Biological Navigators and Nanorobot Red Cells: Characterization and Applications

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ABSTRACT

In human body, nanorobot-like red blood cells get exposed to human body fluids and many physico-chemical changes inside while these nanorobots (fullerene structure coated hemoglobin embedded iron inorganic elements) remain safe and perform killer action against bacteria or virus. We propose this killer action as 'nanorobot driven nanomedical treatment' to combat a bacterial or viral infection. The red cells also act as imaging agent due to oxygen binding character. Our experiments were focused on the application of nanorobot (red cells) to make them immune resistant against viruses and making them as useful contrast agents in magnetic resonance imaging use based on their behavior in nanomagnetic fields. It consists of an injection of perhaps a few cubic centimeters of nano-sized nanorobots suspended in specific pH fluid (probably a water/saline suspension). The typical therapeutic concentration was up to 1-10 trillion (1 trillion = 1012) individual nanorobots, although in some cases treatment only require a few million or a few billion individual nanodevice-like red cells to be injected. Each nanorobot cell was on the order of perhaps 0.2 micron up to perhaps 0.3 microns in diameter e.g. artificial mechanical red cell floating along in the bloodstream. Nanorobots intended to travel through the bloodstream to their target will probably be 500-3000 nanometers. New technology of 'passive diamond exteriors' may turn out to be ideal to make immunoresistant nanorobot red cells against opsonization. Since nanorobot red cells metabolize local glucose and oxygen for energy, they are potential contrast agents for 13C-MRI, ultrasound imaging and fMRI. We believe the near possibility of travelling nanorobot carrier cells holding nanocomputer CPU working at the rate of 10 teraflops (1013 floating-point operations per second) as nanomedicine robot devices. Nanorobot red cells in medical applications may be used in the form of red cells coated with diamond or diamondoid/fullerene nanocomposites in presence of inorganic elements like hydrogen, sulfur, oxygen, nitrogen, fluorine, silicon etc. for special purpose in nanoscale gears.

Keywords: nanorobot, red cells, imaging

1 INTRODUCTION

Red blood cells in the human body serve as oxygen carrier. They are only cells with capability of respiration due to the fact that hemoglobin a red iron rich pigment serves this oxygen carrying load. Hemoglobin is carrier of genetic information with active glucose metabolism as a result it acts as main bullwork to keep organs with constatnt supply of energy every moment. Mainly neurons in brain and cardiac muscles in heart and nephrons in kidneys, hepatocytes in liver are major targets of red blood cell activity.

In recent years, they have been named based on their function as nanorobots, respirocytes, nanomissiles etc. mainly to emphasize their urgent need at the target. Because of their immediate effect on oxygen supply to organs we intend to call them as 'nanonavigators' simply because of their function in navigation of distant organ function. In this direction, blood oxygen level dependent (BOLD signal by MRI due to red cells) is an example to know the neuroactivation in brain and thought process.

Nanonavigation and robotics have played significant role in perfecting the red blood chemical sensing and physical sensing based on iron content seated in center of red cells.

2 RBC AS NAVIGATORS ACTING AS NANOROBOTS

In human body, red blood cells commonly known as RBC, play a major role in the body by two ways:

1. RBC in blood oxygenation and hemoglobin reduction-oxidation reactions: Blood oxygenation is linked with glucose oxidation or glycolysis and glucose recovery by gluconeogenesis reactions triggered by oxygen. Such reactions do have control over several biochemical reactions responsible for molecular modulation, immunity, signaling pathways, differentiation, hypoxia, ischemia, protein synthesis. As a result of these metabolic reactions, physiological functions do get changed. In other words, red blood cells act as regulated action worker with capability to change the physiological events in the body. These RBC cells are called 'Respirocytes'. Examples are functional MRI and MR angiography.
2. RBC cells have specific molecular recognition memory on their surface so called 'antignicity' due to the fact that membrane protein make-up is very specific. It imparts a specific antigenicity to the person for antibodies. It is the basis of blood grouping.
3. Next question is how in vivo nanorobots communicate?

a.acoustic messaging. A device similar to an ultrasound probe would encode messages on acoustic carrier waves at frequencies between 1-10 MHz; .b.Rf frequency sensitivity; c.biochemical sensors and signaling pathways. Such as in vivo medical nanodevice could metabolize local glucose and oxygen for energy.

3 RED BLOOD CELL NANOCARRIER AS RESPIROCYTES

Most cellular repair nanorobots will not need more than 10^6-10^9 operations/sec of onboard computing capacity to do their work. This is a full 4-7 orders of magnitude below (even the potential for) true human-equivalent computing at 10 teraflops (~10^{13} operations/sec). Faster computing capacity is simply not required for most medical nanorobots such as fMRI. Opsonization and inflammatory signaling pathways may be fooled by inert passive diamond exterior surface. Leukocytes donot become hyperactive due to passive surface.

Recently more advanced silicon, nitrogen, diamond or fullerene nanoparticles and nanocomposites have been reported which can attach on RBC. We emphasize in this paper on magnetic field application can control the path of RBC and visualizes RBC-nanoparticle action. RBC carry the nanomaterials sitting on surface of cell exterior in a controlled path pre-determined (robotic action) by applying magnetic field

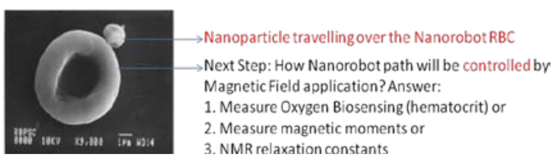

Figure 1: A red blood cell is shown with nanoparticle as carrier. Nanoparticle acts as paramagnetic biosensor while red cell acts as chemical and physiological sensor(respirocyte).Reference [3]

3 NANOMEDICAL TREATMENT

The red cells also provide the information of muscle action in heart based on molecules leaked away from organ. This action is useful in both drug therapy monitoring and staging of disease process. Example: myocardial infarction monitoring is based on the following facts:

• RBC (carrier) along with antiviral peptide bound silicon (nanoparticle) sitting on its surface reaches at the infection site to combat the virus => Not established yet

• RBC (carrier) along with antimyoglobin bound iron (nanoparticles) sitting on surface tracks the muscle injury and recovery.

• RBC (carrier) along with antitroponin bound iron (nanoparticles) sitting on surface tracks the leakage of troponin in infarction and recovery.

• RBC (carrier) along with antimyosin bound iron (nanoparticles) sitting on surface may track the muscle fibers [1].

What Property of RBC and Nanoparticles Are Significant?[2]

Where RBC NMR Property Takes Us?

The red cells can have hemoglobin in two forms either oxidized hemoglobin (HbO_2) or deoxy-hemoglobin(H.Hb). It distinguishes the NMR property of red cells well known in hemoglobinopathy and can be monitored by switch of chemical shifts and spectra in different physiological conditions. Because of iron in center these cells act as magnetic resonance sensitive plates with paramagnetic characteristics to give out blood oxygen dependent MR signal to detect neuron function in brain (functional MRI) and show up track as angiogram or MRA.

The iron superparamagnetic property makes red cells as suitable biomarker based on relxivity or 1/T1 constant. The relaxivity of red cells is temperature and pH sensitive as used as 'Nanonavigator' of physiological action like Respiraocytes.

How Nanorots can navigate?

If carrier nanosphere load (10-100 nm) on these respirocytes (4.5 micron) is a specific antibody, antigen, drug, peptide or lipid or protein, hormone, enzyme molecules to correct the disease at site, the path and action of these respirocytes can be controlled based on robotics principles. The navigation is primarily is chemical sensing by oxygen state in cell, intracellular elements Mg++, Ca++, Na+, iP as pH and electromagnetic potential markers. Figure 2 shows this property under influence of magnetic field based on the facts:

• RBC protons are NMR visible (specific 1/T1 constant values) => Blood **MR Angiography**

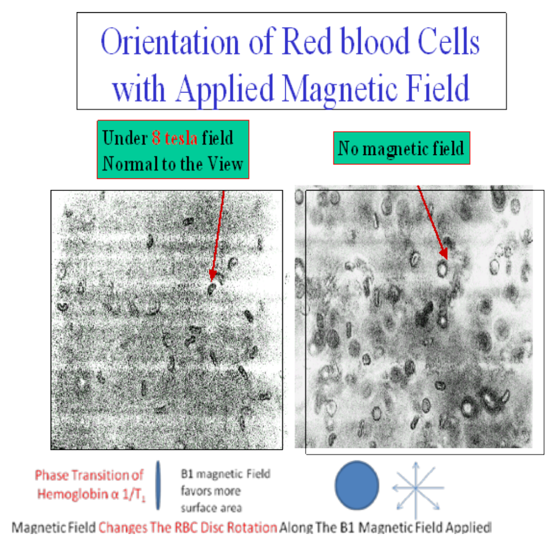

Figure 2: On left: red cells align along the applied magnetic field; On right: normal red cells flow freely in no magnetic field.

• RBC (Hemoglobin-iron) is Oxygen sensor (good for Physiological MRI or perfusion MRI or Diffusion MRI)

• RBC (Hemoglobin-iron) is magnetic field sensitive (keeps maximum RBC surface along the NMR magnetic field B1) or DISC rotates in parallel to B1 field (see Figure 2)

• NMR sensitive RBC and Nanoparticle both contribute in relaxation constant rates (1/T1) measurement
• Dependence of 1/T1 on phase transition at different temperatures, pH and oxygen availability.
• Enhancing the measurement sensitivity of relaxation rates (1/T1) by doping with $MnCl_2$ is an art to enhance the red cell sensitivity

4 NANOROBOT RBC CELLS IN IMAGING

Imaging was performed in experimental animals by following method:
• RBC
• Nanoparticles (maghemite Fe_2O_3)
• $MnCl_2$ (2.5% w/v)
• 90 MHz NMR Minispec® and 400 MHz NMR Oxford Spectrometer
• Temperature range: (150 K-500 K)
• 500 MHz NMR Microscopy of animal
• NMR Relaxation times of RBC (Oxygen Biosensing)
• The diffusional water permeability (P_d) of the red blood cell (RBC) membrane in presence of Mn^+($MnCl_2$) at 400 MHz proportional with oxygen concentration in the blood (Oxygen Biosensor or hematocrit). (Hematocrit 45%).
• RBC rotational Reynolds number (due to specific nanomaterial load and oxygen uptake) and mass transfer => result with <u>RBC disc rotation</u> and increased $1/T_1$ or hematocrit

Phase dependence on RBC Relaxation Times
• $1/T1_{RBC} = 6A^2M/h\nu_o\, J[\pi/16z]^{1/2}$
• Where 'A' is hemoglobin(iron) energy (A=2.21 x 10^{-21} erg (0.665 MHz),
J is exchange coupling constant,
z is number of neighbors and
$h\nu_o/J \ll 1$ is extreme narrowing phase limit. [3]

5 NANOROBOT CELL MR SIGNAL IS TEMPERATURE SENSITIVE

Red cell hemoglobin iron imparts a role in MR siensitivity based on the following facts.
• Higher 1/T1 indicates bound metallic state of Hb molecule phase at low temperature

$$\frac{1}{T_1} \approx \frac{2\pi\sqrt{6}}{9\hbar} A^2_{\rm dip} N(E_F)^2 k_B T \ .$$

• The dipolar couplings and orbitals from $2p_z$ functions show 1/ T1 dependence on temperature because of $A^2_{\rm dip}N(E_F)^2$; where Fermi energy $A_{dip} = 1 \times 10^{-20}$ erg and $N(E_F)^2$=34 eV^{-1} per fullerene molecule. T is temperature in K.
• <u>Higher 1/T1 indicates bound metallic state of molecule phase at low temperature</u>
• Change in T1 Relaxation constants of RBC in Presence of Nanoparticles

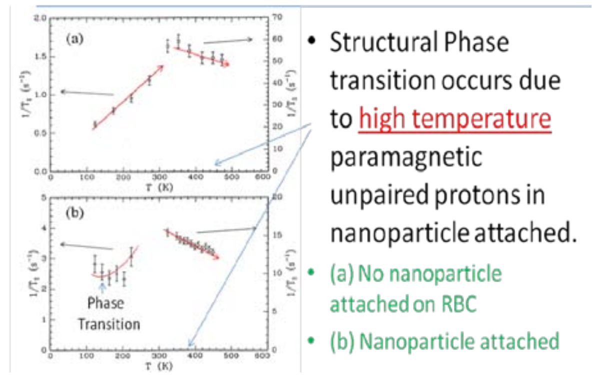

Figure 3: The effect of temperature on red cell relaxivity (1/T1). Notice the phase transition effect on relxivities. Refenerence [4].

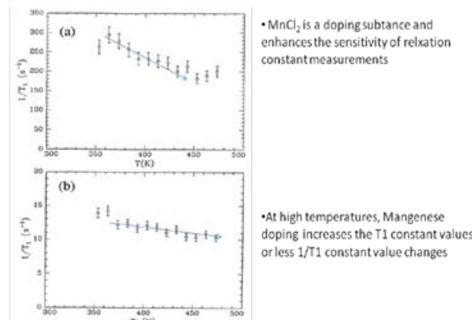

Figure 4: The effect of Mangnese doping and temperature on red cell relaxivity (1/T1). Refenerence [4].

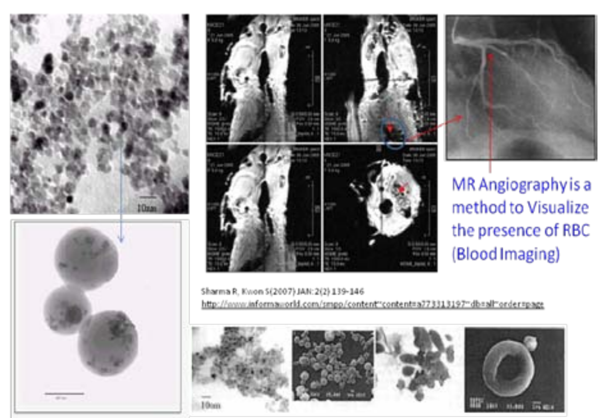

Figure 5: Nanoparticles in red cells are highlighted on left panels. In middle, an animal was injected nanoparticles and MR imaging was done by MRI at TE/TR 15/1500 ms by multislice multiecho spin echo method. On right panel, red blood sensitive MR angiogram is shown [2].

What Are Potentials of RBC Nanorobots?

• RBC as carrier and Nanomaterials bound with(physiological or biochemical or immunological, biosensor, drug compounds) serve as Magnetic field controlled Robot

- They can be used in:

1. Monitoring disease or therapy;
2. Targeted delivery of RBC with specific properties;
3. Sensing physiology signals or structural-function property of enzymes, hormones, active neurotransmitters
4. fabricated nanorobots with molecular precision by communication and navigational mechanisms(programmed therapeutic antibody nanodevices) to act precisely-specified set of RBC surface antigens populating the surface of the target tumor mass.

6 IMPLICATIONS OF NANOROBOTICS

Polymer cage as nanorobot device carries the drugs at the tumor site. A 1 cm^3 injection of 1-micron polymer can hold at least 0.5 cm^3 of drug. Virtually all of these billions of nanites (in the 1 cm^3) will be smart enough to target the correct tumor cells for destruction, so delivery efficiency is virtually 100%. Nanorobot sensors can test for ambient levels of the drugs, to prevent overdose. "anachronistic" application—one that could be done using medical nanorobots.

Other possibilities of RBC Nanorobots

- Use as respirocytes by ^{13}C NMR spectroscopy
- Use of 13C-fullerene based MR Angiography
- RBC can hold nanocomputers in future to function and travel in blood.
- Use of RBC as nanosystems embedded inside as “functional physiology lab”. Risk: attack by viruses and bacteria on RBC
- fail-safe design, the nanodevices to examine a given piece of tissue, surveying its biochemistry, biomechanics, and histometric characteristics in great detail.

7 FUTURE IMPLICATIONS

Nanomedicine will eliminate virtually all common diseases of the 20th century, virtually all medical pain and suffering, and allow the extension of human capabilities—most especially our mental abilities. Consider that a nanostructured data storage device measuring ~8,000 $micron^3$, a cubic volume about the size of a single human liver cell and smaller than a typical neuron, could store an amount of information equivalent to the entire Library of Congress. If implanted somewhere in the human brain, together with the appropriate interface mechanisms, such a device could allow extremely rapid access to this information.

A single nanocomputer CPU, also having the volume of just one tiny human cell, could compute at the rate of 10 teraflops (10^{13} floating-point operations per second), approximately equalling (by many estimates) the computational output of the entire human brain. Such a nanocomputer might produce only about 0.001 watt of waste heat, as compared to the ~25 watts of waste heat for the biological brain in which the nanocomputer might be embedded. But perhaps the most important long-term benefit to human society as a whole could be the dawning of a new era of peace. We could hope that people who are independently well-fed, well-clothed, well-housed, smart, well-educated, healthy and happy will have little motivation to make war. Human beings who have a reasonable prospect of living many "normal" lifetimes will learn patience from experience, and will be extremely unlikely to risk those "many lifetimes" for any but the most compelling of reasons. Malfunction might involve some unexpected emergent machine-machine interaction Mismatched nanorobot programming

8 CONCLUSION

A new role of red blood cell navigation is introduced for their constant physiological supply of oxygen to organs and monitoring any malfunction of oxygen in the organ. The oxygen carrying capacity also makes them useful in MR angiography, functional MRI. Nanomaterials can be attached on red cells and sent or target the tumor sites with nanospheres sitting over red cells. These red cells generate temperature, pH sensitive magnetic resonance signal in high magnetic field as basis of NMR/MRI. Some salient RBC features are:

- RBC can work as biochemical genomic SSN
- Future nanorobot programming

Conclusion

- Red blood cells contain hemoglobin with iron as paramagnetic and sensitive to magnetic field.
- Under the effect of magnetic field their path can be controlled and tracked by their magnetic moments and NMR relaxation constants.
- Red blood cells have capability of carrying payload of nanoparticles.
- NMR relaxation constants predict physiological function of red blood cells in the target organ.

9 REFERENCES

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