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Review Article

Resealed Erythrocytes as Drug Carrier Systems

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Abstract

Among the various carriers used for targeting drugs to various body tissues, the cellular carriers meet several criteria desirable in clinical applications, among the most important being biocompatibility of carrier and its degradation products. Leucocytes, platelets,erythrocytes, nanoerythrocytes, hepatocytes, and fibroblasts etc. have been proposed as cellular carrier systems. Among these, the erythrocytes have been the most investigated and have found to possess greater potential in drug delivery. Biopharmaceuticals, therapeutically significant peptides and proteins, nucleic acid-based biological, antigens, anticancer drug and vaccines, are among the recently focused pharmaceuticals for being delivered using carrier erythrocytes**.** Erythrocytes, also known as red blood cells, and have been extensively studied for their potential carrier capabilities for the delivery of drugs. The biocompatibility, nonpathogenicity, non-immunogenicity and biodegradability make them unique and useful carriers. Carrier erythrocytes are prepared by collecting blood sample from the organism of interest and separating erythrocytes from plasma. By using various methods the cells are broken and the drug is entrapped into the erythrocytes, finally they are resealed and the resultant carriers are then called "resealed erythrocytes". So many drugs like aspirin, steroid, cancer drug which having many side effects are reduce by resealed erythrocyte. Current review highlights isolation, drug loading methods, Evaluation methods and applications of resealed erythrocytes for drug delivery.

Keywords: Resealed erythrocytes, Drug carriers, Drug loading, Drug Efficiency

INTRODUCTION

Resealed erythrocytes are most commonly known drug delivery system. Parental route is preferable. Therefore, it is parental control release formulation. which it is used as potential carrier capacity and ability to deliver the drug and drug loaded microspheres. Such drug-loaded erythrocytes are used for the treatment of various diseases or disorders, which are not cured by general therapy, hence it is called carriers. It is prepared simply by collect the blood samples from the different organism, which you have selected, separates erythrocytes from plasma by centrifugation technique, entrapping the drug in the broken erythrocytes and resealed [1]. Therefore, it is called resealed erythrocytes. Used for carrying the drug. Blood contains different cells like erythrocytes (RBC), leucocytes (WBC) and platelets; among them erythrocytes are the most interested and present in bulk quantity. This carrier posse's great potential in drug delivery due to their significance to circulate throughout the body. The properties such as zero order kinetics, reproducibility and ease of preparation primary cause for the development of this drug delivery system is to maximize therapeutic activity and to reduce the undesirable adverse effects of drug as well as increase patient compliance. Generally the drug has to be administered in large quantities, to show the required pharmacological action due to some amount of drug which is wasted in normal tissues. Ideally, a "perfect" drug should exert its therapeutic action only at the target site, using the lowest concentration as possible and without negative effects on non-target compartments. The delivery systems currently available enlist carriers that are either simple, soluble macromolecules (such as monoclonal antibodies, soluble synthetic polymers, polysaccharides and particulate biodegradable polymers) or more complex multicomponent structures (microcapsules, Microparticles, cells, cell ghosts, lipoproteins, liposomes, erythrocytes).The process is

based on theresponse of these cells under osmotic conditions [2].

Erythrocytes: Erythrocytes are the most common blood cell. It is biodegradable and biocompatible in nature. In vertebrate organisms the delivering oxygen (O2) to the body tissues through the blood flow by the circulatory system. They are produced in bone marrow and life span is around 120 days and shed in spleen, recycled by macrophages. The duration of circulation is 20 seconds. It can be loaded with a variety of chemically and biologically active compounds using various chemical and physical method. It was derived from two words like **Erythro** = red and **cytes**= cell erythrocyte is red cell. Erythrocytes is enucleated Filled with haemoglobin (Hb), a protein that functions in gas transport. It contains the plasma protein **spectrin.**

Healthy adult male= 4.5millions/ml
Healthy adult female= 4.8million/ ml
Immature RBC is called "**RETICULOCYES** "

General Anatomy, physiology and of RBCs: Erythrocytes have shapes biconcave discs with a diameter of 7.8 μm and thickness near 2.2 μm. Mature RBCs have a simple structure, elastic in nature [3]. Their plasma membrane is strong and flexible, which allows them to release the drug without rupturing as they squeeze through narrow capillaries. RBCs lack a nucleus, other organelles and can neither reproduce nor carry on extensive metabolic activities. Mature RBCs have no nucleus, total space is available for O2transport.The biconcave shape is provides large surface area for transport of oxygen to tissueses and organs. The red blood cell membrane is a dynamic, semi permeable components of the cell, associated with energy.

Metabolism of the drug is maintained by the permeability characteristic of the cellular parts of various cations (Na+, K++) andanions (Cl- HCO3). The components of RBC contains erythrocytes include water (63%), lipids (0.5), glucose (0.8%), mineral (0.7%), non-hemoglobin protein (0.9%), methyl hemoglobin (0.5%), and hemoglobin (33.67%) is about 280 millions.

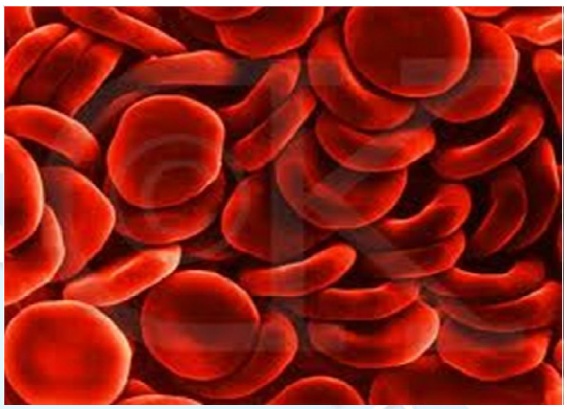


Figure No: 1 Shape of Erythrocytes

Source and isolation of erythrocytes: Erythrocytes are obtained from mammalian blood, have been used for drug delivery, other organisms are including mice, cattle, dogs, sheep, goats, monkeys, chicken, rats, pigs, and rabbits. Blood is collected in heparinised tubes by venipuncture for isolation of erythrocytes. For encapsulation, fresh whole blood is used. The blood that is collected and immediately chilled to 4°C and stored for less than two days [4]. The erythrocytes are then harvested and washed by centrifugation. The washed cells are suspended in buffer solutions at various hematocrit values as desired and are often stored in acid–citrate–dextrose buffer at 4_C for as long as 48 h before use. Jain and Vyas have described a well-established protocol for the isolation of erythrocytes

***Properties of resealed erythrocyte*[5]**

1) The drug should be made as release controlled manner at target site.
2) The loaded erythrocytes should be compatible with natural erythrocytes such as appropriate size, shape and should permit the passage through capillaries. In addition, Minimum leakage of drug should take place.
3) It should not produce harm to body tissues.
4) It should have the ability to carry a broad spectrum and potent drug.
5) It should possess specific physicochemical properties by which desired target size could be recognized.
6) The degradation product of the carriers system, after release of the drug at the
Selected site should be biocompatible. It should be physic -chemically compatible with drug.
7) The carrier system should have an appreciable

stability during centrifugation.

ADVANTAGE [6]

1. Biocompatible, particularly when autonomous or homologous cells are used hence no possibility of triggered immune response storage.
2. The compounds are easily biodegradable after showing its therapeutic action with no generation of toxic products.
3. The shape and size of the resealed cells are similar and uniform as normal cells. It makes the drug to easy movement.
4. The prepared cells are inert intracellular and does not interact with other tissues.
5. Isolation, Selection and drug loading is easy in REDD.
6. The drug can be activated and Prevention of degradation by endogenous enzymes.
7. Different types of drugs Entrapment can be possible.
8. Entrapment of drug can be occurring without chemical modification of the substance to be entrapped.
9. It is one of the targeted drug delivery system. It is parental controlled release formulation.
10. It follows zero-order kinetics of drug release.
11. Due to long time circulation of drug in systemic circulation maintained the release of drug in Prolong period.

DISADVANTAGES [7]

1. Resealed erythrocytes have limited potential and carring capacity is there.
2. If the combination drugs are used Possibility of mixing of drug as well as dumping of large amount of drug at target site.
3. It destroy the other erythrocytes by stimulation of our immune system

Basic Requirement for encapsulation [8]***:-***

- The compounds which are showing therapeutic action (5000-60,000 daltons) can be entraped or loaded in erythrocytes.
- Non- polar molecules may be entrapped in the form of salts. Example : tetracycline HCl salt can be appreciably entrapped in bovine Red Blood Erythrocytes.
- The compounds have either polar or non – polar molecules can loaded in erythrocytes.
- Some molecules are hydrophobic in nature there are loaded by absorbing over the molecules.
- Charged molecules are stable long period of time when compared to uncharged molecule.
- The size of the drug molecule is significantly larger than B – galactosidase .

Methods of drug loading in erythrocytes [9]

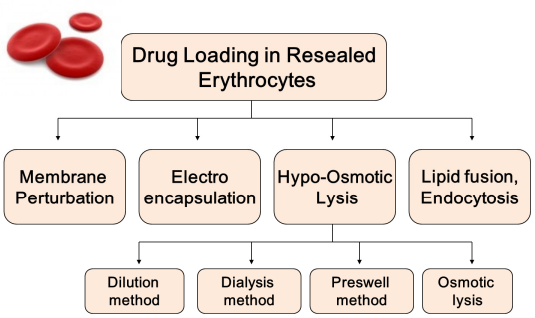


Figure Number: 2 methods of drug loading in erythrocytes

Hypo- osmosis lysis method: The intra and extra cellular concentrations of the drug in RBCs will be varied with by using osmotic pressure at last they get exchanged in osmotic lysis method.

Hypotonic dilution: In this preparation, The already prepared ,packed and stored resealed erythrocytes is diluted as different concentrations by using 2-20 ml of distilled water drug, the tonicity get maintained by adding a hypertonic buffer having similar P^H finally the mixture is washed by the application of centrifugal force.

Hypotonic Dialysis method: Klibansky in 1959 and used in 1977, Deloach, Ihler and Dale are explained about the loading of enzymes and lipids. Where, erythrocytes buffered suspension was prepared in different haematocrit value is between 70-80 and immersed in 10-20 volumes of hypotonic buffer and shake the medium slowly at 2 hrs. Determine the rate of drug release by placing the packed erythrocytes

Hypotonic Pre swelling method: This method was developed by Rechsteiner in 1975 and was modified for drug loading. This method is based on the principal of swelling of erythrocytes without lysis or breakdown of cell when it placed in hypotonic solution. Apply the low centrifugal forces to swelled

cells. It make the compound homologues to the cell matrix. Where the damages of other tissues are quietly reduces. E.g :propranolol, asparginase , cyclophosphamide, insulin metronidazole etc.

Isotonic osmotic lysis method: This method was reported by Schrier et al in 1975. This method is also called as osmotic pulse method. Physical and chemical methods are used to isotonic haemolysis. (urea solution, polyethylene glycol, and ammonium chloride) . The drug is loaded into the erythrocytes by diffusion method on the principle of concentration gradient. It occur un till the equilibrium is maintained. As like suspend the erythrocytes in an isotonic solution of dimethyl sulfoxide (DMSO) . After the cells were separated, they were sealed at- 37°C.

Electro-insertion or Electro encapsulation method: Its also known as electroporation, Wher the electrical shock brings about irreversible changes in an erythrocyte membrane also called as electroporation. In this process the form the pore on the erythrocytes and entrap the drug into the erythrocytes. This pore can be resealed by placing under incubator at 37°C in isotonic medium. The various chemical encapsulated into the erythrocytes are primaquin and 8- amino quinolone, vinblastin, chloropromazine and related phenothiazine, propanolol, tetracaine and vitamin A.

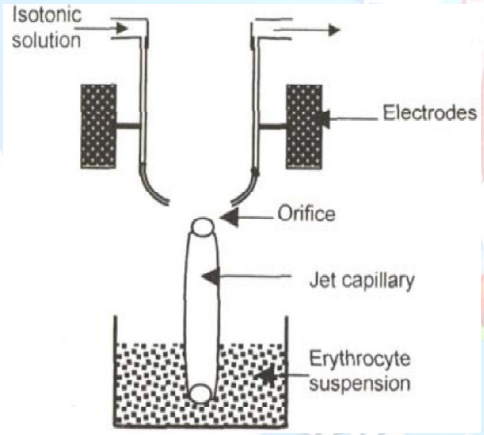


Figure No: 3 Electro encapsulation method

ENTRAPMENT ENDOCYTOSIS: It is explained Schrier in 1975. Where the resealed erythrocytes are washed by using 9ml buffer solution contains 2.5MM ATP, 2.5MM mgcl2 and 1MM $CaCl_2$. sealed by incubation for 2 minute at room temperature with 154MM of NaCl Several chemicals are primaquine and related 8- aminoquinoline, vinblastin, chlorpromazine, and related phenothiazines, hydrocortisone, tetracaine and vitamin A entrapped in cells[10].

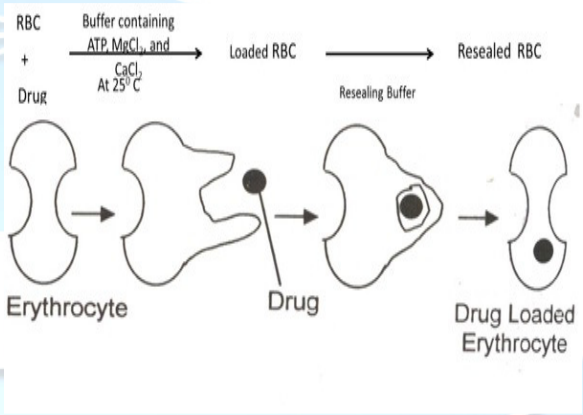


Figure No: 4 Entrapment endocytosis

Chemical perturbation of the membrane: This method of preparation, the permeability of the membrane is increased by application of chemicals such as polyene antibiotic such as amphotericin B in1980.It is majorly applicable in anti cancerdrugs such as daunorubicin in mices or mouse erythrocytes. This may induce irreversible destructive changes in the cell membrane [11].

Lipid fusion method: Where the drug can enclosed in lipids. It can be directly fused to human erythrocytes, It is useful in entrapment of 161 drugs. The drugs such as inositol monophasphte used to improve the oxygen carrying capacity of cells and entrapment efficiency [12].

Loading by electric cell fusion: It is similar to nanoerythrosomes. Where the drug is loaded in erythrocytes ghosts. By adhesion with the target organ. Electrical pulse is applied due to fusion [13].

Use of red cell loader: It is implemented due to improve non diffusible materials. They developed a piece of equipment called a "red cell loader". With as little as 50 ml of a blood sample, different biologically active compounds were entrapped into erythrocytes within a period of 2 hrs at room temperature under blood banking conditions.

Mechanism of actions [14]:

The various mechanisms are proposed in drug release

- Passive diffusion.
- Specified membrane associated carrier transport.
- Phagocytosis of releasd cells by macrophages of RES , subsequent accumulation of drug in macrophages interior , slow release of drug.

Accumulation of drug in lymph nodes upon subcutaneous administration followed by haemolysis to drug release.

Resealed erythrocytes

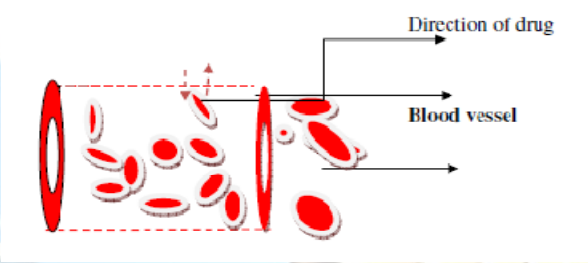
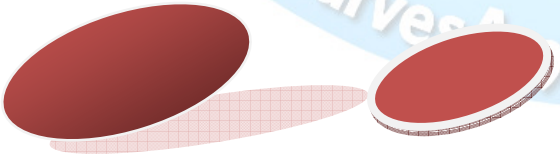


Figure NO: 5 Brane Passive diffusion of drug in cell membrane

EVALUATION OF RESEALED ERYTHROCYTES: After loading of therapeutic agent on erythrocytes, the carrier cells are exposed tophysical, cellular as well as biological evaluations [15].

Shape and Surface Morphology: The morphological characters such as sizesurface area and shape of erythrocytes are must be similar to the normal erythrocytes.Themorphological characterization of erythrocytesis undertaken by comparison with untreatederythrocytes by the process such as transmission electron microscopy (TEM)or Scanning electron microscopy (SEM). Other methods are also used such as like phase contrast microscopy can also be used.



Normal RBCs **resealed RBCs**

2. Drug Content: Drug content of the cells determines the entrapment efficiency of the cells. Whereof packed, loaded cells (0.5 mL) with 2.0 mL acetonitrile and centrifugation at 2500 rpm for 10 min. The process involves de proteinization The clear supernatant is analyzed for the drug content by spectrophotometrically.

3. Cell Counting and Cell Recovery: It was used to count the number cells are present in unit volume of the blood. Now days the automated machines are used to determine or count the number of cells are intact with in cubic mm of blood. They are collected and packed with drug [16].

4. Turbulence Fragility: It is determined by the passage of RBCs in small blood vessels for e.g: suspension passed through needles with smaller internal diameter was about 30 gauges and vigorously shaking the suspension. From these, the release of haemoglobin and drug can be determined [17].

5. Erythrocyte sedimentation rate (ESR): From these we estimate the suspension stability of RBC in plasma and determine the number and size of the red blood cells and concentration of plasma protein, such as fibrinogen and α, β globulins. Rate of sedimentation can be determined in standard tube. Normal blood ESR is 0 to 15 mm/hr. higher rate is indication of active but obscure disease processes.

6. Determination of entrapped magnetite: Atomic absorption spectroscopic method is used for estimate the concentration of particular metal ions in the sample. Then add small amount of HCl to a fixed amount of magnetite bearing erythrocytes and content were heated at 600^{0}C for 2 hours, and add 20 %w/v tri chloro acetic acid and supernatant liquid is obtained by the application of centrifugal forces. From these liquid we estimate the metal ion concentration by using Atomic absorption spectroscopy [18].

7. In vitro stability: The stability of the loaded erythrocytes is assessed by means of the incubation of the loaded erythrocytes in the autoclave with plasma or iso osmotic buffer, having different haematocrit values is between0.5% and 5% at temperatures of 40^{0}C and 37^{0}C.

8. Haemoglobin release: The content of haemoglo-

bin from the erythrocytes may be eliminated or removed by the alterations in the permeability of the membrane of the RBCs during the entrapment procedure. From these, the relationship between the rate of haemoglobin and rate of drug release of the substance encapsulated from the erythrocytes. The haemoglobin or drug leakage is tested using a red blood cell suspension by recording absorbance of supernatant at 540nm on a UV/ visible spectrophotometer [19].

9. In-vitro drug release and Hb content: The 5% cell suspensions were stored at 40^0Cand placed in ambered colour glass container. Supernant liquid was cleared by using a hypodermic syringe equipped with filters having pore size 0.45, If any proteins are present can be de proteined by using methanol and were estimated for entrapment efficacy. The supernatant liquid was collected from each sample after centrifugation assayed it, calculate the %Hb release by using formula, **% Hb release=A540**

10. Osmotic shock: In osmotic shock studies, 1 ml erythrocytes suspension (10%) was diluted with distilled water (5 ml) and placed in centrifuge at 300 rpm for 15 minutes. It forms two layers. The supernant liquid (plasma) was separated and sediment layer(serum) was used to estimate for the % haemoglobin release analytically [19].

Route of administration: Intra peritoneal injection administered through I.V injection. As results 25% of resealed cell remained in circulation for 14 days. The extra vascular targeting of RBCs to peritoneal macrophages. Subcutaneous route for slow release of entrapped agents. They results the loaded cell released encapsulated molecules at the injection site.

Applications of resealed erythrocytes [20]:

In Vitro Applications: RES are used for in vitro test to study the loading of enzymes. The enzymes content within carrier could be visualized with the help of cyto chemical technique. Where commonly studied about the mediated microinjection. A protein or nucleic acid to be injected into eukaryotic cells by fusion process, they immediately diffuse throughout the cytoplasm. Antibody RBC auto injected into living cells have been used to confirm the site of action of fragment of diphtheria toxin.

In Vivo Application

This includes the following

1) Slow drug release: Erythrocytes are used for sustained release drug delivery system contain circulating depots and incorporate drugs such as antineoplastics, antiparasitics, veterinary antiamoebics, vitamins, steroids, antibiotics, and cardiovascular drugs [20].

2) Drug targeting: It is site specific and target oriented to show the maximum therapeutic activity with less side effects. Resealed erythrocytes can act as drug carriers and targeting tools as well as Surface modified erythrocytes [20].

3) Targeting reticulo endothelial system organs: The reticulo endothelial system, the changes in reticulo endothelial membrane are recognized by macrophages. In Surface modification system the erythrocytes are used to target organs of mononuclear phagocytes systems the various approaches are, Surface modification coatingof loaded erythrocytes by antiRh or other types of antibodies. Surface modification with glutaraldehyde. Surface modification with sulphydryl. Surface chemical crosslinking. Surface modification with carbohydrates [20].

4) Targeting the liver-deficiency/therapy: Many metabolic disorders related to deficientor missing enzymes can be treated by injecting these enzymes. It is applicable only for shorter half- life enzymes. Allergic reactions, and toxic manifestation, P- glucoronidase and P-galactosidase. e.g: The disease caused by an occurs due to accumulation of gluco cerebrosidaes in the liver and spleen can be treated by gluco cerebrosidase loaded erythrocytes.

5) Treatment of parasitic disease: The ability of resealed erythrocytes to selectively accumulate with in RES organs make them useful tool during the delivery of anti parasitic agents. Where the studies involved in animal models for erythrocytes loaded with anti malarial, anti leishmanial and anti amoebic drugs.

6) Removal toxic agents: The inhibition of nitrile intoxication with murine carrier erythrocyte containing bovine rhodanase and sodium thio sulphate Cannon *et al* .introduced by Antagonization of organo phosphorus intoxication by released erythro-

cyte containing a recombinate phosphodiestrase also has been reported.

7) Treatment of hepatic tumours: Antineoplastic drugs such as methotrexate (MTX), bleomycin, asparginase and adiramycin have been successfully deliveredby erythrocytes. E.g. in a study, the MTX showed preferable drug targeting toliver a among them lungs, kidney and spleen.

8) Delivery of antiviral agents: Several reports have been cited in the antiviral agents entrapped in resealed erythrocytes for effective delivery and targeting. Because most antiviral drugs arenucleotides or nucleoside and their analogues for entrapment.

9) Enzyme therapy: Many metabolic disorders related to deficient or missing enzymes can be treated by administering these enzymes as resealed erythrocytes.

E.g: βGlycoside, βglucouronidase, βgalactosidase.

10) Removal of RES iron overloads: Desferrioxamine loaded erythrocytes have been used to treat excess depots because of multiple transfusions to thalassemia patients. By targeting this drug to the RES is very beneficial because the age erythrocytes are destroyed in RES organs,which results in an accumulation of iron in these organs.

11) Targeting Non RES: Erythrocytes loaded with drugs have also beenused to target organs outside the RES. The various approaches for targeting non - RESorgans include:

- Entrapment of paramagnetic particles alongwith the drug.
- Entrapment of photosensitive material.
- Use of ultrasound waves.
- Antibody attachment to erythrocytes membrane to get specificity of action.

Other approaches include fusion with liposome, pectin pre treatment of resealed cells etc. ***Recent developments:- Nanoerythrosomes:*** Nanoerythrosomes are similar to the resealed erythrocytes. Where the vesicles are prepared by the squeeze out of the RBC ghosts, the average diameter of these vesicles being 100nm. The process where small vesicles have size of a liposomes. These spheroid particles were named 'nanoerythrosomes' and appear to be stable and maintain both the cytotoxic and antineoplastic activity of daunorubicin against mice leukaemia P338D cells.

Other: Significantly the use of erythrocyte for specific targeting to cells of the immune system. Several laboratory techniques have developed for the encapsulation of allosteric effector of haemoglobin, inositol , hexaphosphate, which are effective at oxygen delivery, much more effective than normal erythrocytes.

CONCLUSION: During the past ten year, the resealed erythrocytes have various applications have been introduced about the use of resealed erythrocytes as a drug carrier , replacement of missing enzymes during therapy etc. Until other carrier systems depends upon the age as well as immune system. Resealed erythrocytes technology will play an active role in further research. It is economically have more applications as carrier. Europe by a recently develop the company that is make the products for human use. In near future, erythrocytes based delivery system with their ability to provide controlled and site specific drug delivery will revolutionize disease management. The International Society for the use of Resealed Erythrocytes (ISURE) is conduct the biannual meetings and complete information regarding drug usage. It is an excellent plat form for exchange of information to the scientist in this exciting and rewarding field of research.

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