EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 5
137-146
Year: 2020

A REVIEW ARTICLE ON TARGETED DRUG DELIVERY SYSTEM: DRUG TARGETING TO BONE MARROW

[1*]Shireen Kahkashan Fatima and [2]Dr. S. Shahid Mohammed

[1]Student, Deccan School of Pharmacy,
[2]Associate Professor, Deccan School of Pharmacy,
Department of Pharmaceutics, Deccan School of Pharmacy, Dar-us-salam, Aghapura, Hyderabad 500001, Telangana, India.

***Corresponding Author: Shireen Kahkashan Fatima**
Student, Deccan School of Pharmacy, Dar-us-salam, Aghapura, Hyderabad 500001, Telangana, India.

Article Received on 13/03/2020 **Article Revised on 02/04/2020** **Article Accepted on 23/04/2020**

I. ABSTRACT
Targeted drug delivery (TDDS) an advanced method of delivering drugs to the patients such that increases the concentration of delivered drug to the targeted body parts only (organs/tissues/ cells) which in turn improves efficacy of treatment by reducing side effects.. Basically, targeted drug delivery assist the drug molecule to reach desired site i.e., bone marrow. Bone marrow is the organ which is responsible for production of blood cells in humans beings. BM also the 4th largest organ of the body by weight, consisting of bone, muscle, and fat. It is the seat of production of haematopoietic cells. It is estimated that, in humans, bone marrow accounts for approximately 4–5 % of the total body weight. The stem cells lines in the bone marrow produce new blood cells and stromal cells. It has been estimated that as many blood cells are eliminated from the blood circulation per day in adult human. Development of effective targeted bone marrow drug delivery systems is an important goal for development of diagnostic, protective, and/or therapeutic agents for hematopoietic disorders and infectious diseases.

II. KEYWORDS: Blood cell production,stromal cell, blood cells, haematopoietic cell, bone marrow disease, hematopoietic disorders.

INTRODUCTION
The bone marrow is basically a connective spongy tissue found inside bones. There are two types of bone marrows in the human body, yellow marrow and red marrow.

Yellow marrow consists mostly of adipose tissue, and red marrow consists of haematopoietic or blood forming tissue that produces red and white blood cells.

The yellow marrow is normally located in the shafts of long bones and the red marrow is found at the ends of long bones and short, flat and irregular shaped bones.

The bone marrow in the breast, bone, skull, hips, ribs and spine contains stem cells also known as “mother cell’s as mature blood cells evolve from these cells.

The most primitive of these stem cells is the pluripotent stem cell that is believed to be the origin of all blood cells. It is able to differentiate following number of pathways and thereby generate erythrocytes, granulocytes, monocytes, mast cells, lymphocytes and megakaryocytes.

Pluripotent stem cells differ from other blood cells in that they are capable both of unlimited self-renewal and differentiation. Self-renewal is the ability of the cell to reproduce another cell identical to it, thus maintaining a steady number of these types of cells in the body.

Differentiation is the process of generating one or more subsets of more mature cells that eventually evolve into components of blood either as erythrocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes or platelets.[1]

BONE MARROW
DEFINITION: Bone Marrow is the soft spongy tissue that lies within the hollow interior of long bones. In adults, marrow in large bones produces new blood cells. Bone marrow forms around 4% of total body weight (around 2.6 kg in a healthy adult). Bone Marrow is found in the centre of most bones and has many blood vessels.[2]

ANATOMY

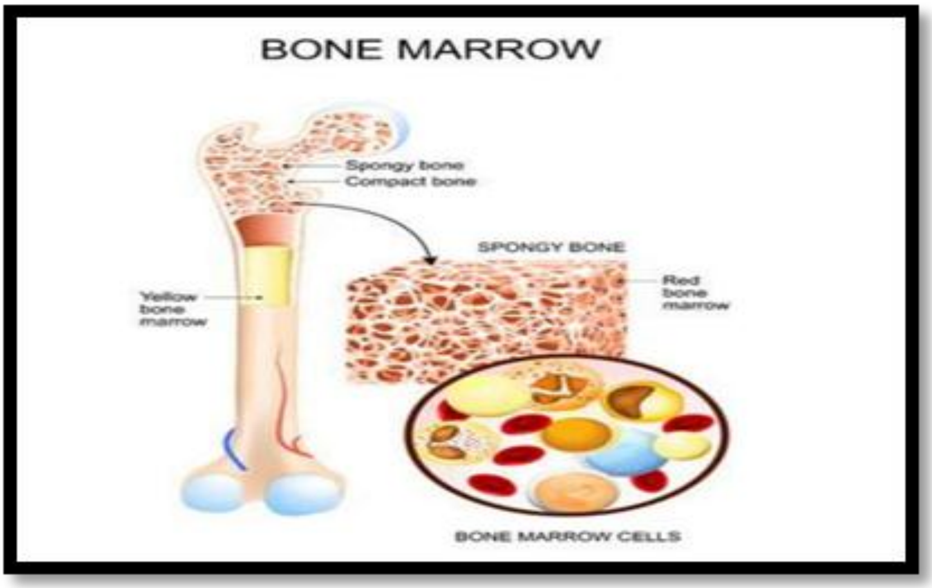

Figure 1: showing bone marrow, yellow, red and blood cells.

Bone marrow is separated into a vascular section and non-vascular sections. The vascular section contains blood vessels that supply the bone with nutrients and transport blood stem cells and mature bloodcells away from the bone and into circulation.

The non-vascular sections of the bone marrow are where haematopoiesis or blood cell formation occurs. This area contains immature blood cells, fat cells, white blood cells (macrophages and plasma cells), and thin, branching fibres of reticular connective tissue. While all blood cells are derived from bone marrow, some white blood cells mature in other organs such as the spleen, lymph nodes, and thymus gland.[3]

The bone marrow is found within the central cavities of axial and long bones. It consists of hematopoietic tissue islands and adipose cells surrounded by vascular sinuses interspersed within a meshwork of trabecular bone.

It accounts for approximate 3% of the body weight in adult rats, ~2% in dogs and ~5% in humans. The bone marrow is the major hematopoietic organ, and a primary lymphoid tissue, responsible for the production of erythrocytes, granulocytes, monocytes, lymphocytes and platelets.

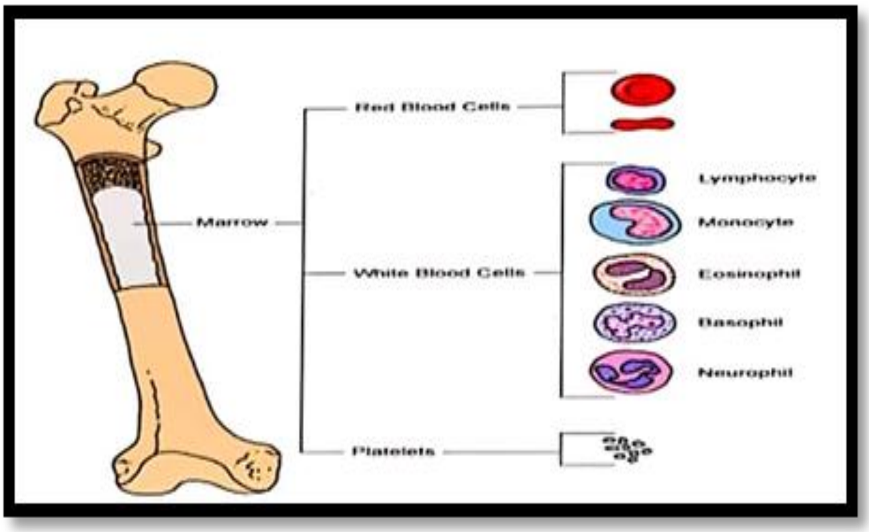

Figure 2: showing bone marrow and blood cells.

The inner surface of the bone cavities and the outer surface of the cancellous bone spicules within the cavities are covered by an endosteal lining consisting of a single layer of flat “bone-lining cells” supported by a thin layer of reticular connective tissue; osteoblasts and osteoclasts are also found within the endosteal lining.

The only bones to carry redbone marrow throughout life are the vertebrae (back bones), sternum (breast bone), hipbone, and skull bones.

Bone marrow innervation occurs with myelinated and non-myelinated nerves that enter through the nutrient canals. Some innervation also occurs through epiphyseal and metaphyseal foramina.[2]

VI. BONE MARROW STEM CELLS

Red bone marrow contains hematopoietic stem cells that produce 2 other types of stem cells; myeloid stem cells and lymphoid stem mast cells.

Myeloid stem cells: develop into red blood cells, platelets, mast cells, or Myeloblast cells. Myeloblast cells develop into granulocyte and monocyte white blood cells.

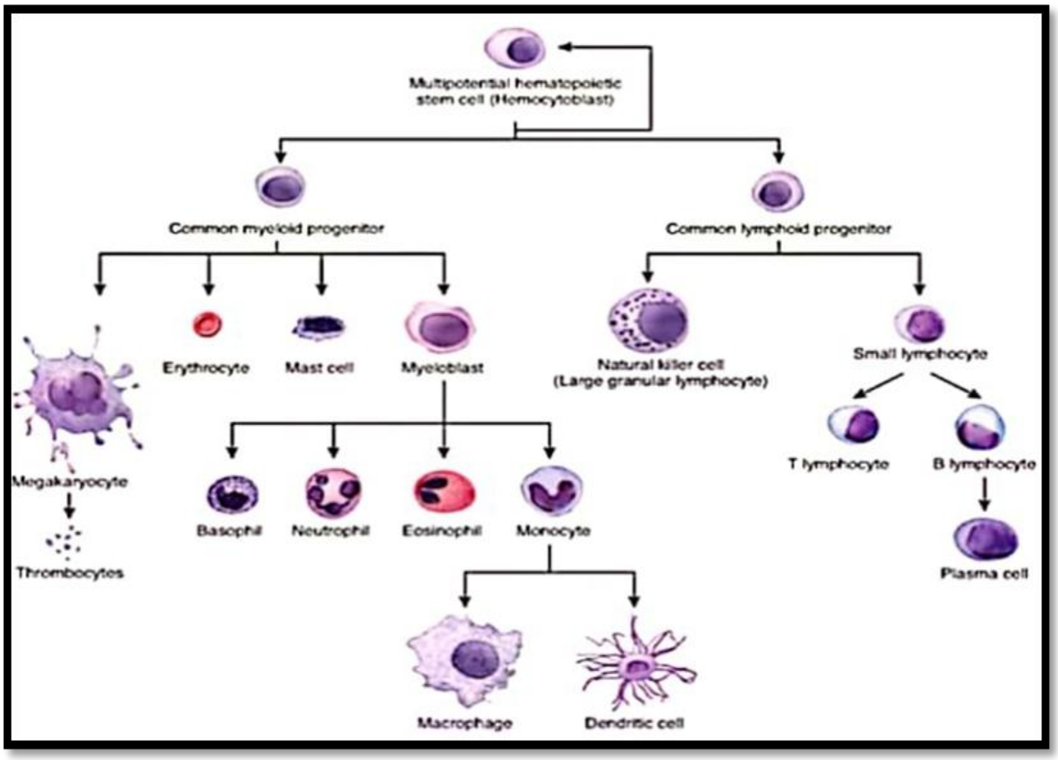

Figure 3: shows the formation, development, and differentiation of blood cells.

- **Red Blood Cells**—also called erythrocytes; these cells transport oxygen to body cells and deliver carbon dioxide to the lungs.
- **Platelets**: also called thrombocytes; these cells develop from megakaryocytes (huge cells) that break into fragments to form platelets. They aid in the blood clotting process and tissue healing.
- **Myeloblast Granulocytes** (white blood cells)—develop from Myeloblast cells and include neutrophils, eosinophils, and basophils. These immune cells defend the body against foreign invaders and become active during allergic reactions.
- **Monocytes**—these large white blood cells migrate&develop into macrophages anddendritic cells. Macrophages remove foreign substances, dead or damaged cells, and cancer cells from the body by phagocytosis.
- **Dendritic cells-** aid in the development of antigen immunity by presenting antigenic information to lymphocytes, commonly found in the skin, respiratorytract, and gastrointestinal tract.
- **Mast Cells**—these white blood cell granulocytes develop independently from Myeloblast cells. They are found throughout body tissues, particularly in the skin and lining of the digestive system. Mast cells mediate immune responses by releasing chemicals, such as histamine, stored in granules. They aid in wound healing, blood vesselsgeneration, and are associated with allergic diseases (asthma, eczema, hay fever, etc.)[3]

Once mature, these blood cells move from the marrow into the bloodstream, where they perform important functions required to keep the body alive and healthy.[9]

Lymphoid Stem Cells—develop into lymphoblast cells, which produce other types of white blood cells called lymphocytes. Lymphocytes include natural killer cells, B lymphocytes, and T lymphocytes.

- **NaturalKiller Cells**—these cytotoxic cells contain enzymes that cause apoptosis in infected and diseased cells. They are components in the body's innate immune response protecting against pathogen and tumour development.

- **B Cell Lymphocytes**—these cells are important for adaptive immunity and long lasting protection against pathogens. They recognize molecular signals from pathogens and produce antibodies against specific antigens.
- **T Cell Lymphocytes**—these cells are active in cell-mediated immunity. They help to identify and destroy damaged, cancerous, and infected cells.[3]

Mesenchymal stem cells are found in the bone marrow cavity. They differentiate into a number of stromal lineages, such as.

- chondrocytes (cartilage generation)
- osteoblasts (bone formation)
- osteoclasts
- adipocytes (adipose tissue)
- myocytes (muscle)
- macrophages
- endothelial cells
- fibroblasts.

RED BONE MARROW

Red bone marrow produces all red blood cells and platelets in human adults and around 60 to 70 percent of lymphocytes. Other lymphocytes begin life in the red bone marrow and become fully formed in the lymphatic tissues, including the thymus, spleen, and lymph nodes. Together with the liver and spleen, red bone marrow also plays a role in getting rid of old red blood cells.

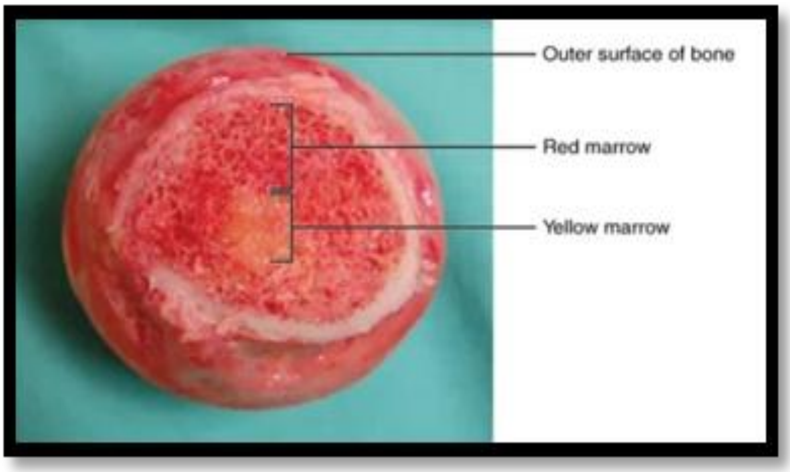

Figure 4: showing type of bone marrows.

YELLOW BONE MARROW

Yellow bone marrow mainly acts as a store for fats. It helps to provide sustenance and maintain the correct environment for the bone to function. However, under particular conditions, such as severe blood loss or fever, the yellow marrow may revert to red marrow.

Yellow marrow tends to be located in the central cavities of long bones, and is generally surrounded by a layer of red marrow with long trabeculae (beam-like structures) within a sponge-like reticular framework.

IX. BONE MARROW TIME LINE

Before birth, bone marrow first develops in the clavicle toward the end of foetal development. It becomes active about 3 weeks later. Bone marrow takes over from the liver as the major hematopoietic organ at 32 to 36 weeks' gestation.

Bone marrow remains red until around the age of 7 years, as the need for new continuous blood formation is high. As the body ages, the red marrow is gradually replaced by yellow fat tissue. Adults have an average of about 2.6 kg (5.7 lbs) of bone marrow, about half of which is red.

In adults, the highest concentration of red marrow is in the bones of the vertebrae, hips (ilium), breastbone (sternum), ribs, skull and at themetaphyseal and epiphyseal ends ofthe long bones of the arm (humerus) and leg (femur and tibia). All other cancellous, or spongy, bones and central cavities of the long bones are filled with yellow marrow.[4]

X. PHYSIOLOGY OF BONE MARROW

1. **Haematopoietic (haemopoietic) function (Production and release of blood cells):** Production of myeloid elements is the important function of bone marrow. It has been described that red bone marrow is active and has the capacity of forming red cells as well as other blood cells.

- All the blood cells like erythrocytes, granulocytes, platelets, monocytes and lymphocytes are formed in the red bone marrow. It has been studied that the marrow contains about 5.6×10^9 erythroid precursors per Kg body weight and 11.4×10^9 neutrophilic precursors per Kg body weight.
- Mechanisms by which the blood cells are released in the blood are not clear. Under certain urgent need and in case of anaemia, mature and even immature cells may be released in' the circulation.

2. **Erythroclasia** or **destruction of R.B.C**:

- In the bone marrow not only the blood cells are formed but also the abnormal, imperfect, damaged and aged R.B.C. are destroyed.
- These cells are sequestered or trapped and phagocytised in the macrophages of' the bone marrow. Iron portion is stored as haemosiderin and ferritin in the liver, spleen, R. E. cells and bone ' marrow and the rest of haem is ultimately converted into bile pigments.

3. **Storage functions:**

- Bone marrow is an important site for storage of iron in the form of ferritin and of haemosiderin coming from food sources as transferrin and also from destruction of R.B.C. through phagocytosis.
- These stored irons are easily utilised for the synthesis of haemoglobin.

4. **Reticulo-endothelial function**

- Bone marrow plays an important role in the inactivation of toxins or other toxic substances of the body.
- The free macrophages of the bone marrow are increased during the invasion of toxins or during rapid haemolysis.

5. **Immunological function**

- Regarding its immunological function, the marrow is not so competent as it is found in spleen and lymph nodules. Presence of lymph nodules in the bone marrow has been reported by many.

6. **Osteogenic function**

The cellular elements which take part in the formation of bone are formed in the marrow. The osteoclast, osteoblast, osteocyte, endosteum blood vessels are found within the marrow.

7. **Connective tissue functions**

Due to its different connective contents, the bone marrow performs several functions associated with the connective tissues.[5]

8. **Mesenchymal stem cells**

Theseare multipotent stem cells that can differentiate into a variety of cell types. MSCs have been shown to differentiaten vitro or in vivointo osteoblasts, chondrocytes, myocytes, adipocytes and beta-pancreatic islets cells.

9. **Bone marrow barrier**

The blood vessels of the bone marrow constitute a barrier, inhibiting immature blood cells from leaving the marrow. Only mature blood cells contain the membrane proteins, such as aquaporin and glycophorin, that are required to attach to and pass the bloodvessel endothelium.[9] Hematopoietic stem cells may also cross the bone marrow barrier, and may thus be harvested from blood.

10. **Lymphatic role**

The red bone marrow is a key element of the lymphatic system, being one of the primary lymphoid organs that generate lymphocytes from immature hematopoietic progenitor cells. The bone marrow and thymus constitute the primary lymphoid tissues involved in the production and early selection of lymphocytes. Furthermore, bone marrow performs a valve-like function to prevent the backflow of lymphatic fluid in the lymphatic system.

11. **Compartmentalization**

Biological compartmentalization is evident within the bone marrow, in that certain cell types tend to aggregate in specific areas. For instance, erythrocytes, macrophages, and their precursors tend to gather around blood vessels, while granulocytes gather at the borders of the bone marrow.[6]

XI. BONE MARROW DISEASES AND DISORDERS

Leukaemia

Leukaemia is a cancer of the white blood cells that can affect any of the five WBC types. The cancer affects a line of cell that begins to replicate non-stop clogging the bone marrow and decreasing production of other cells.

Patients with leukaemia may have frequent infections, anaemia, bleeding, bruising, night sweats, and bone and joint pain.

The spleen that normally filters the blood and gets rid of old cells, may become enlarged. Lymph nodes that house the WBCs may also enlarge.

Blood picture shows immature cells from the bone marrow called blast cells. These are released due to excess production within the bone marrow.

Myelodysplastic Syndrome (MDS)

MDS is a group of diseases where there is abnormal bone marrow cell production. There are not enough normal blood cells being made. This leads to anaemia, bleeding and risk of infections.

MDS syndromes are classified by how the cells in the bone marrow and blood smear look under the microscope. This includes anaemia that are resistant to treatment, those that are inherited or genetic and a complex form of MDS. Over time, MDS tends to progress to acute myeloid leukaemia.

Myeloproliferative disorders (MPD)

“Myelo” means bone marrow and MPD signifies proliferation of the bone marrow. These are a group of diseases.

There is overproduction of a precursor (immature form) of a marrow cell. This results in release of the immature forms of other precursors as well that are released in blood as blast forms when the body requires them.

The bone marrow in MPD shows a mixture of cells in various stages of maturity.

Aplastic anaemia

This is a condition where there is loss or suppression of production of RBCs. This may be due to a defect in the stem cell producing them or due to an injury to the bone marrow environment.

e.g. Fanconi'sanaemia or associated with a viral infection with parvo virus.

Iron deficiency anaemias
Iron deficiency anaemias lead to the formation of deformed and smaller RBCs released from the marrow. These are pale and small and are called microcytic RBCs.

Anaemias may also be caused by deficiency or dysfunction of erythropoietin, a chemical produced by the kidneys that stimulates RBC production.[7]

Chronic lymphocytic leukaemia
Chronic lymphocytic leukaemia is a type of blood, lymph node and bone marrow cancer in which too many abnormal white blood cells called lymphocytes accumulate in your body.

Paroxysmalnocturnalhaemoglobinuria
(PNH) is an ultra-rare failure disease in which red blood cells break apart. Normal red blood cells have a shield of proteins that protect them from coming under attack by the body's own immune system. PNH occurs because that protein shield is missing. PNH is often associated with reduced bone marrow function (low blood counts) caused by aplastic anaemia.[8]

Others
Other diseases and disorders of the bone marrow include

- **Disorders of plasma cells** or **Plasma cell dyscrasia**
- **Thrombotic thrombocytopenic purpura**
- **Unexplained cytopenia –** This results in decrease in production of all cell types.
- Other causes include small cell tumours of childhood, Mast cell disease, Disseminated granulomatous disease, Primary amyloidosis, Metabolic bone disease etc.
- Bone marrow depression may be caused due to cancer chemotherapy, bone marrow transplantation and cancer radiation therapy.

XII-BONE MARROW- APPLICATIONS, ADVATAGES AND LIMITAIONS[9]

APPLICATIONS:	ADVANTAGES	LIMITATIONS/PITFALLS:
Engineering cartilage, bone, muscles, fat, and tendon for cell replacement strategies	Existence of MSCs in multiple tissue, no death of cell source, relative reproducible differentiation protocols, hypo immunogenicity in nature, extensive in vitro proliferation of BMSCs maintaining their stemness	Need to optimize differentiation protocols depending on the source tissue, Biosafety/BMSC senescence/transformation upon Iong-term culture Homing to the damaged tissue is desired, Lack of a commercial GMP licenced BMSC product Optimal route of BMSC delivery must be defined for Individual Indications BMSC purity and optimal dose remain to be specified
Gene therapy	Easy to transfect/transduce BMSCs proliferate extensively in vitro while maintaining their stemness	No clinical data Need for confirming potential transgene silencing Risk of Insertional stage mutagenesis
Enhance engraftment in HSCT	BMSCs are capable of homing to the bone marrow and survive, no risk of rejection due to their hypo immunogenicity, encouraging preliminary preclinical/ clinical data with low toxicity	Allo-BMSCs may mount a T-cell memory response In non-myeloablated hosts logistic/timing Issues In auto-HSCT Lack of a commercial GMP licensed BMSC product Optimal route of BMSC delivery must be defined for Individual Indications BMSC purity and optimal dose remain to be specified
Treatment/ minimize GvHD	Hypo immunogenicity immunomodulatory in nature, encouraging preliminary preclinical/ clinical data with low toxicity	Amount, timing and source of BMSCs are crucial and must be considered Multiple but not Single BMSC infusion may be required Lack of a commercial GMP licensed MSC product Optimal route of M80 delivery must be defined for Individual BMSC purity and optimal dose remain to be specified Indication Potential Increased risk of relapse.

CARRIERS FOR BONE MARROW TARGETING

The main organs for uptake of the Nano-sized materials are the liver and spleen in general. Little attention has been given to the bone marrow though the bone marrow is a part of Mononuclear phagocyte system, because the contribution of the bone marrow for uptake of Nano-sized materials is believed to be small compared with those of the liver and spleen. However, results of several studies have shown that bone marrow is the most important organ for the uptake of nanoparticles that have been modified with specific molecules on their surfaces as presented in table.

Table 2: Proposed drug delivery carriers targeting bone marrow. These carriers based on surface-modified nanoparticles or polymers target bone marrow phagocytes such as macrophages and endothelial cells.

CARRIER TYPE:	TARGETING	TARGETCELL	SPECIES
Liposomes	Passive (reduced size)	Macrophage	Dog
Liposomes	Active (succinic acid lipid) and passive (PEG- DSPE)	Macrophage	Monkey, rabbit, hamster.
Polystyrene microspheres	Active (poloxamer 407)	Endothelial cells	Rabbit
Polymer complex	Active (cationic peptide)	Monocytes, T cell, lineage cells	Mouse
Porous silicon particles	Active (E- selection thioptamer ligand)	Endothelium	Mouse
Nanoparticles of dendritic molecules	Active (guanidinium group)	Osteoclast precursors	In vitro
Branches polypeptides	Active (succinyl group)	Macrophages	In vitro

Liposomes

Liposomes were 1st described by ***Bangham in 1960s*** as self assembled lipid vesicles composed of one or more lipid bilayers. They are microscopic closed vesicles consisting of mainly phospholipid bilayers, surrounding an aqueous medium. Most widely used lipids are phospholipids especially phosphatidylcholine, phosphatidic acid, phosphatidylglycerol, phosphatidylserine, and phosphatidyl ethanolamine.[10,11]

Schettini and co-workers[12] prepared a novel liposomal formulation of meglumine antimoniate, a drug used for treating leishmaniasis, to deliver drug to the bone marrow. The targeting of antimony to the bone marrow was improved approximately 3 fold with the small liposomal formulation compared to large liposomal formulation. These liposomes had no active targeting factor to bone marrow, but the passive targeting of liposomes to the bone marrow was improved by the reduction of vesicles size from 1200nm to 400nm.

The size of the liposomes between 200 to 270 nm is not significant factor for uptake by bone marrow. The liposomes were designed to have high entrapment capacity with the interfacial electrostatic interaction to form a unilamellar membrane. These characteristics are expected to facilitate the application of the bone marrow targeted liposomes as pharmaceutical carriers to bone marrow.

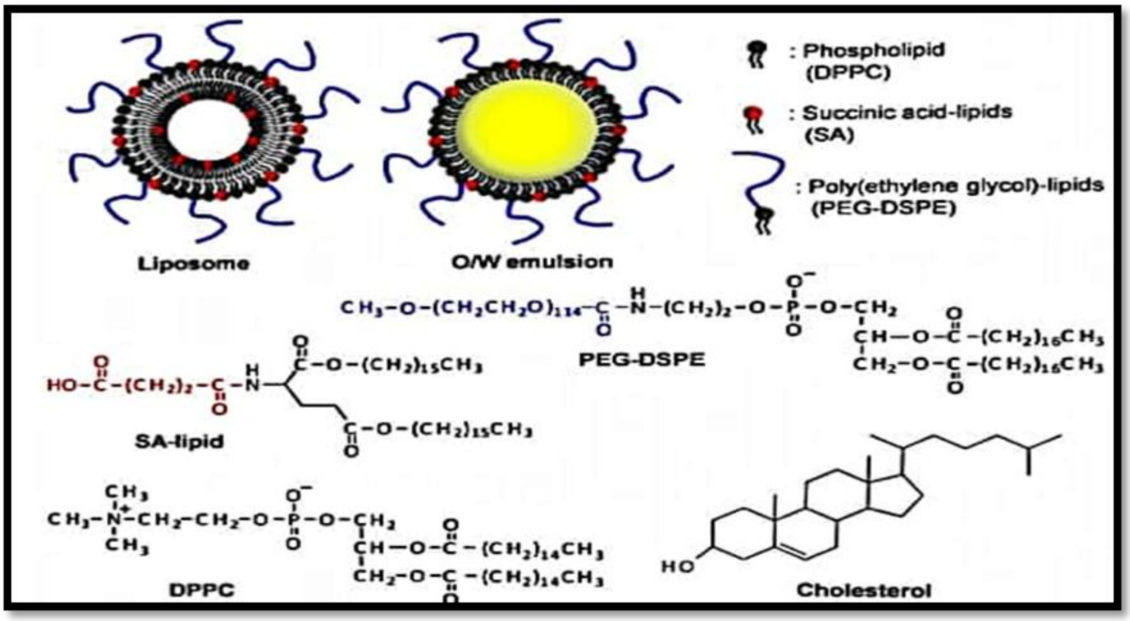

Figure 5: showing Lipid components of bone marrow-targeted lipid-based nanoparticles.

Figure 5 showing that the bone marrow-targeted liposomes comprise lipids of four kinds: 1,2-dipalmitoyl-sn-glycero-3- phosphocholine (DPPC), cholesterol, L-glutamic acid, N-(3-carboxy-1-oxopropyl)1,5-dihexadecyl ester (SA-lipid), and poly(ethylene glycol) (PEG).

The SA-lipid component has been identified as the active factor leading to their phagocytosis by bone marrow phagocytes.[13] The active targeting factor of SA-lipid and passive targeting factor of PEG-DSPE appear to increase the distribution of the liposomes to bone marrow cooperatively.

Polymeric nanoparticles

Regarding engineered colloidal particles, Porter and co-workers observed remarkable accumulation of small colloidal particulates (150 nm and smaller diameter) that were coated by the block co-polymer poloxamer-407, a non-ionic surfactant, in the bone marrow after intravenous administration in rabbits.[14]

Chi and ***co-workers*** prepared dendritic amine and guanidinium group-modified nanoparticles for the delivery of model peptide drug into primary osteoclast precursor cells (bone marrow macrophages).[15] It can be speculated that positively charged guanidinium groups have favourable interactions with negatively charged functional groups in the cell membrane of osteoclast precursors.[16] Physicochemical interaction between a positively charged drug carrier and a negatively charged cell surface can enhance the cellular uptake in cells of various kinds with a negatively charged surface.

Harris and ***co-workers*** studied tissue-specific gene delivery via nanoparticle coating.[17] They prepared cationic nanoparticles with plasmid DNA and then coated their cationic surface with poly anionic poly (glutamic acid)-based peptides with and without cationic insert.

Particles coated with a low 2.5:1 peptide: DNA weight ratio (w/w) form two large micro-sized particles that can facilitate specific gene delivery to the liver in mice. However, the same particles coated at a higher 20:1 peptide with cationic insert: DNA (w/w) form small 200 nm particles that can facilitate specific gene delivery to the spleen and bone marrow.

They have confirmed that the terminal sequence insert, cationic amino acid sequence G-dP-dL-G-dV-dR-G, to the poly(glutamic acid)-based peptides is a critical factor enhancing bone marrow and spleen-specificity of gene delivery in vivo.

E-selectin is an attractive molecular target for active targeting of a drug carrier to bone marrow because E-selectin is expressed selectively on endothelial cells of adult and fatal hematopoietic organs.[18]

It has been suggested that the E-selectin plays a role in the homing of hematopoietic progenitor cells and that its constitutive expression on endothelial cells of hematopoietic organs is necessary in the initial step of the homing process.

Mann and ***co-workers*** confirmed that the thioaptamer ligand selectively binds to E-selectin with Nano molar binding affinity while exhibiting minimal cross reactivity to P-selectin and L-selectin. Recently, they developed porous silicon particles modified with E-selectin thioaptamer ligands to target bone marrow endothelium.[19]

A mice study demonstrated that the accumulation of the porous silicon particles modified with E-selectin thioaptamer ligands in the bone marrow was eight times higher than control porous silicon particles, which were accumulated primarily in the liver and spleen instead of bone marrow.

Moghimi reviewed the clearance mechanism of particulate materials from the circulation by bone marrow.[20] The endothelium of bone marrow sinusoids can remove particles from circulation by both trans cellular and intercellular routes. The intercellular route occurs through the fenestrate in the endothelial wall. Therefore, this mechanism is strongly dependent on the particle size. The intercellular route is a possible pathway to target bone marrow through circulation. Liposomes consisting of DSPC, cholesterol, PEG(5000)-DSPE, and α-tocopherol prepared in various sizes (136–318 nm diameter) have been tested for organ distribution in rabbits. None of these liposomes show a significant accumulation in bone marrow.[21] Therefore, the passive diffusion of nanoparticles from blood circulation to extravascular space through an intercellular route is not an important factor in bone marrow targeting when no active targeting factor exists.

Indeed, based on the proposed drug delivery carrier described above, the surface modification of nanoparticles with specific molecules is a critical factor to achieve bone marrow targeting with nanoparticles, although further study is necessary to ascertain details of its molecular mechanism. Consequently, discovery of receptors specifically expressing in bone marrow tissues facilitates the development of drug carriers targeting bone marrow.

XIV. FUTURE PROSPECTS FOR BONE MARROW TARGETED DRUG CARRIER SYSTEM

- The balance between blood cell production and removal in blood cells of each type is important to maintain the number of circulating blood cells. When blood cell production is suppressed, erythrocytopenia, leukopenia, and thrombocytopenia are induced.

- The blood cell production suppression results from the direct bone marrow dysfunction or indirect factor such as deficiency of the hematopoietic growth factors such as erythropoietin (EPO), granulocyte colony-stimulation factor (G-CSF), and thrombopoietin (TPO). These growth factors function with hematopoietic cells in bone marrow, so that a drug delivery system to target bone marrow can be expected to offer an improved therapeutic system.
- Recently, ***Winkler*** and ***co-workers***[[22] reported that the bone marrow macrophages are pivotal to maintain an endosteal hematopoietic stem cell niche and that the loss of such macrophages engenders the egress of hematopoietic stem cells into the blood.[22]
- Leishmaniasis is an infectious disease caused by a protozoan parasite that is parasitic on resident macrophages. The typical symptoms in leishmaniasis are damage to the spleen and liver, and anaemia by damage to bone marrow.
- Therefore, macrophages in bone marrow as well as in the liver and spleen are target cells in leishmaniasis treatment. Thus several nanoparticles loaded with therapeutic agents such as nanoparticles loaded with amphotericin B.[23,24] PLGA nanoparticles loaded with saponins, lipid nanoparticles loaded with oryzalinhave been developed to deliver the drugs in leishmaniasis-infected macrophages.
- Drug carriers targeting bone marrow, especially bone marrow macrophages, would have a great potential to deliver these therapeutic agents in leishmaniasis-infected macrophages.
- The abnormal increase of cancerous cells such as leukaemia cells, which are immature white blood cells in bone marrow, suppress normal haematopoiesis. Different from a solid cancer, surgical resection is ineffective as a treatment for leukaemia.
- Several pharmaceuticals are available to protect soft tissues from chemotherapy and irradiation. Drug carriers targeting bone marrow offer a promising platform to deliver such pharmaceuticals to bone marrow effectively.

XV. CONCLUSION

Conventional drug delivery to bone marrow is uncontrolled passive diffusion of drugs into bone marrow through blood circulation. The fraction of drugs reaching the target site through such passive diffusion is negligibly small. Bone marrow-targeted drug delivery carriers provide a platform to develop more efficient and safer diagnostic and therapeutic systems. These therapeutic systems can target bone and bone marrow diseases such as rheumatoid arthritis, bone regeneration and repair, bone metastases, osteoporosis, infectious diseases, multiple myeloma, and hematopoietic dysfunction.

REFERENCES

1. S.pvyas, r.kkhar “A text book of targeted and controlled drug delivery system: novel carrier systems, CBS publishers, new delhi, 2002; 562 (intro).
2. About bone marrow (internet), available from https://www.assignmentpoint.com/science/biology/about-bone-marrow.html.
3. *Dean, Laura. “Blood and the Cells It Contains.” Blood Groups and Red Cell Antigens [Internet]., U.S. National Library of Medicine, 1 Jan. 1970,* http://www.ncbi.nlm.nih.gov/books/NBK2263/. *Blood and Bone Marrow Transplant.” National Heart Lung and Blood Institute, U.S. Department of Health and Human Services,* http://www.nhlbi.nih.gov/health/health-topics/topics/bmsct/.
4. Hannah Nicholas “about bone marrow” 15 dec, 2017 available from https://www.medicalnewstoday.com/articles/285666.php#what_is_bone_marrow.
5. Dr. C. C chatterjee “ A text book of human physiology, 11 edition, CBS publishers, 2016; 144-145
6. Park, B; Yoo, KH; Kim, C (December 2015). "Hematopoietic stem cell expansion and generation: the ways to make a breakthrough.". Blood research, 50(4): 194–203.doi:10.5045/br.2015.50.4.194 (physiology)
7. Dr.ananya manual, bone marrow diseases (internet) last updated 29 may 3019, available from https://www.news-medical-net/amp/health/bone-marrow-diseases.
8. Diseases, AAMDS international foundation, available from https://www.aamds.org/diseases
9. Garcia Castro J, trigueros C, madrenas J, perez-simon JA, rodriguez R, menendez P. Mesenchymal stem cells and their use as cell replacement therapy anf disease modelling tool. J cell mol med, 2008; 12: 2552-2565.
10. Adrain JE, poelstrab K, scherphof GL, meijer DKF, reker-smit C, morselt HWM et al. Interaction of targeted liposomes with primary cultures hepatic atate cells: involvement of multiple receptor system. Journal of hepatology, 2006; 44(3): 560-567.
11. Socaciu C, jessel R, diehl RA. Competitive carotenoid and cholesterol incorporation into liposomes: effects on membrane phase transition, fluidity, polarity and ansiotropy. Chemistry and physics of lipids, 2000; 106(1): 79-88.
12. Schettini, DA; riberio, R. R; demicheli, C; rocha, OG; melo, M.N; michalick, MS; frezard,F. Improved targeting of antimony to the bone marrow of dog using liposomes of reduced size. International journal of pharm, 315: 1-2, pp140-147,ISSN 0378-5173.
13. Sou, K.; goins,B; tokeoka, S; tsuchida, E and Phillips, W.T (2007). Selective uptale of surface

modified phospholipid vesicles by bone marrow macrophages in vivo. Biomaterials, 28(16): 2655-2666, ISSN 0142-9612.

14. Porter, CJ; mooghimi, S. M illum, L. And davis, S. S(1992). The polyoxyethylene block copolymer poloxamer 407 selectively redirects Iv injected microspheres to sinusoidal endothelial cells of rabbit bone marrow, FEBS lett, 305(1): 62-66, ISSN 0014-5793.
15. Chi, B.; park, s. J,; M. H.; lee, S. Y and jeong, B. (2010). Oligopepetide delivery carrier for osteoclast precursors. Bioconjung, chem, 21(8): 1473-1478, ISSN: 1043-1802.
16. Rothbard, J. B; jessop, T. C &wnder, P. A (2005). Adaptive translocation: the role of hydrogen bonding and membrane potential in the uptake of guanidium rich transporters into cell. Advanced drug delivery review, 57(4):. 495-504, ISSN 0169-409X.
17. Harris, T. J.; green, J. J.; fung, P. W.; langer, R.; anderson, ad. G &bhatia, S. N (2010). Tissue specific gene delivery via nano particle coating. Biomaterials, 2010; 31(5): 998-1006, ISSN 0142-9612.
18. Schweitzer, K. M.; drager, A.m.; vandervalk, P.; thijsen, S. F.; zevenbergen, A.; theijsmeijer, A. P.; vander shoot, C. E.&langenhuijsen, M. M (1996). Constitutive expression of E- selection and vascular cell adhesion cell molecule-1 on endothelial cells of haematopoietic tissues. Am J pathol, 148(1): 165-175. ISSN 0002- 9440.
19. Mann, A. P.; tanaka, T.; somasunderam, A.; liu, X.,gorenstein D. G., ferrari M. (2011). E- selection targeted porous silicon particle for Nano particle delivery to the bone marrow. Adv mater, 23(36): H278- 282, ISSN 1521- 4095.
20. Moghimi, S. M (1995). Exploiting bone marrow micro vascular structure for drug delivery and future therapies. Advance drug delivery review, 17(12): part 1, pp. 6387- 6392, ISSN 1538-7445.
21. Awasthi, V. D.; garcia, D., goins, B. A &phillips, W.T (2003). Circulation and bio distribution profiles of long circulating PEG liposomes of various sizes in rabbits. International journal of pharm, 253: No. 1-2, pp. 121- 132, ISSN 0378-5173.
22. Wrinkler, I. G., sims, N. A., pettit, A. R., barbier, V., nowlan, B., helwani, F., poultan, I. J., van rooijen, N.,alexander, K. A., raggatt, L. J &levesque, J.p (2010). Bone marrow macrophages maintains haematopoietic stem cells niches and their depletion mobilizes HSC. Blood, 116(23): 4815- 4828, ISSN 1528-0020.
23. Gupta, s. & vyas, S. P (2007). Development and characterizations of amphoterecin B for passive and active macrophages targeting j drug target, 15(3): 206-217, ISSN 1029-351X.
24. Nahar, M., dubey, V.,mishra, D., mishra, P.kdube, A. &jain, N. K (2010). In vitro evaluation of surface fictionalized gelatin nanoparticles for macrophage targeted in the therapy of visceral leishmaniasis. J drug target, 18(2): 93-105.