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Biomimetic Lipid Nanoparticles: Bio-Sensing and Bio-Functional Applications

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14. ABSTRACT
We developed lipid-functionalized nanoparticles that bind extremely tightly to potent biological toxins. In the case of Gramnegative bacterial endotoxin (i.e. LPS) the high-density lipoprotein-like nanoparticles (HDL-NPs) bind tightly to the toxin, serve as an antidote to the presence of even trace amounts of the toxin in simple or complex matrices, and there is tremendous promise in this system with regard to the health and well being of the men and women of the United States Armed Forces. In addition, we have made tremendous progress on the development of an entirely new class of materials, hollow crystalline superparticles, that are formed at highly curved liquid-liquid interfaces, and that provide unique properties due to the ensemble effects of tightly packed nanoparticle building blocks, like surface-enhanced Raman spectroscopy (SERS), that will enable tremendous advances in biosensing.

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Biomimetic Lipid Nanoparticles: Bio-Sensing and Bio-Functional Applications

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Introduction:

Over the past six years, our work has focused on biological toxins that pose an enormous threat to the health and well being of the men and women of the US Armed Forces. We have developed materials to sense and detoxify biological systems. Biological toxins, many of them amphiphilic or lipophilic proteins and small molecules, can integrate into host cell bilayer membranes. Our work is focused on understanding the interaction of some of the most deadly and potent biotoxins with biomimetic lipid nanoparticles (BLNs) that can bind to the toxins, inactivate them, and facilitate their removal from simple or complex matrices. BLNs have surface lipid layers that mimic those found in biological systems. Understanding the fundamental chemistry that controls lipid-toxin interactions was critical to our long-term parallel goal of (1) developing tailorable and field-deployable biosensors capable of toxin detection and (2) developing nanotechnology-based antidotes capable of specific toxin neutralization. Bacterial lipopolysaccharide (LPS, aka endotoxin), a highly potent biotoxin that causes significant morbidity and high mortality in humans, and an array of other amphiphilic/ lipophilic small molecule toxins were the focus of development efforts. **Ultimately, we successfully synthesized and characterized BLN biosensors capable of toxin detection and as powerful antidotes for rapid toxin sequestration and neutralization in complex biosystems.**

The Thaxton Group pioneered the synthesis and characterization of biomimetic high-density lipoprotein nanoparticles (HDL NPs).[1] HDL NPs have the size, shape, and surface chemistry of natural HDLs and function to sequester cholesterol.[2] Cholesterol is a lipophilic molecule that integrates into biological membranes, can cause significant morbidity and mortality when in excess, and served as an excellent candidate molecule to provide us with data suggesting that the approach would be successful for other biological toxins. Data demonstrated that HDL NPs, and more generally BLNs, can be tailored to manipulate cholesterol binding such that it can be sequestered by the particles even when present at low concentrations (nM).[3] As a direct result, this platform provides an opportunity to tune the structure and chemical composition of BLNs, using natural and unnatural surface ligands, in order to develop biomimetic nanostructures to sense and sequester biological toxins like LPS and other small molecules.

Because of the tremendous toxicity and the threat that it poses to the men and women of the United States Armed Forces, we first focused on developing a BLN to bind and sequester Gram-negative bacterial

endotoxin [aka lipopolysaccharide (LPS)]. We completed our initial studies investigating the ability of the HDL NPs to scavenge LPS and prevent inflammation/ toxic effects using *in vitro* and cell-based biosensor assays that are molecularly tuned to exquisitely sense LPS.[4] Data demonstrate that HDL NPs that have been molecularly configured to optimally bind LPS can drastically reduce the cellular response to LPS, and the LPS bound to the HDL NPs can be easily removed from the biological system. We also demonstrated that the HDL NPs do not affect viability of normal blood cells.

Meanwhile, our efforts further focused on developing the HDL NPs and related BLNs into a biosensor for detection of biotoxins and similar substrates. We firstly investigated the behavior of the phospholipid bilayers of HDL NPs efficiently seizing important blood components, which provides a firm foundation for HDL NPs based biosensors. Due to the localized surface plasmon resonance (LSPR), surface enhanced Raman scattering (SERS) is a trace detection technique that extends even to single molecule detection by means of coinage-metal (for example, Au, Ag and Cu) nanostructures. SERS-based platforms offer several distinct advantages over other methods for biomedical detection, such as high stability and sensitivity, easily performing and multiplexing with simple instrumentation.[5,6] In order to address the challenge of developing a sensor technology capable of detecting low abundant biological toxins, we have also turned our attention to the synthesis of Au NP-based BLN SERS platforms. Admittedly, this has been a much more difficult task because of the vanishingly low concentration of some of these toxins in biological systems, and also because our work demonstrated that our library of BLNs bind toxins, at the most sensitive, in low μM quantities (unpublished data).

In the past year, our efforts continuously concentrated on developing the prototypes of BLN based biosensors; however with a new approach. It's notable that many invertebrates have a very well-developed visual system with the capacity to see motion, color and the pattern of objects in their environment due to advanced compound eyes – instead of one lens they see through a spherical self-assembly of nano-sized eyes composed of many hundreds or thousands of so-called ommatidium (Figure 1).[7-9] Such structure-function relationships suggest that a self-assembly of nano-sized building blocks at a spherical interface can either enhance the intrinsic properties of the component nano-size building blocks via high-density assembly or create novel properties due to synergistic effects. We hypothesized that synthesis of these types of materials with lipid cores and surfaces may provide for binding of toxins at low concentration and then a high sensitivity mechanism, SERs, to detect them. Based on the synthesis of Au NP superparticles in the last report, we further explored to the synthesis of Au NP hollow crystalline

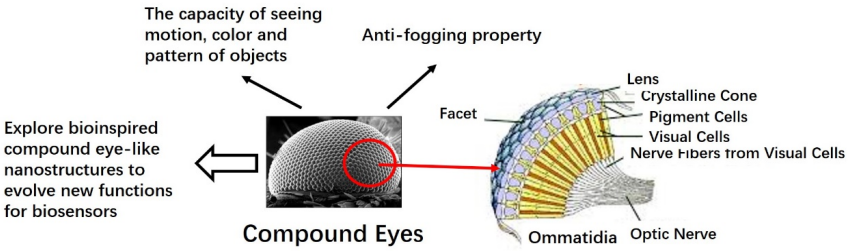

Figure 1 Schematic of compound eye.

superparticles (HCSs), mimicking compound eye-like super nanostructures. We expect that it will enable us to develop exquisite new biosensors for detection of biotoxins and similar substrates.

The following is a summary of our progress based upon the original goals of our grant, including some new work on nanoparticle superparticles that we have completed over the course of the last year as the grant has been in a no-cost extension.

Objective 1: We will synthesize and characterize a suite of BLNs using gold nanoparticle templates to control for BLN size, shape, and surface chemical composition and then measure their capacity to bind and sequester fluorescent analogs of cholesterol and lipopolysaccharide (LPS).

Progress towards objective 1: None within the last year. See previous reports and published manuscript.

Objective 2: Fluorescence-based displacement biosensors will be developed that specifically respond to lipophilic and amphiphilic molecule binding to the surface of BLNs. A number of different assays will be developed such that displacement of common fluorescently tagged biotoxins (e.g. cholesterol and LPS) will be used to detect and identify a host of lipophilic and amphiphilic molecules that compete for binding to BLNs.

Progress towards objective 2: Previous reports have focused on the fluorescence-based sensors for a host of biological molecules and toxins. To address the challenge of developing a sensor technology capable of detecting low abundant biological toxins, we have also turned our attention to the synthesis of Au NP-based BLN SERS platforms, including bio-inspired compound eye-like superparticles.

Circumventing The Thermodynamic Challenge of Confining NPs at Curved Liquid-Liquid Interfaces (CLLIs). To successfully synthesize compound eye-like HCSs, confinement of NPs at CLLIs is a major prerequisite. In an emulsion, the energy to hold a particle at the CLLI can be represented by an energy well between the energy of the particle in the organic solvent and non-solvent, where the CLLI can hold particles for assembly can be represented at the bottom of an energy well diagram (Figure 2). For a lipophilic particle in an o/w emulsion, the energy difference (ΔE) between the CLLI and the oil phase (inside droplet) is dominated by the effective radius of the particle (R), according to the equation:[10-13]

$$\Delta E=-\pi R^2\gamma_{o/w}(1+\cos\theta)^2 \qquad (1)$$

where $\gamma_{o/w}$: the interfacial tension between oil (solvent) and water (non-solvent); θ: the contact angle. From Equation (1), when R→1 μm, ΔE is much more than the thermal energy, kBT (kB: Boltzmann constant; T: absolute temperature), by many orders of magnitude. Accordingly, the energy well of the o/w emulsion is deep and lipophilic micrometer-sized particles can stably reside at the CLLI and resist dissolving back in the oil phase (Figure 2a). When R→1 nm, the ΔE between the solvent and the CLLI is comparable

to the thermal energy, kBT, of the particle. Diagramatically, the energy of the particle at the CLLI becomes very shallow with regard to the energy of the particle in the solvent (Figure 2b). As such, a small lipophilic NP (d $\leqslant$ 50 nm) in an oil droplet is hard to confine at the CLLI whereby even thermal fluctuation can draw the particle back into the solvent phase.[10-13] Up to now, macromolecules or polymers have to be used to anchor NPs at the CLLIs.[12,13] However, these molecular interconnects surrounding individual NPs impedes their tight packing at CLLIs and precludes generating unique physical properties that arise from strong interactions between closely neighbored NPs as observed in superparticle systems (e.g. SERS).[12,13]

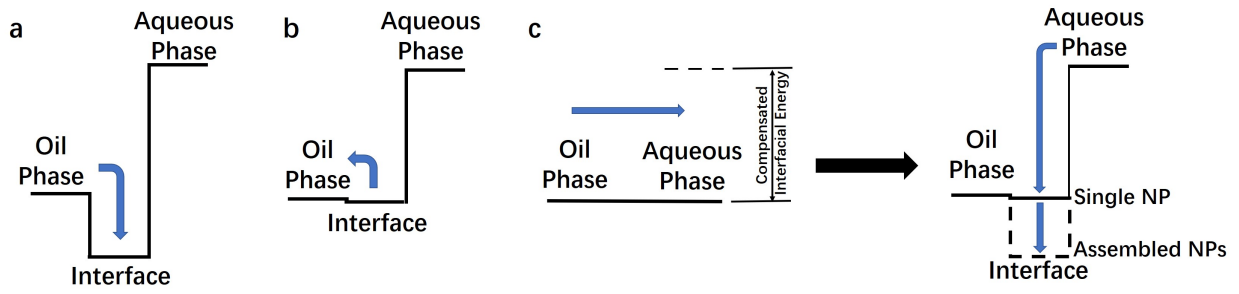

Figure 2 Schematics of energy wells in the o/w emulsion. (a–b) Energy well for the micrometer-sized particle (a) and the NP (b). (c) Hypothesis of delivering lipophilic NPs to the aqueous phase for confining them at CLLIs.

Our first step to circumventing this thermodynamic challenge is by using a solvent-diffusion-triggered "entropic switch (Figure 2c)." As proof-of-concept, we utilized highly monodispersed oleylamine (OLA)-capped gold nanoparticles (Au NPs, mean diameter: 4.7 ± 0.6 nm) as building blocks (Figure 3). The solvent, oil phase was composed of a mixture of chloroform and 1-octadecene and contained 36 mg/mL OLA-Au NPs. Sodium deoxycholate, a natural emulsifying surfactant,[14] was dissolved in water (non-solvent) with a concentration of 30 mg/mL to form the non-solvent, aqueous phase. A primary o/w emulsion was prepared by mixing the oil phase and the aqueous phase (v/v 1:4) and sonicated. Notably, with a higher dipole moment due to the asymmetrical molecular structure, chloroform molecules possess active protons to associate with polar organic solvent molecules, presumably by weak hydrogen bonds.[15,16] Next, acetonitrile was quickly added into the primary o/w emulsion with a ratio of 1:5 in volume. The addition of acetonitrile triggered the diffusion of chloroform from the oil droplets to the aqueous solution. Solvent diffusion leads to an instantaneous "entropic switch," which either counteracts the interfacial tension or facilitates the mixing of the solvents in oil droplets and non-solvents in the aqueous solution at the CLLIs.[17,18] The oil droplets in the primary o/w emulsion thus were spontaneously emulsified[17,18] into small droplets to further form the secondary o/w emulsion. Meanwhile, OLA-Au NPs close to CLLIs were destabilized and aggregated by non-solvent.[17,18] The droplets in the secondary o/w emulsion were investigated in the vitrified, frozen-hydrated state by cryogenic scanning transmission electron microscopy (cryo-STEM)[19] to image them as close to their native state. Data in Figure 3 illustrate assembled OLA-Au NPs at the CLLIs

in a form of fractal-like aggregates. As the size is comparable to that of micrometer-sized particles, it means that the assembled OLA-Au NPs confined at the CLLIs behave similarly to micrometer-sized particles. [20,21]

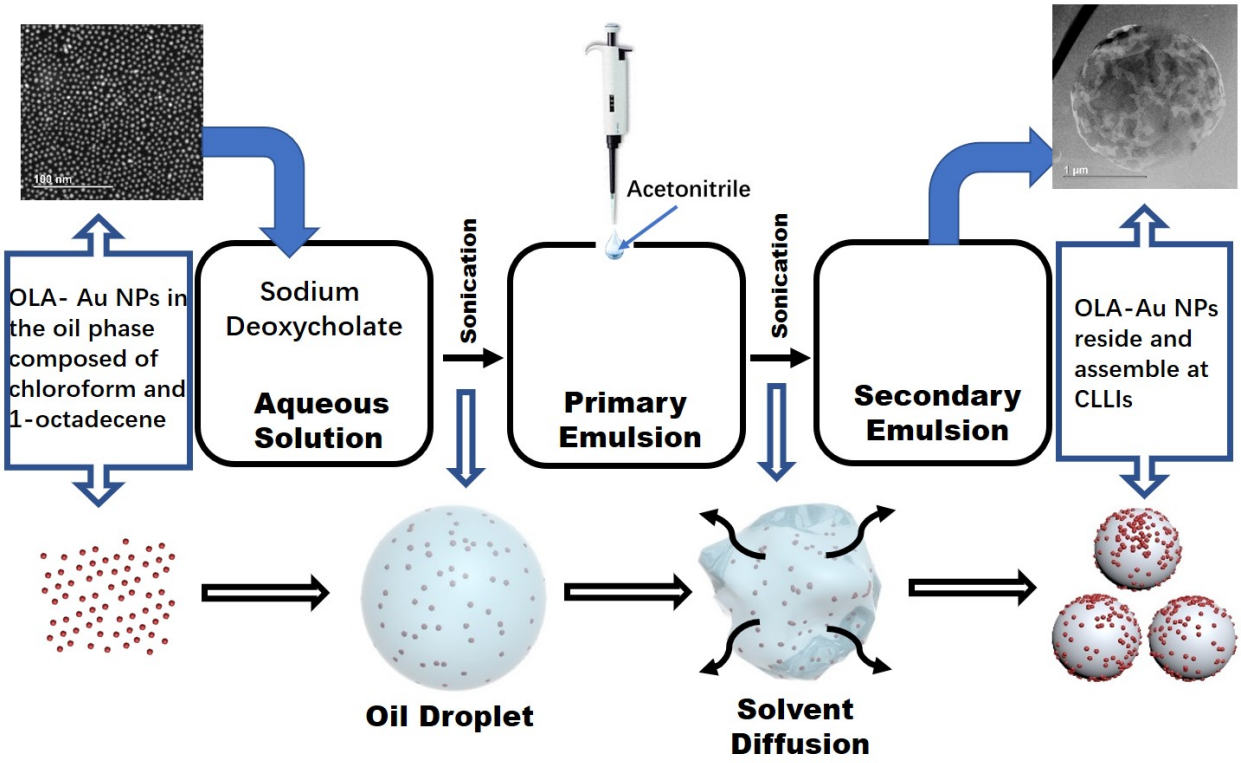

Figure 3 Entropic strategy to stably concentrate NPs assemblies at CLLIs using spontaneous emulsification induced by solvent diffusion. Top left inlet: HAADF-STEM image of monodispersed OLA-Au NPs; top right let: cryo-STEM image of OLA-Au NPs absorbed at CLLIs.

Fabricating High-Quality Intact NP Shells at CLLIs. The size of the oil droplet in the o/w emulsion is governed by the amount of chloroform in the oil phase (Figure 4a). The less chloroform in the oil phase, the smaller the droplet becomes after extraction and the higher the coverage of OLA-Au NP aggregates at the CLLI on the remaining oil droplets. As the softness of the OLA-Au NP is ~ 0.4 (the length of OLA, L: ~ 1.0 nm; the radius of the Au core: ~ 2.5 nm), OLA-Au NPs behave as hard-spheres.[21] When annealing, upon increase in temperature of the solution, the alkylene chains are melted which lowers the sticking coefficient between aggregated OLA-Au NPs and they can move freely over the CLLI. Driven by entropy, OLA-Au NPs thus smoothly find equilibrium sites to form crystalline shells of HCSs (Figure 4a).[21]

The methods of extracting chloroform from the solvent phase greatly influence the quality of NP shells. When annealing at a temperature higher than the boiling point of chloroform, about 61 °C, vaporization of chloroform takes place. The bubbles of chloroform are thus formed in the oil droplets. As more chloroform vaporizes, the bubbles swell and finally explode under extremely high vapor pressure to

release chloroform. The NP shells at CLLIs around the oil droplets are then damaged by breakage of the bubbles in the oil droplets (Figure 4b). When annealing at a temperature lower than the boiling point of chloroform, evaporation of chloroform can easily occur due to the high curvature of the oil droplet. As chloroform continues to evaporate from the droplets, the size of the oil droplets shrinks and the CLLIs can be fully covered by OLA-Au NP aggregates. The residual chloroform in the oil droplets further diffuses into the NP shells by capillary absorption and then evaporates. As more chloroform leaves the oil droplets, the depressed deformation of NP shells takes place. Due to less elasticity, the deformation leaves a dimple in the NP shell (Figure 4c).

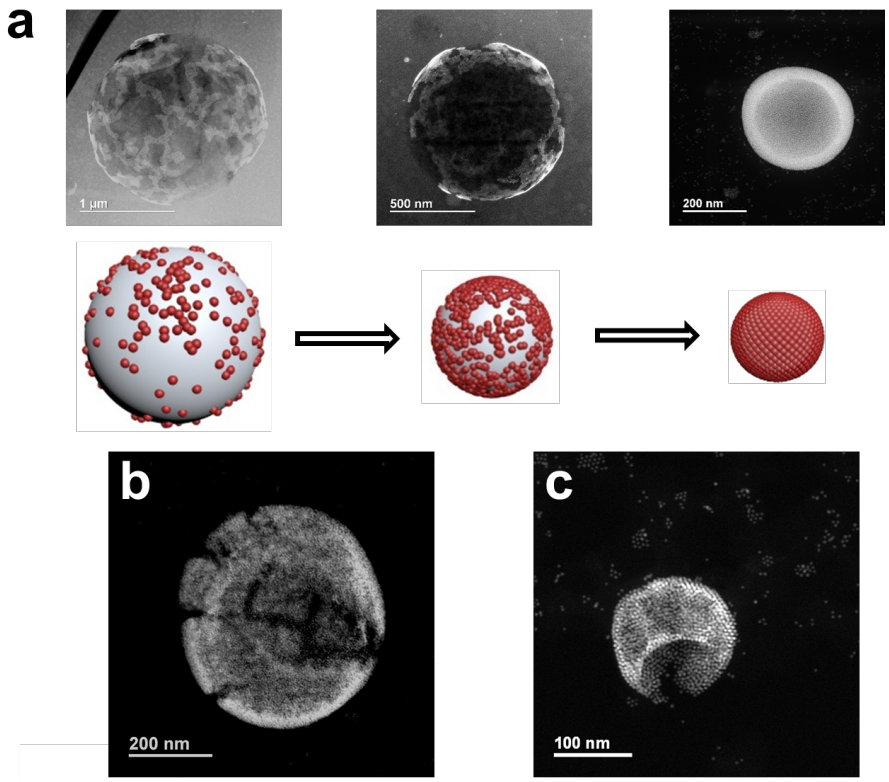

Figure 4 (a) Mechanism of forming intact NP shells at CLLIs from fractal-like patches. Top left and middle inlets: cryo-STEM images of OLA-Au NPs absorbed at CLLIs; top right inlet: HAADF-STEM image of Au NP HCS. HAADF-STEM images of Au NP HCS (b) annealed at 80 °C and (c) annealed at 58 °C, respectively.

We then tried to tune the volume ratios between chloroform and 1-octadecene to find an optical condition to make the surface area of the NP shell matches that of the oil droplet. The data show that the concavity of the NP shell disappears when the ratio between chloroform and 1-octadecene in the oil droplet is 1:1.

Pyrene-Loaded Au NP HCSs as SERS Platform. HCSs merge the properties and advantages of crystalline superparticles with microcapsules with regard to structure and function. This synthetic platform provides access to a wide variety of materials with unique properties that can be used to realize advances in many fields of biosensors. The Au NP shells can provide the SERS matrices, while the oil core acts as the carrier to load lipophilic SERS reporters. Pyrene is a lipophilic SERS reporter,[22] which can be easily loaded in the oil core of Au HCS. Data illustrate SERS spectrum of pyrene loaded Au HCSs (Figure 5). As both pyrene and OLA-Au NP are lipophilic, the strong SERS signal comes from pyrene molecules diffused into the nanogaps between neighboring OLA-Au NPs via capillary absorption. Nowadays, tremendous challenges are still remaining in the SERS platforms due to sophistication in molecularly engineering plasmonic nanogap and Raman reporter.[23] The result suggests that combining the advantages of crystalline superparticles and microcapsules in function can facilitate setting up powerful platforms to deal with these challenges.

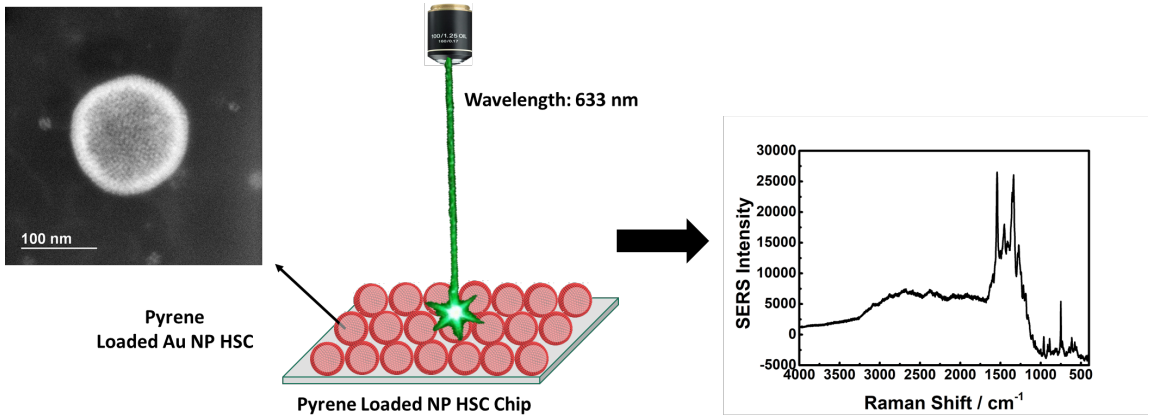

Figure 5 SERS spectrum of pyrene-loaded HCSs.

Summary. As we have completed Objectives 1 and 3, we are using the remaining time, effort, and funding to profoundly investigate the ability to utilize BLNs and novel strategies to develop ultra-sensitive and specific sensor platforms specific for biological molecules, such as toxins, of interest.

Objective 3: We will perform bioassays to investigate the potency of BLNs with regard to their ability to prevent immune cell expression of inflammatory mediators with biotoxin exposure.

Progress towards objective 3: None within the last year. See previous reports and published manuscript.

Conclusion:

We developed lipid-functionalized nanoparticles that bind extremely tightly to potent biological toxins. In the case of Gram-negative bacterial endotoxin (i.e. LPS) the HDL-NPs bind tightly to the toxin,

serve as an antidote to the presence of even trace amounts of the toxin in simple or complex matrices, and there is tremendous promise in this system with regard to the health and well being of the men and women of the United States Armed Forces. In addition, we have made tremendous progress on the development of an entirely new class of materials, hollow crystalline superparticles, that are formed at highly curved liquid-liquid interfaces, and that provide unique properties due to the ensemble effects of tightly packed nanoparticle building blocks, like surface-enhanced Raman spectroscopy (SERS), that will enable tremendous advances in biosensing.

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The full name of the principal investigator on the grant or contract.

Colby Shad Thaxton

Program Officer

The AFOSR Program Officer currently assigned to the award

Jung-Hwa A Gimm

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Reporting Period End Date

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Abstract

We developed lipid-functionalized nanoparticles that bind extremely tightly to potent biological toxins. In the case of Gram-negative bacterial endotoxin (i.e. LPS) the high-density lipoprotein-like nanoparticles (HDL-NPs) bind tightly to the toxin, serve as an antidote to the presence of even trace amounts of the toxin in simple or complex matrices, and there is tremendous promise in this system with regard to the health and well being of the men and women of the United States Armed Forces. In addition, we have made tremendous progress on the development of an entirely new class of materials, hollow crystalline superparticles, that are formed at highly curved liquid-liquid interfaces, and that provide unique properties due to the ensemble effects of tightly packed nanoparticle building blocks, like surface-enhanced Raman spectroscopy (SERS), that will enable tremendous advances in biosensing.

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Archival Publications (published) during reporting period:

1. Foit, L., Giles, F.J., Gordon, L.I., and Thaxton, C.S. Synthetic High Density Lipoprotein-like Nanoparticles as Cancer Therapy. Expert Rev of Anticancer Ther 15(1):27-34 (2015). 10.1586/14737140.2015.990889

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New discoveries, inventions, or patent disclosures:

Do you have any discoveries, inventions, or patent disclosures to report for this period?

Yes

Please describe and include any notable dates

The Thaxton Lab has pursued an entire platform of intellectual property based upon lipid-functionalized nanoparticles. In 2014, based upon work that was completed under the auspices of this grant, Thaxton and Foit submitted an invention disclosure to Northwestern University that was, subsequently, converted to a PCT Application and submitted to the US Patent and Trademark Office. We continue to pursue allowance/ issuance of this patent world-wide.

Do you plan to pursue a claim for personal or organizational intellectual property?

Yes

Changes in research objectives (if any):

None.

We pursued an entirely new bio-sensing platform, the hollow crystalline superparticles, under a no-cost extension of the grant.

Change in AFOSR Program Officer, if any:

The original AFOSR Program Officer was Hugh DeLong. The current Program Officer is Jung-Hwa A Gimm.

Extensions granted or milestones slipped, if any:

No milestones slipped. We were granted a no-cost extension over the past year. We studied the synthesis and characterization of hollow crystalline superparticles, a next generation bio-sensing platform.

AFOSR LRIR Number

LRIR Title

Reporting Period

Laboratory Task Manager

Program Officer

Research Objectives

Technical Summary

Funding Summary by Cost Category (by FY, $K)

	Starting FY	FY+1	FY+2
Salary			
Equipment/Facilities			
Supplies			
Total			

Report Document

Report Document - Text Analysis

Report Document - Text Analysis

Appendix Documents

2. Thank You

E-mail user

Aug 12, 2019 14:46:23 Success: Email Sent to: cthaxton003@northwestern.edu