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CURE FOR SICKLE CELL ANEMIA -USING THE CONCEPT OF NANOCAR

[1]NAGARAJAN C, VISHNU KALYAN GOUTHAM [2] & SRI. ONKARA PERUMAL P[3]

[1,]Department of Physics and Nanotechnology, SRM University

[2],Department of Chemical Engineering, NIT Warangal

[s3,]Department of Biotechnology, NIT Warangal

Abstract

Nanocars - complex molecules measuring 3-4 nanometers long and thinner then DNA, contain four wheels attached to two axles. The nanocars would act like enzymes for industrial application. α Spectrin is an actin cross linking and molecular scaffold protein having receptors for NF- γ and GATA -2, so the factors bind to these receptors that links the plasma membrane to the actin cytoskeleton giving defenite cell shape. Mutations results in a variety of hereditary red blood cell disorders. Fetal hemoglobin can't take on the dysfunctional sickle shape as there is a competition for transcription factors NF-γ and GATA-2. So If we can increase NF- γ and GATA -2, maybe both the beta and gamma genes will be activated without one suppressing the other. Nanocar molecules would be given intravenously in the form of injections as drugs having the inducer attached to it. With the help of individual and combinatorial deletions of GATA -2 and NF- γ, we can pin-point the particular transcription factors with the respective position on α Spectrin gene. These factors would assist RNA polymerase. As a result normal Hb and fetal Hb would not compete for factors together and the higher affinity of fetal Hb towards oxygen would make its expression higher. Sickle cell anaemia would then turn assymptomatic.

Keywords: Nanocars, GATA - 2, NF- γ

I. Introduction

Nanotechnology is the Science of creating or modifying materials at atomic or molecular level to develop new or enhanced products and this is where Nanocar comes into the limelight. The discovery of Nanocar took almost eight years. What we propose is to elicit a higher positive response from the immunologically sensitive cells suffering from Sickel cell anemia. Nanocar would help to bring about the above transformation.

1.1 What is Nanocar

The necessary structural elements are: four Ferric wheels, two staffenes, graphitic sheets and a reinforcing element - buckytubes. These are Complex molecules measuring 3-4 nm long containing four wheels. Each wheel is a Bucky ball containing 60 Carbon atoms. The nanocar consists of a rigid chassis and four alkyne axles that spin freely and swivel independently of one another. Palladium acts as a catalyst in attaching Bucky ball to the rest of the car. They are about the same width as a strand of DNA, but much shorter than DNA. The idea behind the research is to create molecules that will act as tools in the chemical reactions.

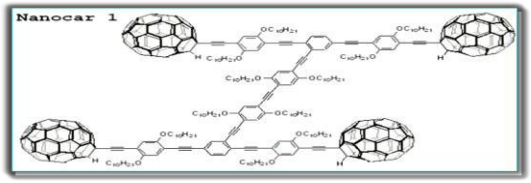

Fig 1 shows the Nanocar molecule with "Bucky balls".

1.2 Events Leading To the Discovery of Nanocar

1.2.1. Nanoputians : These are a series of organic small molecules whose structural formula appear human like in appearance. James Tour (in 2003) used this compound as a part of sequence of chemical reactions for the students. Compound consist of two benzene rings connected via a few a carbon atoms as the body, four acetylene units each carrying an alkyl group at each end which represents hands and legs and ring as head.

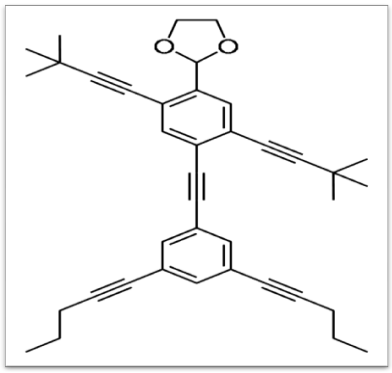

Fig 2 shows the Nanokid molecule resembling a human figure in appearance.

1.2.2. Molecular Propeller

Molecules that can propel fluids when rotated due to its spherical shape is designed in analogy to macroscopic propellers having several molecular scale based attached at certain pitch angle around shaft"s circumfe rence. Blade is formed by planar aromatic molecules and shaft is Carbon nanotube. Pumping depend on interface between blades and liquid. If hydrophobic blades, then water does not stick to it due to little bond polarity and propellers can pump well.

1.2.3. Bucky Ball

Fullerenes are a class of closed, hollow carbon compounds that comprise only the third form of pure carbon ever discovered. The most remarkable of the fullerenes is the 60-carbon alkenes "Buckminsterfullerene", also known as a Bucky ball Molecules made up of 60 carbon atoms arranged in a series of interlocking hexagons and pentagons, forming a structure that looks similar to a soccer ball. The buckyball, being the roundest of round molecules, is also quite resistant to high speed collisions.

1.3. What Is Sickle Cell Anemia?

Sickle cell disease (also called as Depranocytosis) is an inherited disorder in which red blood cells (RBCs) are abnormally shaped. This abnormality can result in painful episodes, serious infections, chronic anemia, and damage to body organs. These complications can, however, vary from person to person depending on the type of sickle cell disease each has. Some people are relatively healthy and others are hospitalized frequently. The disease being – a point mutation disorder (autosomal recessive genetic disorder) is most commonly caused by the haemoglobin variant Hb S in which variant, hydrophobic amino acid valine takes the place of hydrophilic glutamic acid at the sixth amino acid position. It therefore diminishes the protein solubility. Clumping occurs because substitution creates hydrophobic spot outside the protein structure that sticks to the hydrophobic region of an adjacent Hb"s molecule β chain. Common symptoms include frequent fatigue, pain, acute chest pain and strokes. The reason for the above symptoms is impaired Oxygen delivery of Red Blood Cells.

1.4. Haemoglobin

Fetal Hemoglobin: due to presence of gamma chain (γ chain) it has higher affinity for oxygen; this is evident from Bohr"s Dissociation curve. Mutation in αspectrin gene results in dysfunctional shape of red blood cells. Fetal Hb cannot take the dysfunctional shape. For the initial six months the baby retrieves oxygen from mother"s blood. At birth, fetal hemoglobin comprises 50-95% of the child's hemoglobin. These levels decline after six months as adult hemoglobin synthesis is activated while fetal hemoglobin synthesis is deactivated. Soon After, adult hemoglobin takes over as the predominant form of hemoglobin in normal children.

1.4.2 . Adult Hemoglobin: It has low affinity for oxygen as compared to fetal hemoglobin due to the presence of β chain. Shortly after birth, babies start producing adult hemoglobin, which gets oxygen from their own, newly functioning lungs. When the level of one increases, that of other decreases .

1.5 : Involvement Of A Spectrin Gene And Certain Transcription Factors

1.5.1. α Spectrin is an actin-cross linking and molecular scaffold protein that links the plasma membrane to the actin. Cytoskeleton and functions in the determination of cell shape, arrangement of transmembrane proteins, and organization of organelles .Mutations in this gene result in a variety of hereditary red blood cell disorders. α spectrin gene has receptors for transcriptional factors such as GATA -2 and NF γ.

FACTORS	CLASS	BINDING SITE	REQUIREMENT
GATA 1	GATA	(A/T)GATA(A/G)	ERYTHROID
GATA 2	GATA	(A/T)GATA(A/G)	PRPROGENITORS
IKAROS	C2H2 ZINC	GGGAAT	LYMPHOID
p45 NF-E2	b-zip CNC like	(C/T)GCTGA(G/C)TCA(C/T)	DEF.PROGENITOR

Table 1 showing some of the transcriptional factors and their class and function

1.5.2. Fig 1 gives the details of some transcriptional factors involved in Cell Lineage.GATA -2 and NF-γ are our prime focus because these bind to the α spectrin gene receptors .Once these are activated it results in activation of beta and globin genes. Receptors should have a high Signal to Noise ratio.

1.5.3. ERV-9(Human Endogenous Retrovirus) on other hand, currently viewed as junk DNA in the body, performs a critical function in ensuring adult hemoglobin production gets the lion's share of the transcription factors after birth. There are fifty copy of ERV-9 in humans

2. Methodology

In addition to doping Bucky balls with other atoms, the hollow structure of the geodesic molecules makes it possible to trap atoms inside them like a molecular cage. This strange capability of Bucky balls has caught the attention of the medical community. Indeed, many researchers believe that eventually Bucky balls may be used to deliver medicines to specific tissues and cells. Nanocar molecules would thus be injected intravenously containing inducers, enhancers, and co-factor molecules (like FOG-2 for GATA-2) attached at the axial region. Drug basically binds to the „hot spots" on protein surfaces. Single Molecule Fluorescence Imaging, can be used to investigate the translational motion of molecular .Experiments were performed in which nanocar was made to travel on heated gold surfaces (200^0 temperature). Nanocar moved back and forth and was able to roll because fullerenes wheel is tilted to alkynes axial through a Carbon-Carbon single bond. It has been confirmed that the nanocar doesn"t actually slip, it in fact rolls. Results of Scanelling Tunneling Microscope are a proof to the above fact that molecule attach via fullerenes on gold. Combinatorial and individual deletions are performed .Molecular fragments are made to interact with each other before actual experimental trials, removing weak and noisy fragments; so promising ones are left. Activity of GATA-2 and NF-γ is seen at each case. Nanocar molecules would actually express the required transcriptional factors because enhancers and inducers are attached to it for the purpose. Fig 3 shows binding of nanocar. These factors would in turn combine with the receptors for αSpectrin gene. If our hypothesis is correct and the fetal and adult genes are actually competing for NF-Y and GATA-2, what would happen if there is a bigger supply of these transcription factors? "If we can increase NF-Y and GATA-2 so there is plenty around, maybe both the beta and gamma genes will be activated without one suppressing the other. These factors would assist RNA polymerase in initiating transcription. As a result normal Hb and fetal Hb would not compete for factors together. So the beta and globin genes would be e

xpressed and the higher affinity of fetal Hb towards oxygen would make its expression higher. The entire process would be actually tailor made process

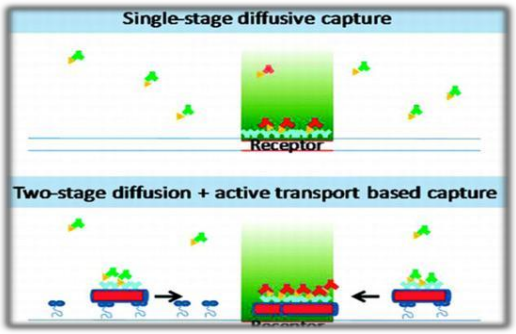

Fig 3 Example of how the nanocar would bind to the receptor site.

1.6. Hydroxyurea-Commonly Used Drug To Cure Sickle Cell Anemia

Hydro xyurea is a chemotherapy agent with potent effects on the bone marrow. The agent was used for many years to treat people with certain malignancies before being used for sickle cell disease. DROXIA ® (hydroxyurea capsules, USP) is available for oral use as capsules. The precise mechanism by which hydroxyurea produces it"s cytotoxic and cytoreductive effects is not known. However, various studies support the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. Fetal hemoglobin levels rise in many patients treated with hydroxyurea, but the response is variable. Other Limiting effects are platelet count of less than 80,000,.neutrophil count (not white count) of less than 2,500 ,hemoglobin of less than

6 g/dl,hair loss, GI upset, rash. The MCV (Mean Cell Volume) rises in many patients treated with hydroxyurea

but the response varies significantly between patients, making it unreliable as a measure of hydro xyurea efficacy or patient compliance with the drug. One of the most difficult issues with hydroxyurea is use in children. Only people 18 years and older can use the drug since the drug blocks cells division.

3. Results

As a result normal Hb and fetal Hb would not compete for factors together, so the beta and globin genes would be expressed and the higher affinity of fetal Hb towards oxygen would make its expression higher. A level of 25% fetal Hb is sufficient to cause it asymptomatic. Normally its level in Sickle Cell patients is 1-2

%. So its symptoms would not be expressed, thereby turning sickle cell anaemia asympto matic. It seems to be a enormous potential for the delivery of cheap and more effective vaccinations in the developing world.Ultimate aim of building machines from bottom up is much the same way as proteins are build to carry task in nature. A greater amount of research still needs to be done on this subject.

4. Future Impact

Work is in progress to develop "NANODRAGSTER" which is 50,000 times thinner than human hair and has six carbon atoms in rear-wheels. Bucky balls would be replaced by Carboranes. It will be like tank with treads. It would be a new step- from Point A to Point B. The technology can be used in manufacturing computer circuits and electronic components, or in conjunction with pharmaceuticals inside the human body, which can treat a large number of fatal diseases. It would be a great boost to nanobiotechnology and especially to the field of human health.

5. Conclusion

Sickle cell anemia would turn asymptomatic .Nanocar therefore can serve as a constructive vehicle in bringing about the transformation. They have enormous potential for the delivery of cheap and more effective vaccinations in the developing world.

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