidence" of potentially fatal infection and sepsis among those treated with the drug.

In the first trial, the researchers recognised the importance of diet, exercise and smoking cessation. In the second trial, they saw the tremendous value of lipid-lowering drugs such as statins.

These findings also indicated "the possibility of slowing the progression of certain cancers.

Some researchers indicate that the effects of anti-inflammatory drugs could be "modest", and the absolute clinical benefit of canakinumab cannot justify its routine use until a better understanding about the efficacy and safety trade-offs, and unless a price restructuring and formal cost-effectiveness evaluation supports it.

Others say anti-inflammatory drugs such as canakinumab could help those at risk of repeat heart attacks for whom statins are not enough to reduce their risk of another heart attack.

In conclusion, the findings provided "compelling evidence" but further research is needed.

Source
www.bbc.com/news/health-41071954

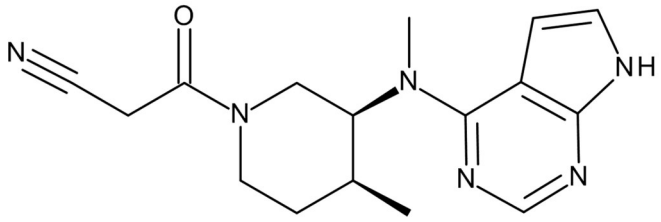
NEWS from the FDA

FDA approves new treatment for moderately to severely active ulcerative colitis

Xeljanz (Tofacitinib)) is used to treat moderate to severe rheumatoid arthritis or active psoriatic arthritis in adults who have tried methotrexate or other medications without successful treatment of symptoms. Xelianz is sometimes given in combination with methotrexate or other arthritis medicines The U.S. FDA expanded the approval of Xeljanz to include adults with moderately to severely active ulcerative colitis. Xeljanz is the first oral medication approved for chronic use in this indication. Other FDA-approved treatments for the chronic treatment of moderately to severely active ulcerative colitis must be administered through an intravenous infusion or subcutaneous injection.

Ulcerative colitis is a chronic, inflammatory bowel disease affecting the colon. Patients experience recurrent flares of abdominal pain and bloody diarrhea. Other symptoms include fatigue, weight loss and fever. More than 900,000 patients are affected in the U.S., many of them experiencing moderately to severely active ulcerative colitis, and there is currently no cure.

The efficacy of Xeljanz for the treatment of moderately to severely active ulcerative colitis was demonstrated in three controlled clinical trials. This included two 8-week placebo-controlled trials that demonstrated that 10 mg of Xeljanz given twice daily induces remission in 17 to 18 percent of patients by week eight. In a placebo-controlled trial among patients who achieved a clinical response by week eight, Xeljanz, at a 5 mg or 10 mg dose given twice daily, was effective in inducing remission by week 52 in 34 percent and 41 percent of patients, respectively. Among patients who achieved remission after 8 weeks of treatment, 35 percent and 47 percent achieved sustained corticosteroid-free remission when treated with 5 mg and 10 mg, respectively.



Tofacitinib (Xeljanz, Pfizer); $C_{16}H_{20}N_6O$; MW = 312

The safety of chronic use of Xeljanz for ulcerative colitis was studied in the 52-week placebo-controlled trial. Additional supportive safety information was collected from patients who received treatment in an open-label long-term study.

The most common adverse events associated with Xeljanz treatment for ulcerative colitis were diarrhea, elevated cholesterol levels, headache,

herpes zoster (shingles), increased blood creatine phosphokinase, nasopharyngitis (common cold), rash and upper respiratory tract infection.

Less common serious adverse events included malignancy and serious infections such as opportunistic infections. Xeljanz has a boxed warning for serious infections and malignancy. Patients treated with Xeljanz are at increased risk for developing serious infections that may lead to hospitalization or death. Lymphoma and other malignancies have been observed in patients treated with Xeljanz.

Use of Xeljanz in combination with biological therapies for ulcerative colitis or with potent immunosuppressants, such as azathioprine and cyclosporine, is not recommended.

Xeljanz, made by Pfizer Labs, was previously approved in 2012 for rheumatoid arthritis and in 2017 for psoriatic arthritis.

Source
https://go.usa.gov/xQvw3

First neonatal magnetic resonance imaging device

The U.S. FDA cleared the first magnetic resonance imaging (MRI) device specifically for neonatal brain and head imaging in neonatal intensive care units (NICU), which enables safer imaging for this vulnerable patient population.

An MRI is a medical imaging procedure that records images of the internal structures of the body. MRI scanners use strong magnetic fields and radio waves (radiofrequency energy) to generate the images. The signal comes mainly from the protons in fat and water molecules in the body. When interpreted by a trained physician, images from an MRI provide information that may be useful in determining a diagnosis.

The Embrace Neonatal MRI System is designed specifically for imaging of the neonatal head. It may be used on neonates with a head circumference up to 38 cm and weight between 1 and 4.5 kg. The system has a temperature-controlled incubator placed directly into the MRI system, minimising movement of the baby. If urgent access to the baby is necessary during the imaging process, the baby can typically be removed from the system in less than 30 sec.

The Embrace Neonatal MRI System can be placed inside a NICU environment because it does not require a safety zone or a radiofrequency shielded room. Since the system is fully enclosed, medical device implants in close proximity to the system are not required to be "MR Conditional" or "MR Safe."

To avoid putting vulnerable patients at risk, the efficacy of the Embrace Neonatal MRI System was demonstrated primarily based on non-clinical testing including images of phantoms simulating an infant brain that were determined to be of sufficient quality for diagnostic use by an independent board-certified radiologist. The safety of the Embrace Neonatal MRI System was demonstrated through performance testing, including a review of electrical and mechanical safety measures.

The Embrace Neonatal MRI System is contraindicated for patients weighing more than 4.5 kg or with a head circumference of more than 38 cm. It is also contraindicated for all infants with metallic or electronically active implants since the MRI may cause tissue near the implant to heat or the implant to malfunction.

The Embrace Neonatal MRI System was reviewed through the premarket clearance (510(k)) pathway. A 510(k) is a premarket submission made to the FDA to demonstrate that the new device is substantially equivalent to a legally marketed predicate device.

The FDA granted clearance of Embrace Neonatal MRI System to Aspect Imaging Ltd.

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from January to August 2019

Adwimove Topical Gel; Salicylic acid – 2g Mucopolysaccharids polysulphoric acid ester – 0.2g;
Al-Wazzan, ADWIYA/Egypt

Aimovig Solution for Injection; PFP 70mg, Erenumab (rDNA) – 70mg/ml, Al-Mojil; Novartis/Switzerland

Amoklavin BID Forte Powder for Oral Suspension 457mg/5ml; Amoxicillin (as trihydrate) – 400mg
Clavulanic acid (as potassium clavulanate) – 57mg; Golden Care, Deva Holding A.S./Turkey

Cafnea Injection 40mg/2ml; Caffeine citrate (equivalent 20mg caffeine base); A-Rwani, Phebra Pty Limited/Australia
Cafnea Oral Solution 25mg/5ml; Caffeine Citrate – 25mg (equivalent to 12.5mg caffeine base); A-Rwani, Phebra Pty Limited/Australia
Dienille Film Coated Tablet;, Ethynylestradiol – 0.03mg Dienogest – 2.0m; Warba, Exeltis Germany GmbH/Germany
Dupixent Solution for Injection 300mg; Dupilumab (rDNA) – 300mg; Central Circle Co., Sanofi-Aventis Groupe/France
Esmya Tablets; Ulipristal acetate – 5mg; Al-Hajery, Ferring GmbH/Germany
Glycopyrronium Bromide Solution for Injection 200mcg/ml; Glycopyrronium Bromide – 200mcg/ml; Ali Abdulwahab, Martindale Pharmaceuticals Ltd./UK
Kepcitam Tablets 500mg; Levetiracetam – 500mg; Safwan, Hexal AG/Germany
Ketesee Solution for Injection or Concentrate for Solution for Infusion 50mg/2ml; Glecaprevir – 100mg Pibrentasvir – 40mg; Maseela Pharmaceuticals, Menarini International Operations Luxembourg S.A./ Luxembourg
Letrozole Denk Tablets 2.5mg; Letrozole – 2.5mg; Al- Wazzan, Denk Pharma GmbH & Co. KG/Germany
Mavenclad Tablets 10mg; Cladribine – 10mg; Safwan, Merck Serono Europe Ltd./UK
Maviret Tablets 100/40mg; Glecaprevir – 100mg Pibrentasvir – 40mg; Al-Mojil, AbbVie Ltd./UK
Mirtaza Tablets 15, 30mg; Mirtazapine – 15, 30mg; Ali Abdulwahab, Apotex Inc./Canada
Monoclox Powder for Solution for Injection/Infusion 250; 500mg, Cloxacillin (as sodium) – 250, 500mg; Al-Mojil, Medochemie Ltd./Cyprus
Olexa Orodispersible Tablets 5, 10mg; Olanzapine – 5, 10mg; Deltamed International, Al-Taqqaddom Pharmaceutical Industries/Jordan
Onsett Injection 4mg/2ml; Ondansetron – 4mg; R & E Medical Co., Cadila Pharmaceuticals Ltd./India
Onsett Injection 8mg/4ml; Ondansetron – 8mg; R & E Medical Co, Cadila Pharmaceuticals Ltd./India
Phenasen Injection Concentrate 10mg/10ml; Arsenic Trioxide – 10mg; Al-Rwani, Phebra Pty Ltd./ Australia
Prodein Effervescent Tablets 8/500mg; Paracetamol – 500mg Codeine Phosphate – 8mg; Al-Hafez, Oman Pharmaceutical Products Co, LLC/Sultanate of Oman
Remsima Powder for Solution for Infusion 100mg; Infliximab (rDNA) – 100mg/vial; Al-Hajery, Jazeera Pharmaceutical Industries/Saudi Arabia
Veloce Film Coated Tablets 8mg; Lornoxicam – 8mg; Palestine Pharmacy, The United Pharmaceutical manufacturing Co. Ltd./Jordan
Zaeer Film Coated Tablets; Tadalafil – 20mg; Al-Hafez, Global Pharma Co. LLC/UAE
Zoledro-Denk Concentrate Solution for Injection 4mg/5ml; Zoledronic Acid – 4mg; Al-Wazzan, Denk Pharma GmbH & Co. KG/Germany
Zolinda Tablets 5, 10, 15mg; Aripiprazole – 5, 10, 15mg; Warba, Spimaco/ Saudi Arabia

Answers to: Test your knowledge

Correct answers:
1-D; 2-A; 3-C

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs as received from the MoH. It aims to provide instructive reviews and topical news items on a range of drug and medically related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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