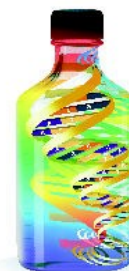


Gene therapy for cardiovascular disease

For many years, gene therapy has been proposed as a strategy for the potential treatment of a wide range of both inherited and acquired diseases such as cancer, acquired immune deficiency syndrome (AIDS), infectious diseases, cystic fibrosis and X-linked severe combined immune deficiency (X-linked SCID).¹ This strategy involves correcting the underlying genetic defects responsible for these diseases, by replacing a missing or defective gene, resulting in the expression of the required protein and achieving the required therapeutic response. Gene therapy requires development of effective delivery techniques and vectors that transport the desired therapeutic gene to the target cells while overcoming various barriers and protecting it from bio-degradation. This report will review the various vectors, their relative merits and applications in a number of disease conditions particularly cardiovascular events.



Gene delivery systems

Viral vectors

RNA viral vectors

Retroviruses are the most commonly used gene delivery vectors. Their production involves removal of the replication elements from the viral genome and replacing them with the desired therapeutic gene while retaining certain necessary RNA regions. The lentiviral delivery system is considered relatively safe, since it lacks the accessory genes needed for viral replication/recombination.²

DNA viral vectors

Adenoviral systems involve the use of the well-characterized, non-integrated, large, non-enveloped adenoviruses as vectors.³ Adeno-associated viral systems (AAV), are an additional type derived from a non-pathogenic satellite virus of human adeno-virus and the herpes simplex virus (HSV), known as the parovirus. The same strategy used for developing adenoviral vectors is used for herpes simplex viral systems (HSV), which may also be beneficial in gene therapy.

Specific characteristics and the advantages/ disadvantages of each viral delivery system are listed in Tables 1 and 2.

Non-viral vectors

Since many of the studies of viral gene delivery systems have disadvantages, such as severe immu-

nologic and oncogenic adverse effects, non-viral gene delivery systems have gained ground in the field of gene therapy.³ Non-viral systems, are considered safer, their immune response is low, which allows for re-administration, and they are easy to produce at lower cost and in large quantities. In addition, they have easier cell/tissue targeting, and these systems do not have insert size limitations as with viral systems, allowing insertion of large transgenes or elements in the expression cassette. They can be stored for longer periods of time due to their stability. On the other hand, non-viral systems have low transfection efficiency, which limits their use on a large scale. Non-viral systems are classified into physical and chemical based methods.

Physical delivery methods

Gene delivery directly into tissues by needle injection is the simplest physical method. However, it is of low efficiency and the gene expression is only limited to the needle track. Another physical method includes the gene gun or ballistic DNA delivery system. This involves delivering heavy metal particles such as gold, silver and tungsten with attached DNA, that are propelled against cells to force intracellular DNA entry. This method can be used to transfer genes into a number of cell lines and has the capacity

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Table 1. Specific characteristics of viral vectors

| Virus type | Titers pfu/mL | Insert size Kb | Integration | Transgene expression | Inflammatory potential | Tropism |
|----------------------|-----------------|----------------|------------------------------------|----------------------|------------------------|--|
| Retrovirus | 10^6 - 10^7 | 9-12 | Integration into cellular genome | Long-term Stable | Low | Dividing cells only |
| Lentivirus | 10^6 - 10^7 | 8 | Pseudo-random | Long-term | Low | Broad (dividing/non-dividing) |
| Adenovirus | 10^{12} | (4-5 | No (episomal) | Transient | High | Broad (dividing/non-dividing) |
| AAV | 10^{10} | 5 kb | Chromosome 19 (wild type AAV only) | Long-term | Low | Broad with the possible exception of hematopoietic cells |
| Herpes simplex virus | 10^4 - 10^8 | 40-50 | No (episomal) | Transient | High | Strong for neurons |

to deliver precise DNA dosages. Additional advantages of this method are that it does not require toxic chemicals or complex biological systems, delivery is achieved without the need for host cell receptors, and wide ranges of DNA sizes can be delivered to host cells. On the other hand, the genes delivered are only expressed transiently and minimally and cell damage might occur at the site of discharge and requires a surgical procedure for it to be applied to internal organs.

Electroporation is also a reliable physical method that involves creating pores on cells' membranes by the use of electric pulses. This method is very efficient; however, irreversible tissue damage might occur as a result of the high temperature due to high voltage application and gene delivery is limited to the targeted area and also requires a surgical procedure if applied to internal organs.

Sonoporation is also another physical method, involving the use of ultrasound to temporarily permeabilize cell membranes allowing the DNA to be taken by the cells. The DNA is carried in microbubbles that are destroyed by the ultrasound applied to the targeted host tissue. Although this method has the advantage of restricting the effect needed to the area where ultrasound is applied, it is considered a method of low efficiency, and may cause tissue damage.

Another physical method is known as hydrodynamic gene delivery, also called hydroporation, involves the use of hydrodynamic pressure that is created by injecting large volumes of DNA solution with blood pressure inside the veins, resulting in an increase in the permeability of the capillary endothelium. This method is simple, of high effi-

ciency and site specific; however, it requires catheter insertion.

Chemical delivery methods

These methods have three main objectives; masking the negative charge of DNA, compressing the DNA molecule to a smaller size, and protecting it from nuclease degradation. These methods employ cationic lipids, polymers and peptides that complex with DNA, and condense it to particles of size 100-300 nm.

Liposome-based vectors

Currently, the most effective non-viral vectors are liposome-based vectors, involving the use of microscopic particles that consist of one or more concentric lipid bilayers enclosing an aqueous phase. Liposomes that are synthesized with cationic lipids are the most effective in gene delivery. These spontaneously interact with DNA to form lipoplexes giving 100% DNA loading efficiency. Lipoplexes have several advantages, being synthetic and cheap to synthesize, and they offer a degree of protection to DNA from nuclease degradation. Additionally, they are able to carry large DNA molecules.

These vectors are considered effective even at small doses, and can have prolonged dosing intervals, and they are ideal for transferring substances with a short half-life. Moreover, they do not carry the biological risk of viral vectors and they are of high efficiency *in vitro*. On the other hand, these vectors are of low efficiency *in vivo* and may provoke an immune response. In addition, their gene expression time is short and it is generally difficult

to transfer the desired transgene to the target cells.

Polymer-based vectors

Many polymers, including polyethylenimine, poly-amidoamine, polyallylamine, chitosan and dendrimers, have been studied for *in vivo* and *in vitro* gene delivery. Polyplexes are formed by complex-

ciency *in vivo* is low. Furthermore, they have to overcome several barriers, such as their toxicity, polymer polydispersity, and there is lack of information about the mechanism of gene transfer of these vectors.

Peptide-DNA complexes are also types of chemical gene delivery methods that are synthesized by

Table 2. Advantages and disadvantages of viral vectors

| Vector | Advantages | Disadvantages |
|----------------------|--|--|
| Retrovirus | <ul style="list-style-type: none"> -Prolonged integration into cellular genome -Prolonged stable expression -Requires cell division for transduction -Large gene insert size -Relatively high titers achieved | <ul style="list-style-type: none"> -Inefficient transduction -Require cell division for transfection -Prone to insertional mutagenesis -Requires packaging cell line for effectiveness |
| Lentivirus | <ul style="list-style-type: none"> -Transduces proliferating/non-proliferating cells -Transduces hematopoietic cells -Prolonged expression of genes -High titers achieved | <ul style="list-style-type: none"> -Safety concern: derived from human immunodeficiency virus -difficult manufacturing and storage -Limited insert size -Limited clinical experience |
| Adenovirus | <ul style="list-style-type: none"> -Very high titers produced easily -High transduction efficiency <i>ex vivo</i> and <i>in vivo</i> -Transduction of many cell types -Transduction of proliferating/non-proliferating cells | <ul style="list-style-type: none"> -Remains episomal -Gene expression is transient - Requires packaging cell line for effectiveness -Immune-related toxicity after repeated administration -potential replication competence -No targeting -Limited insert size |
| AAV | <ul style="list-style-type: none"> -Wild-type integrates on human chromosome 19 to establish latent infection -Prolonged expression -No cell division required for transduction -Small genome without viral genes | <ul style="list-style-type: none"> -Not well characterized -No targeting - Requires packaging cell line for effectiveness - Prone to insertional mutagenesis -Difficulty in producing high titers -Limited insert size |
| Herpes simplex virus | <ul style="list-style-type: none"> -Large insert size -Neuronal tropism -Latent expression -Efficient transduction <i>in vivo</i> -Replicative vectors available | <ul style="list-style-type: none"> -Cytotoxic -No targeting - Requires packaging cell line for effectiveness -Transient gene expression, no integration into cellular genome -Moderate titers achieved |

ation of a cationic polymer with DNA, condense it into small particles by self-assembly via electrostatic interactions. In addition, polyplexes offer protection to DNA from bio-degradation and their small size improves transfection efficacy as a result of increased cellular internalization. Like lipoplexes, polyplexes are of high efficiency *in vitro* and they are easy to prepare; however, they may provoke an acute immune response and their effi-

binding basic amphiphilic peptides to nucleic acids as means of destabilizing liposomes. The ppTG1 and ppTG20 peptides, which consist of 20 amino acids, have been complexed with DNA, and this has led to improvements in transfection of various murine and human cell lines.⁴

The most common DNA-condensing peptides used are poly-L-lysines (PLL).⁵ Like polyplexes,

peptide-DNA complexes are positively charged and they interact with the negatively charged DNA by electrostatic interactions. These DNA-condensing peptides prevent DNA biodegradation by cytosolic nuclease enzymes as well. These systems also prolong the half-life of the DNA carried. Additionally, the net positive charge of these systems allows them to internalize into cells both *in vivo* and *in vitro*, overcoming membrane barriers and resulting in gene delivery and expression. Peptide-DNA complexes are of low toxicity and immunogenicity; however, conjugation reactions may reduce the biological activities of the proteins and peptides.⁶

Gene therapy in cardiovascular diseases

The second most important clinical target for gene therapy, after cancer, involves cardiovascular diseases.¹ This is a result of the fact that current therapeutic modalities for cardiovascular diseases have several limitations and the desired outcomes are unmet without serious side effects. Coronary artery disease, heart failure and cardiac arrhythmias are the main cardiovascular diseases studied.

Coronary artery disease (CAD)

CAD is characterized by a narrowed coronary arterial lumen that results from the presence of plaques of lipids, calcium, and inflammatory cells along the inner wall of these arteries, reducing the delivery of the oxygenated blood to the myocardium. Despite the increase in long-term survival of patients treated with pharmacologic therapy and re-vascularization techniques, some patients remain refractory to these modalities. As a result, a new treatment option, known as therapeutic angiogenesis, is currently being developed.⁷ Angiogenesis is a physiological process that involves the development of new blood vessels from pre-existing ones, or the process by which vessels expand, lengthen or sprout. This treatment option involves administering genes for angiogenic growth factors that aid in collateral vessel development. Angiogenesis is



complex, requiring multiple growth factors to stimulate and sustain new vessel growth. Many angiogenic growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), platelet derived growth factor (PDGF) and hypoxia-inducible growth factor (HIF α), have been investigated. Most of the clinical trials have focused on VEGF and FGF.

Heart failure (HF)

HF is another serious cardiovascular disorder, characterized by the inability of the heart to maintain proper blood flow to meet the metabolic demands of the body. Gene therapy in HF focuses on targeting the β -adrenergic system and Ca^{2+} cycling proteins. Several clinical trials have mainly involved testing the roles of the sarcoendoplasmic reticulum calcium-ATPase 2a (SERCA2a), stromal-derived factor-1 (SDF-1) and adenylate cyclase-6 (AC6) in HF. In addition, other preclinical studies have tested the roles of the S100 calcium-binding protein A1 (S100A1), a c-terminal fragment of the β -adrenergic receptor kinase (β ARKct) and parvalbumin (PVALB).

Results of many studies have shown cardiac improvement when SERCA2a was transferred to failing human cardiomyocytes, as this procedure resulted in restoration of the calcium transient and improvement of cardiac contraction and relaxation velocity to levels similar to non-failing myocytes. Moreover, a phase 1 clinical trial that have been recently completed showed improvement in HF symptoms in patients suffering from ischemic cardiomyopathy when SDF-1 gene therapy was applied by injecting SDF-1 DNA plasmid endomyocardially.

Additionally, studies have shown that over-expression of AC6 resulted in increased left ventricular (LV) function and cAMP levels, as data have shown that AC6 was the rate-limiting step in β -adrenergic receptor stimulation. When the AC6 was transferred using intracoronary delivery in an adenoviral vector, cardiac function improved. In addition, AC6 over-expression leads to reversal of β -adrenergic receptor signaling and increased survival.

Cardiac arrhythmias

Cardiac arrhythmias are associated with abnormal cardiac electric rhythms that severely impair cardiac performance. A reduction in ventricular arrhythmias susceptibility was demonstrated with transgenes that increase either myocyte refractory properties or myocardial conduction velocity. The main gene therapy

targets that have been tested for treating cardiac arrhythmias are listed in Table 3.

Gene delivery vectors in CVD - mechanisms and effectiveness

Viral-based vectors

Retroviral vectors

created.⁸

The retrovirus transfects the host cell by interactions between cellular receptors on receptor-positive target cells and virally encoded proteins, which are embedded in the viral membrane. The viral envelope combines with the target cell membrane before the viral components are emptied inside the target cell, and the envelope glycoprotein (Env) of retroviruses is responsible for determining the vector tropism, as

Table 3. Molecular targets for cardiac arrhythmias

| Molecular target | Stage | Findings | Model |
|--|--------------|---|--------------------------|
| KCNH2-G628S | Pre-clinical | Prolonged refractory period by shutting down I_{Kr} , eliminating arrhythmia inducibility | Pig Dog |
| Cardiac sodium channel 4a (SCN4a) | Pre-clinical | Reduced VT ^a inducibility, increased Vmax causing rapid conduction, and decreased electrogram fragmentation | Dog |
| Connexin 32 | Pre-clinical | Improved gap junctional conductance but no antiarrhythmic effect and larger infarct size | Dog |
| Connexin 40 | Pre-clinical | Enhanced atrial conduction and prevented atrial fibrillation | Pig |
| Connexin 43 | Pre-clinical | Improved conduction and reduced arrhythmia susceptibility | Pig |
| Sarcoendoplasmic reticulum calcium-ATPase 2a (SERCA2a) | Pre-clinical | Reduced VT and VF ^b during reperfusion. Reduced premature ventricular contraction and non-sustained VT. Decreased APD ^c alternans | Pig Rat Guinea pig |
| Adenylyl cyclase 1 (ADCY1) | Pre-clinical | Increased beating rate, provided stable pacemaker effects | Dog |
| Adenylyl cyclase 6 (ADCY6) | Pre-clinical | Provided biological pacing during catecholaminergic stimulation | Pig |
| Kir2.1 | Pre-clinical | Increased pacemaking | Guinea pig |

^aVT: ventricular tachycardia; ^bVF: ventricular fibrillation; ^cAPD: action potential duration

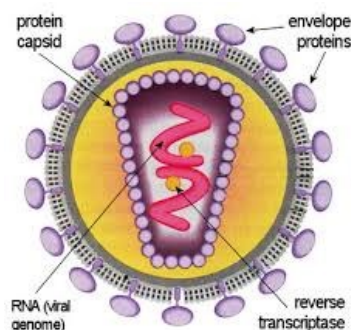
Retroviral vectors were the initial choice among viral vectors in cardiovascular gene therapy, as the immune response to them is limited and their gene expression is sustained, possibly for several years after being transferred; however, since they are of low transfection efficiency, limited cardiac tropism and oncogenic potential, the interest in using these vectors in cardiac gene delivery has de-

the binding of this glycoprotein to the cellular membrane is the first important step in transfection.



Lentiviral vectors

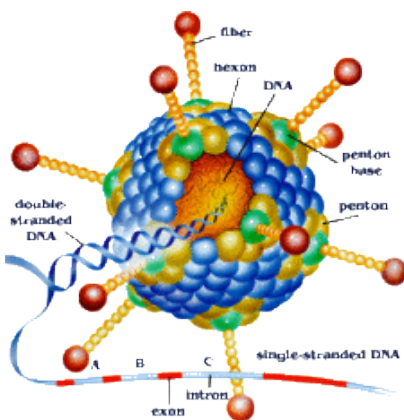
Unlike retroviral vectors, lentiviral vectors do not require active cell division for integration and function. These vectors are of high efficiency of transfection in smooth muscles and minimum immune response, resulting in their extensive use in cardiac applications. Their transduction efficiency has reached 70% in adult cardiomyocytes and 100% in neonatal cardiomyocytes.⁹



The uptake pathway resembles that of the retrovirus, with the use of heterologous Env proteins, mainly the vesicular stomatitis virus glycoprotein (VSV-G), which binds to certain phospholipid components of plasma membranes. In a study, SERCA2 gene was transferred to rat heart myocytes by a lentiviral vector that was infused using hypothermic intra-coronary delivery applied two weeks after myocardial infarction. Hemodynamic measurements showed protection against left ventricular remodeling and an improved survival rate.¹⁰

Adenovirus and AAV based vectors

Currently, the most studied viral vectors for cardiac gene delivery are the adenovirus and the AAV, as the two have shown great effectiveness in cardiac myocytes.⁸ As mentioned above, both vectors infect non-dividing cells and can transduce the heart cells with reasonable efficiency.⁷ A study has shown a measurable recombinant DNA expression in rabbit myocardium and collateral organs for two weeks after a single intracoronary infusion of an adenovirus vector.¹⁰



On the other hand, the repeated administration of adenoviral vectors might provoke a significant immune response, and their gene expression lasts for a short period of approximately 2 weeks, nevertheless, smaller doses of adenovirus result in a minimum inflammatory response, and the use of second and third generation adenovirus produce smaller immune response and can prolong gene expression.⁸ The adenovirus transfects host cells by receptor-mediated endocytosis, and it remains episomal. It binds mainly to the CD46 or coxsackie-adenovirus receptor, that is expressed on the major cell types of the heart and other organs.

The AAV is another useful vector in cardiac gene delivery as it has a natural tropism towards the myocardium. This vector has a more limited immune response compared to adenoviral vectors, leading to its prolonged gene expression. The AAV similarly transfects cells by receptor-mediated en-

docytosis, followed by migration and release of its genome into the nucleus of the host cell.

Non-viral based delivery systems in CVD

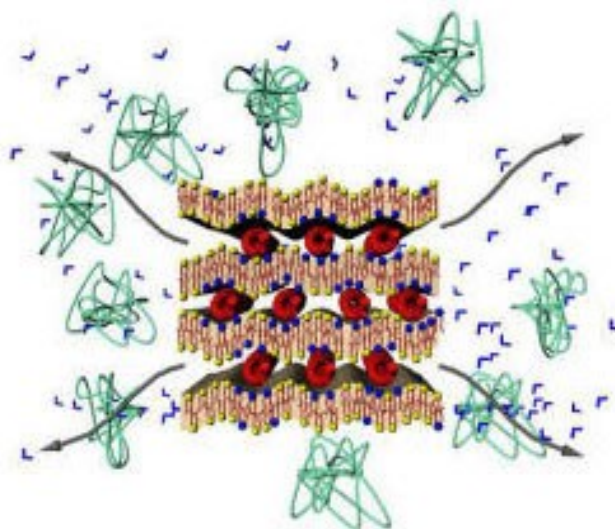
The non-viral delivery systems that have been studied for cardiac gene delivery include use of naked plasmid DNA, chemical vectors and physical delivery systems. The chemical vectors include lipoplexes and polyplexes, and the main physical methods include sonoporation, electroporation and the gene gun.

Naked plasmid DNA

Using naked plasmid DNA was shown to be of low transduction efficiency and expression as it cannot effectively enter the cell by endocytosis due to its hydrophilic structure and large size, and although this method is considered relatively safe, some studies have shown that it can cause fever, inflammation and infarcts in the skeletal muscle and myocardium. On the other hand, combining this method with other physical methods (e.g. electroporation) can be helpful. In the past 10 years, intramuscular injection of plasmid DNA has been applied in a strategy of therapeutic angiogenesis, with positive results.

Chemical vectors: lipoplexes and polyplexes

As mentioned above, lipoplexes and polyplexes are of high efficiency *in vitro*, but their efficiency *in vivo* is low, the gene expression time of lipoplexes is short, and they both may provoke an immune response. The net-positive charge of lipo-



plexes and polyplexes may aid in their fusion with the negatively charged glycoproteins and proteoglycans on the cell membrane of the host cell, subsequently resulting in their cellular uptake by endocytosis.

Table 4. Comparison between CVD gene delivery methods

| Vector/ Method | Transduction efficiency | Gene expression | Tropism/Specificity |
|-----------------------|--|--|---|
| Retrovirus | -Inefficient transduction of non-dividing cells (e.g., cardiomyocytes, smooth muscle cells) | -Long-term -Stable | -Broad cell tropism -Limited myocardial tropism |
| Lentivirus | -Efficient transduction of mitotically non-dividing (e.g., cardiomyocytes and smooth muscles) and dividing cells -Efficiency similar to adenoviral vector but for a longer duration | -Long-term -Recently developed vectors can remain permanently in host cells | -Limited myocardial tropism |
| Adenovirus | -Efficient transduction of dividing and non-dividing cells (e.g., cardiomyocytes) | -Transient expression due to immune response | -Broad, non-discriminating cell tropism (results in myocardial and non-target expression) |
| AAV | -Efficient transduction of dividing and non-dividing cells (e.g., cardiomyocytes) | -Long-term (Longer than adenoviral vector due to minimal immune response) | -Broad cell tropism -Specificity depends on serotype of virus -Natural tropism towards myocardium and vascular smooth muscles; especially, serotypes AAV1, 6, 8, 9; however, significant expression seen in non-target tissue |
| Naked plasmid DNA | -Inefficient, restricted transduction <i>in vivo</i> | -Transient transgene expression -Low transgene expression level | -Can be directed to target with other physical methods (e.g., direct injection into site) |
| Lipoplexes | -Inefficient transduction to myocardium and other non-dividing cells -Low efficiency compared to viral vectors | -Short-term transgene expression -Low transgene expression level | -Off-target expression seen -Difficult to transfect targeted cells |
| Polyplexes | -Inefficient transduction | -literature insufficient | -literature insufficient |
| Sonoporation | -Inefficient transduction -Affected by pulse intensity, duration and frequency | -Relatively short-term transgene expression | -Site specific |
| Electroporation | -Highly efficient -Affected by pulse intensity, duration and frequency | -High transgene expression level | -Site specific |
| Gene gun | -Good efficiency | -Transient transgene expression -Low transgene expression level | -Site specific -Shallow penetration of cardiac tissue. |

Despite the drawbacks of lipoplexes, this method was reported to be effective in animal models of angiogenesis, when growth factors were transferred with these vectors. Moreover, a study of the long

term effects and safety of the local VEGF-A catheter-based gene transfer in 103 patients suffering from coronary artery diseases between three groups (adenoviral vector, liposome-based vector and

control), and using the liposome-based vector, showed positive results. Regarding polyplexes, there are no major clinical trials of cardiovascular diseases that have assessed the effectiveness of these vectors.¹¹

Physical delivery systems

A study showed that the gene gun method is of cardiac specificity, since DNA was detected only in the bombarded hearts and not in surrounding organs; however, the DNA could not be delivered throughout the thickness of the whole myocardium, transfecting only the surface layer of the cardiomyocytes.¹⁰ The transfection efficiency of sonoporation depends on the acoustic pressure, pulse duration and the time of cells' exposure to ultrasound.

In one study, microbubbles containing cytomegalovirus-luciferase (CMV-luciferase) plasmids were transferred to the rat heart, resulting in cardiac-specific transgene expression compared with control hearts. In addition, electrocardiographic and echocardiographic tools were used for examining the murine heart, and the results have shown transient arrhythmias and non-significant changes in ejection fraction and fractional shortening; however, the results of this study showed heart-specific transfection with using sonoporation-based gene delivery that is detected mainly at the sub-endocardial layer of the myocardium.

Another study involved injecting naked plasmid encoding HGF into the rat heart during sonoporation 2 hours after myocardial infarction. The results showed a significantly reduced scar size after 3 weeks after injection, compared with control animals. Moreover, left ventricular remodeling progression was successfully prevented in the sonoporation group.¹⁰

Routes of administration

In-vivo methods

Direct intramyocardial injections are simple and involve injecting the vector from a syringe through a needle that is embedded in the myocardium. Intra-epicardial gene transfer is another route that involves injecting the vector into the pericardial sac, the closed space in close proximity to the myocardium. Since vectors in this space mainly transduce the pericardial cells and are minimally expressed in the myocardium, collagenase and hyaluronidase are administered along with the vector to disrupt the

pericardial cellular lining and extracellular matrix, improving the myocardial transduction.

Another method involves antegrade coronary injection of viral vectors and it provides homogenous delivery of the vector to the myocardium. Moreover, retrograde gene transfer is another method that has shown gene expression levels comparable to those of the antegrade delivery method; however, the antegrade flow pressure is a limiting factor that can be overcome by simultaneous brief blockade of the coronary outflow.¹²

Other methods include endocardial injections, which involve the use of a catheter, and intravenous gene transfer, which is safe and non-invasive.¹³

Ex-vivo methods

This method combines gene therapy and cellular therapy, and it involves the administration of test-tube vectors to isolated stem cells from the bone marrow, or cultures of skeletal myoblasts, and transferring these cells, transformed with transgenes, into the patient afterwards.

Comparison between gene delivery tools in CVD gene therapy

As shown in Table 4, the AAV vector is efficient in both mitotically dividing as well as non-dividing cells, such as the cardiac myocytes. Moreover, this delivery vector has long gene expression time, since the immune response to it is minimal. Additionally, certain serotypes of the adenovirus, including serotypes AAV1, 6, 8 and 9, are considered more cardiotropic than other serotypes, and this tropism can be further improved through direct evolution utilizing DNA shuffling of capsid sequences with error-prone polymerase or development of chimeric AAV capsid structures of different serotypes. These specific characteristics of the AAV vector make it a great vector to be used in cardiovascular gene delivery.

Adenoviral and retroviral vectors vs naked plasmid DNA method for CVD

The naked plasmid DNA delivery method has many advantages that were mentioned previously; however, naked DNA molecules are not able to enter cells effectively since they are of hydrophilic structure. In addition, plasmid DNA is compromised by electrostatic repulsion of the anionic phosphate backbone and the anionic cellular lipids of cell membranes and even if a small portion of plasmid DNA suc-

cessfully enters the cell, a large fraction is degraded within the endosome as a result of acidification of the endosomal and lysosomal compartments. Moreover, naked plasmid DNA molecules are easily fragmented by nuclease enzymes. These drawbacks have led to an inefficient cellular transfection of naked plasmid DNA and temporary transgene expression.

Regarding cardiovascular gene therapy, the first few studies showed positive results when naked plasmid DNA was used; however, in randomized larger tests, involving transferring angiogenic factors to the heart, results have shown that it is not a useful technique in cardiovascular gene delivery due to its very low efficiency.

The interest in using retroviral vectors for cardiovascular diseases, as mentioned previously, has decreased due to their low transfection efficiency in mitotically non-dividing cells, such as cardiac myocytes. To overcome this disadvantage, proliferation induction of these cells can be carried out for short periods of time for these vectors to be effective *in vivo*. On the other hand, these vectors might have a role in *ex vivo* gene transfer to vascular stents or prosthetic graphs.¹⁴ Once the vector transfects the cell successfully and integrates stably into the host cell genome. the expression might be sustained for several years.

As pointed out previously, the adenoviral vector is one of the most studied in cardiovascular gene delivery and can transduce the cardiac myocytes with reasonable efficiency, as it has the ability to transduce both dividing and non-dividing cells, due to its ability to be transported to the host cell nucleus across the nuclear pores. The adenoviral vector binds to CD46 or coxsackie-adenovirus receptor, and results in the efficient transfection of these vectors to the cardiac myocytes. Although the expression of the transgene carried by these vectors is transient, it is robust and the transfer rate is high.

Future perspectives

Although gene therapy has become an interesting area of therapeutics, it requires substantial improvements with regard to both the efficacy and safety of the delivery methods. Despite their high efficiency and selectivity, safety issues limit the application of viral vectors due to uncertainties regarding potentially carcinogenic effects due to recombination events, immune responses and inability to integrate transgenes into selected sites in a

host chromosome to avoid deleterious effects of insertional mutagenesis. On the other hand, the lower effectiveness and efficiency of non-viral delivery vectors make them currently unacceptable for clinical use. With improvements in design, it is hoped that gene therapy may expand to cover more diseases in the future through combining viral-vector mediated gene transfer with newer technologies, such as RNA interference (RNAi) using microRNA, which are already being incorporated into adenoviral, lentiviral and retroviral vectors, and used to suppress gene expression in cell culture and experimental animals.

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TEST YOUR KNOWLEDGE

Answers on back page

1) Which of the following is a physical method for gene therapy?

- gene gun method
- electroporation
- sonoporation
- hydrodynamic delivery
- All of the above

2) Which of the following is an advantage of the AAV vector?

- limited insert size
- prone to insertional mutagenesis
- prolonged expression
- requires packaging cell line for effectiveness
- All of the above

3) Which of the following vectors has a transient gene expression?

- retrovirus
- lentivirus
- AAV
- adenovirus
- None of the above



Is there a problem?

A 65 year old patient with a history of symptomatic arrhythmias was given the following prescription for treatment of sinusitis. Is there any major error in the prescription?

| <u>TTK HOSPITAL</u> | |
|------------------------|---|
| Patient Name: Mr. Tony | Age: 65 years |
| Address: Street No.56 | |
| Rx | Moxifloxacin tablet 400 mg once daily Send one pack |
| Dr. DOX Signature | Date: 12/09/14 |

Answer

Prescription Exercise

Moxifloxacin is contraindicated in a patient with a history of symptomatic arrhythmias.

Source: BNF



TOPICAL ISSUES AND CONTROVERSIES

Medicines for the world

Mounting evidence shows that the existing global system for pharmaceutical research and development (R&D) is badly out of tune with the needs of society. National health systems in the UK and the Netherlands shied away from providing certain recommended medicines due to price. In the USA, waiting lists for state HIV drug assistance are lengthening due to the high cost of drugs (frequently more than US\$20,000 per patient per year)- a painful irony as evidence rapidly mounts that earlier treatment of HIV not only benefits the patient, but also reduces the risk of transmission.

Medicine prices are often just as high in developing countries, though incomes are far lower and



social safety nets much weaker. Governments, insurers, and households everywhere are struggling to afford new medicines. At the same time, illnesses that primarily affect populations with little purchasing power, such as Chagas disease, are “neglected” because they offer little return on investment for industry. It is not only diseases of the poor that get neglected, but also those with small patient populations and any other area of research that fails to generate sufficient market returns. Some believe that the R&D system suffers from declining rates of innovation, unaffordable prices for end products, and a misalignment between research investments and the medical needs of society.

No single country can manage this problem alone.

Today, research advances produced anywhere can benefit people and contribute to scientific progress everywhere. But financing knowledge production is tricky. Some countries may be tempted to benefit from the knowledge contributed by other countries, but not make commensurate investments. Such “free riding” could, in turn, result in global underinvestment in R&D or limitations on knowledge sharing. A set of rules is needed both to ensure that countries contribute fairly and to create norms and incentives to share knowledge as widely as possible.

In April 2012, a group of international experts convened by the World Health Organization (WHO), known as the Consultative Expert Working Group on Research and Development (CEWG), recommended that countries begin negotiations over a binding treaty on medical R&D.



At the moment, the main set of global rules shaping R&D is the 1994 World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which requires countries to provide patent protection for drugs and other health technologies. Patents allow pharmaceutical firms to recoup their investments by charging a monopoly price (higher than the cost of production) for new medicines. All countries purchasing patented medicines are thus making contributions towards R&D through these higher prices. But patents are a blunt policy tool:

they require trade-offs between innovation and the high prices that restrict patient access to medicines.

A global R&D treaty could encompass a number of measures that would improve the existing system. For example, countries could commit to making sustainable contributions to an international R&D fund. This fund could pay the full costs of R&D so that there would be no need to recoup investments and medicines could be sold at cost, making treatments much more affordable and health systems more sustainable.

The system could also drive research into priority diseases, either through traditional grant funding or through novel incentive mechanisms such as prizes for the successful development of products. Furthermore, the treaty could establish norms for open innovation and create incentives to share research findings quickly in order to accelerate the R&D process. Finally, it could codify obligations for the ethical conduct of clinical trials, which are taking place in more and more countries but may not always be overseen by strong, experienced regulatory institutions. All of these measures are geared toward a global R&D system that would deliver both innovation and equitable access to medicines.

While a treaty won't solve every health challenge or all the woes of industry, building a system of global norms, rules, and incentives that makes public health the key driver of pharmaceutical research would move us towards a more equitable, healthier world.

Source: <http://the-scientist.com/2012/10/01/medicines-for-the-world/>

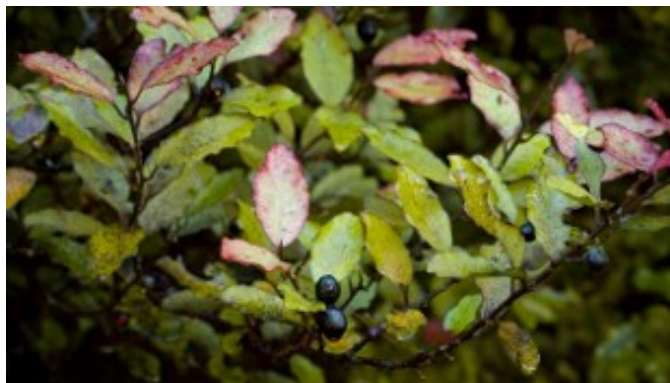
Traditional plant remedies for drug development

The medicinal New Zealand flax *Phormium* species (*Phormium* sp) are used traditionally by Māori people to treat a wide range of conditions, including skin, respiratory and gastro-intestinal problems.

A new phylogenetic study suggests that herbal remedies may hold promise for both medicine and drug development. Researchers from the University of Reading in the UK found that many medicinal plants used by nearly 100 cultures on different continents are related. Because these distant groups of people likely identified their plant therapies independently, such herbal treatments may be legitimate, the researchers argue, and the plants



likely contain bioactive compounds that scientists could exploit for new drug therapies. They constructed genus-level phylogenetic trees of plants



from 3 disparate locations- New Zealand, Nepal, and the Cape of South Africa. Once they assembled their trees, they overlaid ethno-botanical data regarding the therapeutic uses of various plants by cultures from each of the three locations (one culture from New Zealand, three cultures from The Cape of South Africa, and more than 80 cultures from Nepal).

In the flora phylogenies for each of the three continents, medicinal plants clustered into “hot nodes,” meaning they were more related to each other than the other plants in the analysis. Further, categorizing medicinal plants by what condition they treated, the researchers found that medicinal plants clustered into condition-specific nodes, even when the analyses from all three locations were combined- again suggesting a high degree of relatedness for plants used to treat similar conditions and lending some validity to these herbal treatments.

Though more than 80% of plant species have not been tested for therapeutic potential, the last major drug discovered from plants was the cancer drug Taxol in 1967. This lack of interest stems, in part, from skepticism about the legitimacy of traditional plant therapies.

Pseudowintera colorata is a plant species used medicinally in New Zealand by Māori people to treat skin conditions, respiratory problems, and to help heal wounds.

Another criticism facing the study is that cultures sometimes use symbolic visual cues to identify potentially disease-treating plants. For example, it may be common for traditional healers to treat menstrual symptoms with plants that have red flowers. Such appearance-based selection would suggest that relatedness of medicinal plants is due to looks, not bioactivity.

The researchers also looked at plants being developed or already in use as drug therapies around the globe and found a significant number fell in the nodes with the traditional medicinal plants, further supporting the validity of the method in identifying plants useful for drug discovery. The team noted several plant genera related to traditional medicinal plants that have not been tested for bioactivity, which could serve as low-hanging fruit in the search for new therapies.

Adapted from <http://the-scientist.com/2012/09/10/rethinking-herbal-medicine/>

Cancer clinical trials of the future

There is a significant change in the fundamental structure of cancer clinical trials, as the emphasis begins to shift from large-scale studies of relatively unselected patients to smaller studies testing more narrowly targeted therapies in molecularly characterized populations. However, the ability to select subgroups of patients for study has been severely curtailed by a still-limited knowledge of human cancer biology. This is rapidly changing, due to advances in genomics and comprehensive cancer biology research over the last decade.

Large-scale efforts, such as The Cancer Genome Atlas, are compre-

hensively defining many of the crucial molecular characteristics of human malignancies by illuminating genetic alterations that are clinically and biologically important, and which, by virtue of their functional roles, are viable targets for cancer treatment. At the same time, the ability to design small-molecule inhibitors of specific cancer targets is rapidly accelerating.

In 2011, two new agents exemplified the power of these trends: crizotinib was approved for the treatment of lung cancers that harbor a specific mutation in the ALK gene, and vemurafenib was approved for the treatment of melanomas with a specific *BRAF* mutation. Clinical trials are being



transformed by these trends. It is inevitable that there will be a rise in the number of trials that incorporate molecular tumor testing prior to treatment, with treatment selection informed by the molecular features of each individual's cancer. Such personalized trials have the potential to yield better outcomes by increasing the probability of response and to employ less toxic therapies by increasingly targeting cancer-specific functions, rather than normal proliferative functions.

Smaller and more precise trials

To the extent that targeted therapies will prove more effective when given to selected patients, clinical trials should get dramatically smaller. Trial size is largely driven by how effective the treatment is expected to be, so fewer participants are needed when the therapeutic benefit is larger. But the promise of smaller trials will not be universal; for example, when two targeted agents are compared to one another in the same molecularly selected population, the differences in efficacy may be small and larger trials will be required. Smaller trials may not necessarily move faster or be easier to complete, as they will require the "right patients," who may be hard to find.

Today, molecular characterization of tumors is often done as part of the screening process for each trial. Many, and sometimes most, of the patients prove ineligible, making this approach frustrating and difficult to carry out. It would be better to make comprehensive molecular characterization of tumors a routine part of establishing a patient's eli-

gibility for a range of therapies.

New challenges

For rare targets that are present in a minority of cases across many different types of cancers, one will have to consider clinical trials that include a number of different cancers. There are many design pitfalls to such trials, chiefly the additional clinical and molecular heterogeneity introduced by the inclusion of more than one cancer type. It will inevitably make sense in some settings to select patients who share a particular tumor biology, regardless of the tissue of origin.

Another major challenge is how to combine targeted therapies to improve clinical outcomes. To date, targeted therapies have not been able to cure advanced solid tumors. Clinical benefits, while sometimes quite impressive when compared to marginally effective treatments, still fall far short. It stands to reason that redundant survival and growth pathways enable tumors to overcome therapies that inhibit a single target. The simultaneous inhibition of relevant redundant pathways may yield dramatically better results, but will also dramatically increase the complexity of molecularly personalized clinical trials. Fewer than 5% of adult cancer patients participate in a clinical trial. To carry out meaningful clinical trials in the future, that number must increase. This will be most important for treatments that target relatively rare mutations.

Adapted from : www.the-scientist.com/?articles.view/articleNo/34761/title/Cancer-Clinical-Trials-of-Tomorrow/

IN THE NEWS

Source: www.bloomberg.com/news/2012-01-05/drug-approvals-in-u-s-reached-a-seven-year-high-in-2011-on-improved-data.html

Drug approvals on the increase?

US approvals of new drugs hit a seven-year high in 2011 as pharmaceutical companies responded to regulators' demands for better safety data and avoided last-minute requests for more information. The FDA cleared 30 new treatments in 2011 compared with 21 the year before, a Bloomberg review of agency records shows. Johnson & Johnson (JNJ) and GlaxoSmithkline (GSK) each had three products approved after no company had more than one medicine cleared in 2010. Bloomberg tracked approvals from an FDA database of "new molecular entities" that excludes blood products and new vaccines. The 30 drugs cleared in 2011 were the most

since 36 were cleared in 2004.

More frequent approvals may help drug makers overcome a rush of patent expirations. At least 21 medicines were due to lose a combined \$11.5 billion in revenue as a result of patent expirations in 2012, including Paris-based Sanofi (SAN) and Bristol-Myers Squibb Co. (BMY)'s anti-clotting treatment Plavix (clopidogrel), projected to see \$4.5 billion in lost sales, according to Bloomberg Industries. It was expected that drug makers would generate more than \$4 billion in 2012 from products that were introduced in 2010 and 2011.

Compounds approved in 2011 included New York-

based Bristol's Yervoy (ipilimumab), the first drug cleared to prolong the lives of people with advanced skin cancer that uses patients' immune systems to attack tumors, and New Jersey-based J&J's Xarelto (rivaroxaban), the second in a new class of anti-clotting therapies for people with irregular heartbeats.

The agency also cleared Benlysta (belimumab), developed by London-based Glaxo and Rockville, Maryland-based Human Genome Sciences Inc. The compound is the first treatment for lupus, a debilitating autoimmune disorder, in 50 years. The novel design of the drugs gives the agency more flexibility evaluating them.



The US Congress expanded the FDA's oversight powers in 2007 after the agency was slow to react to heart risks associated with Whitehouse Station, New Jersey-based Merck's painkiller Vioxx (rofecoxib) and Glaxo's diabetes pill Avandia (rosiglitazone). The FDA has since raised standards for safety and efficacy data required from

companies. The companies are being a lot more selective around where do they invest their own resources and where can they make the most impact.

The FDA also is holding advance consultation with companies on what data should be included in drug applications to avoid having to make last-minute requests for more information on how a compound works.

Pharmaceutical companies filed 29 novel drug applications with FDA in 2011 compared with 22 in 2010. Nineteen of the 30 therapies approved in 2011 were cleared without requests for more data. In contrast, regulators approved about half of the 21 treatments in 2010 on the first try. The pace of approvals may be influenced by the pace of Congressional efforts to renew the system that allows pharmaceutical companies to pay user fees for product evaluations. The drug industry and the FDA struck a deal in 2011 to extend reviews two months in exchange for additional discussions while a medicine is being tested.

New York-based Pfizer Inc. (PFE) leads drugmakers with 85 products in development, followed by Basel, Switzerland-based Roche AG (ROG) with 83 and Sanofi with 79.

NEWS from the FDA

Possibly fatal blood clots with Ponatinib

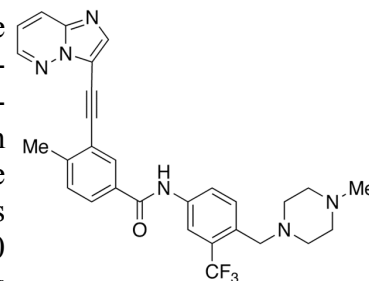
The FDA issued a safety alert and reports it is investigating a high rate of thrombosis and other cardiovascular events in patients taking ponatinib (Iclusig, Ariad Pharmaceuticals) for chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). Ponatinib, approved in December 2012, already contained labeling warnings about blood clots.

In trials that led to approval, the rate of serious arterial clots was 8%, venous blood clots were reported in 2.2% of patients. New data from the PACE trial show that after a median follow-up of 24 months, serious arterial thrombosis occurred in 11.8% of patients receiving the drug. Cardiovascular events were most common (6.2%), followed by cerebrovascular events (4%) and peripheral vascular events (3.6%; some patients had more than one type of event). The rate of serious venous occlusion rose to 2.9% of patients.

According to the company that makes ponatinib, the increased totals of adverse events has not in-

creased the incidence rate of arterial thrombotic events when normalized to the duration of treatment. The rate in the original analysis was 10 events per 100 patient-years, and has actually now dropped to 9.6 events per 100 patient-years. Still, non-serious plus serious arterial and venous events have occurred in approximately 20% of patients treated with ponatinib.

Patients enrolled in the EPIC trial comparing ponatinib and imatinib in newly diagnosed CML (ponatinib approved only in CML that has proven resistant or intolerant to previous tyrosine kinase therapy) will have their dose of ponatinib reduced from 45 mg to 30 mg daily. If patients have achieved a major molecular response or achieve one in the future, the dose will be further reduced to 15



mg per day. Other clinical trial patients will continue on the drug, but dose reductions will proceed on "a trial-by-trial" basis. Finally, the eligibility criteria for future trials of ponatinib will be adjusted to exclude patients who have experienced arterial thrombosis resulting in heart attack or stroke in the past. In spite of the increased thrombosis signal, the company points out the continued efficacy of

ponatinib in the PACE trial; over 90% of patients who achieved a major cytogenetic response maintained that response after a median of 19 months in spite of dose reductions.

Source: www.cancernetwork.com/news/fda-warns-possibly-fatal-blood-clots-ponatinib?GUID=409EAAC3-63BF-4023-8594



First migraine drug for 12-17 year olds

US regulators have approved Janssen Pharmaceuticals' Topamax (topiramate) the first treatment for the prevention of migraine headaches in adolescents aged 12-17 y.



The green light was given on the back of a clinical trial involving 103 participants which showed that the drug reduced the frequency of migraine by approximately 72% as compared to a reduction of 44% in those taking a placebo.

On the safety side, the most common adverse reactions were found to be paresthesia (a burning or prickling sensation felt in the hands, arms, legs or

feet), upper respiratory infection, anorexia (loss of appetite) and abdominal pain.

Topamax was first approved by the FDA back in 1996 for the prevention of seizures, and later in 2004 for migraine prevention in adults.

Adapted from: www.pharmatimes.com/Article/14-03-31-FDA_approves_first_migraine_drug_for_12-17_year_olds.aspx
utm_source=divr.it&utm_medium=twitter#ixzz2xXU8NvU5



STATE OF KUWAIT

Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from June to September 2014

- Advaquin Tabs. 500mg; Levofloxacin 500mg; Oman Pharma-Oman
- Airfast Chewable Tabs 4, 5mg; Montelukast 4, 5mg; Tabuk - KSA
- Ceftazidine Powder for Soln. for Inj./Infn. 2g; Ceftazidime 2g; Fresenius Kabi Deutschland GmbH/Germany
- Cimzia Soln. for Inj. 200mg/ml Certolizumab Pegol 200mg; UCB Pharma S.A/Belgium
- Emipride Tablets 1mg; Glimpiride 1mg; Global Pharma Co. LLC -U.A.E.
- Enemax Adult Enema; Monobasic Sodium Phosphate 19g,
- Di basic Sodium Phosphate 7g; West Coast Pharma Works Ltd./India
- Forxiga Tabs 10mg; Dapagliflozin 10mg; Bristol Myers Squibb/AstraZeneca/U.K.
- Gabapentin ABC Caps. 300, 400mg; Gabapentin 300, 400mg; ABC Pharmaceutici S.p.A/Italy
- Gliolan Powd. For Oral Soln. 30mg/ml; 5-Aminolevulinic acid HCl 1.5g; Medac Gesellschaft fur Klinische Spezialpreparate mbH/Germany
- Glucovance Tabs 1000mg/5mg; Metformin HCl 1000mg, Glibenclamide 5mg; Merck Sante-France
- Humira Soln. for Injn; In PFP 40mg/0.8ml Adalimumab 40mg; Abbvie Deutschland GmbH & Co. KG



Germany

Invokana Tablets 100, 300mg; Canagliflozin 100, 300mg; Janssen-Cilag Int. N.V. - Belgium

Ivarin Tabs. 10, 20mg; Rosuvastatin 10, 20mg; Tabuk-KSA

Levea Tabs 1000, 250, 500, 1000mg; Levetiracetam 100, 250, 500, 1000mg; Lab. Cinfa-Spain

Lipigard Tablets 10, 20, 40mg; Atorvastatin 10mg, 20, 40mg; Julphar Gulf Pharma Ind. -U.A.E.

Logimax PR Tabs. 5/50mg; Felodipine 5mg, Metoprolol Tartrate 50mg; Astrazeneca AB/Sweden

Lotevan Tabs 10/160mg; Amlodipine 10mg, Valsartan 160mg; Tabuk Pharma-KSA

Lotevan Tabs 10/320mg; Amlodipine 10mg, Valsartan 320mg; Tabuk Pharma-KSA

Lotevan Tabs 5/160mg; Amlodipine 5mg, Valsartan 160mg; Tabuk Pharma-KSA

Lotevan Tabs 5/320mg; Amlodipine 5mg, Valsartan 320mg; Tabuk Pharma-KSA

Lyxumia Soln. for Inj. 10, 20mcg; Lixisenatide-10, 20mcg; Sanofi-Aventis Groupe

France

Nervax Capsules 75, 150mg; Pregabalin 75, 150mg; Tabuk Pharm.Mfg. Co. - Saudi

Arabia

Nivestim Soln. for Inj./Infn. 120mcg/0.2ml; Filgrastim-120mcg; Hospira U.K. Ltd./U.K.

Nivestim Soln. for Inj./Infn. 300mcg/0.5ml; Filgrastim-300mcg; Hospira U.K. Ltd./U.K.

Nivestim Soln. for Inj./Infn. 480mcg/0.5ml; Filgrastim-480mcg; Hospira U.K. Ltd./U.K.

Oflam Tabs 50mg; Dicofenac Potassium 50mg; Jazeera Pharma-KSA

Omnitrope Soln. for Inj. 5, 10mg/1.5ml Somatropin 5, 10mg(30 IU); Sandoz GmbH - Austria

Pedea Soln. for Inj. 5mg/ml; Ibuprofen 10mg; Orphan Europe SARL- France

Relvar Ellipta Inhalation Pwdr. Pre-dispensed 100/25mcg; Fluticasone Furoate 92mcg, Vilanterol 22mcg; Glaxo Group Ltd. - U.K.

Relvar Ellipta Inhalation Pwdr. Pre-dispensed 200/25mcg; Fluticasone Furoate 184mcg, Vilanterol 22mcg; Glaxo Group Ltd.-U.K.

Ribomustin Powdr. For Conc. for Soln. for Infn. 25, 100mg; Bendamustine HCl 25, 100mg; Astellas Pharma GmbH/Germany

Signifor Soln. for Inj. 0.3, 0.6, 0.9mg/ml; Pasireotide 0.3, 0.6, 0.9mg; Novartis-Switzerland

Simedill Emulsion; Dil Oil 1mg, Simethicon Emulsion 30% 20mg; Biopharm for Scientific Research & Pharm. Mfg.-Egypt

Toprazole Tablets 20mg; Pantoprazole 20mg; Tabuk Pharma Mfg. Co. /K.S.A.

Trozet Tablets 2.5mg; Letrozole 2.5mg; Fresenius Kabi Oncology Ltd.- India

Vagiclind Vaginal Cream; Clindamycin 20mg; Biopharm for Scientific Research- Egypt

Zincofer Tablets; Vitamins & Minerals; Apex Lab. Pvt. Ltd. - India

Zincofer Nurture Tablets; Vitamins & Minerals; Apex Lab. Pvt. Ltd. - India



Answers to: Test your knowledge

Correct answers:

1-e; 2-c; 3-d

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 from the MOH. It aims to provide instructive reviews and topical news items on a range of drug 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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