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SURFACE FUNCTIONALIZATION OF GOLD NANOPARTICLES FOR ANTIMALARIAL MEDICINES BY SIMULATING THE COUPLING BETWEEN MEROZOITES AND ERYTHROCYTES

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ABSTRACT: Surface functionalized gold nanoparticles that mimic the coupling between merozoites and erythrocytes are proposed for antimalarial medicines and the strategic design is theoretically described. As for the interaction between the gold nanoparticles and the merozoites, the former acts as the adhesive balls for merozoites. This will lead to blocking the invasion of merozoites into red blood cells by suppressing the movement of merozoites on the surfaces of red blood cells.

KEYWORDS: Plasmodium falciparum, erythrocytes (red blood cells), rhoptry, BAEBL, glycophorin C, NANA (N-Acetylneuraminic acid)

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1. INTRODUCTION

Merozoite invasion of human red blood cells by Plasmodium falciparum is essential for blood stage asexual replication and the development of malaria disease [1]. Although there are effective antimalarial medicines such as artemisinin [2] and newly developed vaccines such as BK-SE36 [3], the eradication of malaria needs further basic research and development. In this paper strategic designs for antimalarial medicines by utilizing surface functionalization of gold nanoparticles are

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theoretically investigated. The strategy is based on suppression of the movement of merozoites on the surface of erythrocytes using gold nanoparticles. Usually merozoites have 4-stage movement processes (1.Initial contact 2.Re-orientation 3.Tight junction formation 4. Mature invasion) in order to enter into human blood cells [1]. Therefore during these four processes, it would be possible to suppress the movement of merozoites. The central operating mechanism of this medicine is disturbance of the mechanical aspect of entering process of merozoites into red blood cells rather than the biochemical effects in the conventional medicines. As for the surface functionalization of gold nanoparticles, there are already interesting applications in the field of cell biology, such as intracellular tracking [4], cancer treatment [5], antibiotics [6] and antiviral medicines [7]. In the light of these outcomes in the field of nanotechnology the novel designs for antimalarial medicines are proposed in this paper

2. DESIGN STRATEGY FOR ANTIMALARIAL MEDICINES

It is assumed that the antimalarial medicines in this paper will be medicated through intravenous injection. In order to control the movement of merozoites on the surface of erythrocytes, the first and necessary step is coupling between merozoites and gold nanoparticles in the blood flow, as shown in Figure.1. This coupling or adhesion process is realized by introducing the receptor molecules on the surface of gold nanoparticles, and the coupling will happen before and also after the coupling between merozoites and red blood cells. Although the overall coupling process is a probabilistic phenomenon which depends on the density of gold nanoparticles in blood vessels, there will be the inhibition as for the entry process of merozoites into erythrocytes, as shown in Figure 2.

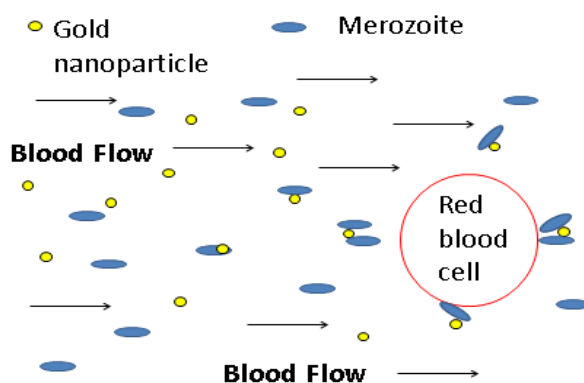


Figure 1: The adhesion between merozoites and gold nanoparticles in blood flow. This adhesion will happen before or after the coupling between merozoites and red blood cells.

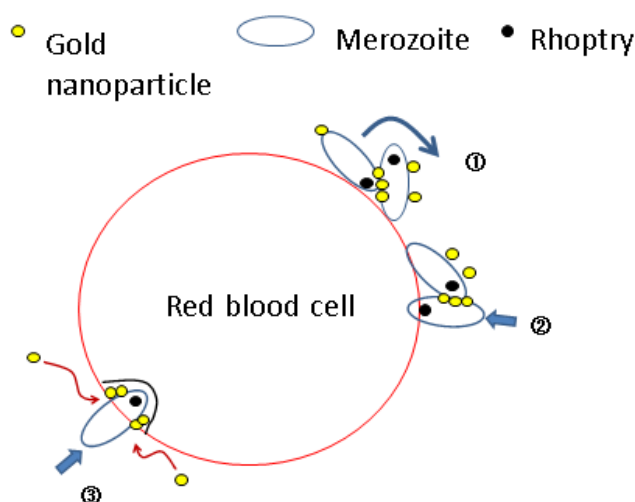


Figure 2: Schematic representation for the triple suppression of the movement of merozoites on the surface of red blood cells. The two effects ① and ② are brought by the coupling between merozoites via gold nanoparticles. The effect ③ is the suppression of the movement of so called “moving junction” caused by gold nanoparticles

The triple suppression mechanisms in Figure 2 against entering merozoites into red blood cells are explained as follows. After the initial contact, re-orientation is necessary for directing the rhoptry close to the surface of red blood cell, which will lead to the tight junction formation. If the two merozoites are coupled by gold nanoparticles, this process will be suppressed due to physical blockade shown in ① of Figure 2. The tight junction formation is the starting point of moving junction formation and forward movement. However, if the two merozoites are coupled by gold nanoparticles, this process will be suppressed due to physical blockade of straight movement as shown in ② of Figure 2. The blockade mechanisms of ① and ② need the coupling between at least two merozoites. However, in the case of single entries of merozoites into red blood cells without coupling with other merozoites, the following third mechanism is still effective. The activating force of the moving junction is generated by Actin-Myosin motor located between the surfaces of merozoites and red blood cells [1]. Therefore, the coupled gold nanoparticles on the surfaces of merozoites will eventually be absorbed between the narrow gap of two surfaces of the red blood cell and the merozoite. This will cause the mechanical stress and malfunction of Actin-Myosin motor, as shown in ③ of Figure 2. The design concept of the surface functionalization for realizing antimalarial medicines can be expressed by the following symbolic equation:

(Au) - **【Conjugation】** -- **【Effective time controller】** -- **【Mimic of receptor and membrane of erythrocyte (red blood cell)】** (1)

where **【Mimic of receptor and membrane of erythrocyte (red blood cell)】** represents molecules which mimic the receptor for antigen of merozoite and membrane of erythrocyte (red blood cell), **【Effective time controller】** represents molecules which will control the delay time before the clearance of gold nanoparticles from blood vessels. Usually, the delay time depends on the size or molecular weight of this part. **【Conjugation】** represents conjugating atoms or molecules such as thiol type -S- [4] or amid coupling -NHCO- type [8].

In order to make the gold nanoparticles function as effective adhesion balls, the optimization for the size of gold nanoparticles is very important. In the case of antimalarial medicines, it is necessary to prevent gold nanoparticles from being buried under fibrillar bundle on the surface of the merozoites. So that the following relationship between D (diameter of gold nanoparticles) and L (length of the fibrillary bundles) is needed, as is shown in p117 of reference [9].

$$D > L \quad (\text{fibrillar bundle : } 18\text{nm} \sim 22\text{nm}) \quad (2)$$

As the length of fibrillar bundle L is about 20nm, D should be larger than 30nm at least.

3. AN EXAMPLE OF SURFACE FUNCTIONALIZATION OF GOLD NANOPARTICLES FOR ANTIMALARIAL MEDICINES

An example of antimalarial medicine based on the equation (1) is shown in Figure 3

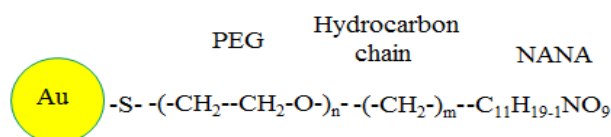


Figure 3: An example of the surface functionalization of gold nanoparticles for antimalarial medicines.

Firstly, **【Mimic of receptor and membrane of erythrocyte (red blood cell)】** corresponds to (CH₂)_m and NANA. (N-Acetylneuraminic acid: C₁₁H₁₉NO₉). Sialic acid NANA was chosen as the mimic of

receptor, based on the research outcomes relating Plasmodium falciparum receptor BAEBL which couples to erythrocyte receptor glycophorin C [10].

Secondly, Conjugation] -- [Effective time controller] corresponds to S and PEG (Polyethylene glycol). There are two important roles of PEG as follows.

The delay time before the clearance of gold nanoparticles from the blood vessels will be controlled by the length of PEG as is explained in the reference [11]. The delay time depends on the nth number of (–CH₂–CH₂–O–)_n in Figure 3. The larger “n” number will increase the delay time before clearance. On the other hand, PEG has potentiality for making gold nanoparticles pass through the cells in intestinal walls. The mechanism is based on the so called “excluded volume effect” [12] and high mobility [13], which will bring about fluctuations to the dynamics of cell membranes in intestinal walls. Therefore the example shown in Figure 3 will have the possibility to be applied for oral medicines in future. Although the example of Figure 3 has the same structure as that of antiviral medicine in my previous paper [7], the diameter D and the numbers of “n and m” should be designed depending on the purposes and specifications of the medicines.

2. CONCLUSION

In this paper strategic designs for antimalarial medicines by utilizing surface functionalization of gold nanoparticles are theoretically investigated. Basic operating principles are based on the suppression of the rotation and straight movement of merozoites on the surface of red blood cells, in addition to the interference to the so called “moving junction”. Consequently, the gold nanoparticles have the triple strategies on blocking the invasion of merozoites into red blood cells. In addition to the variety of strategic designs expressed by equation (1), the generation of drug-resistant merozoites will be suppressed, as the central operating mechanism is based on the interference of mechanical aspects of entering process of merozoites into red blood cells rather than the biochemical effects in the conventional medicines. As it is necessary to prevent gold nanoparticles from being buried under fibrillar bundle on the surface of the merozoites, D (diameter of gold nanoparticle) should be larger than 30nm at least. And finally, the following steps are needed towards the practical use of the antimalarial medicines proposed in this paper.

<1>: Collaborative research between the fields of advanced nanotechnology and the parasitology.

<2>: In-vitro experiments for coupling between erythrocytes, merozoites and gold nanoparticles in order to observe the aggregation phenomena using advanced microscope technologies

<3>: Clinical treatments using the antimalarial medicines in hospitals.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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