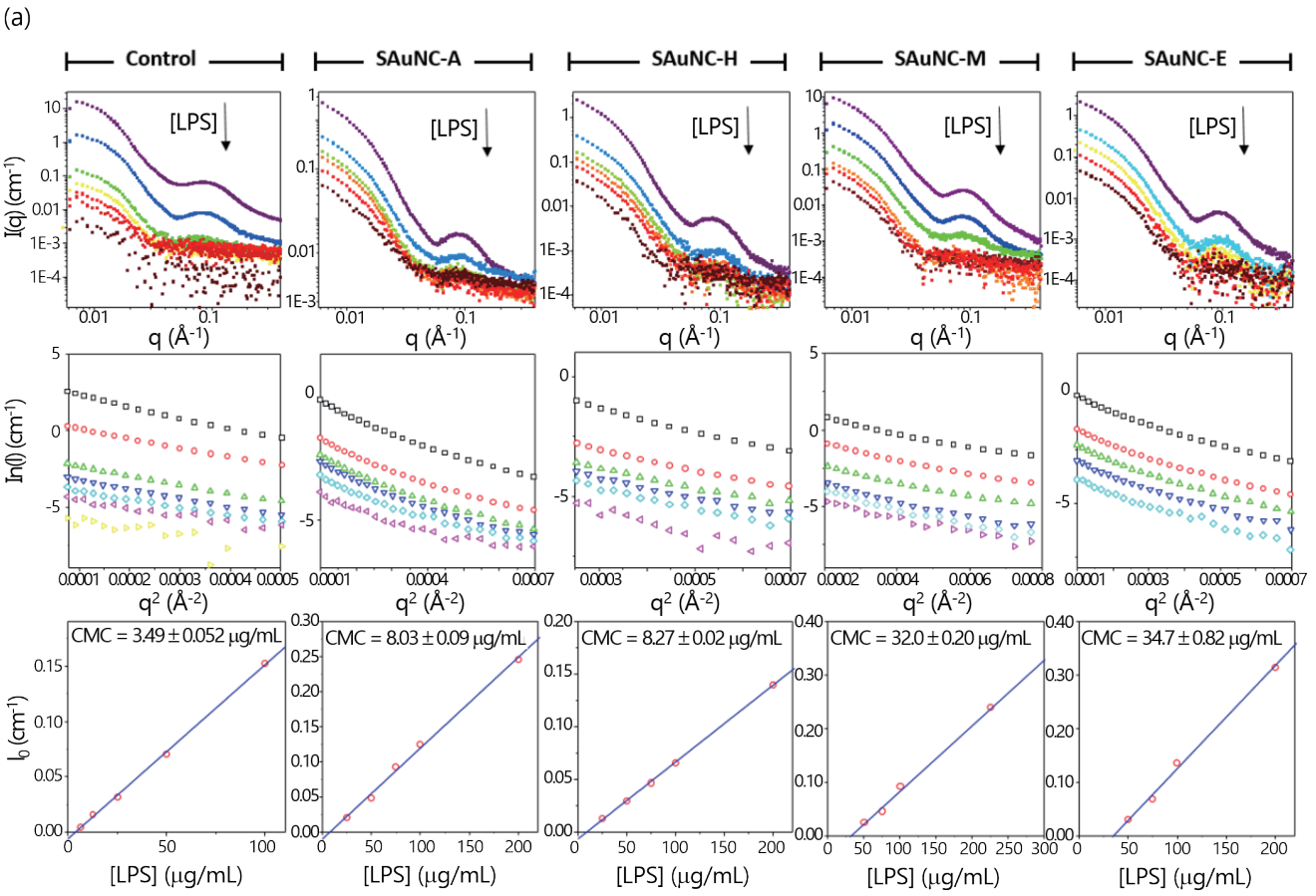
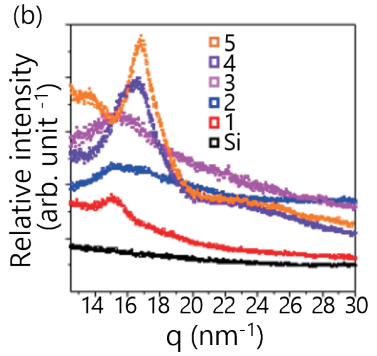
Adsorption of Lipid A by Nanogold Clusters Counteracts Endotoxin-Induced Sepsis

Chemists have succeeded in showing that sub-nanometer gold clusters (SAuNC) can bind an endotoxicity active site, which can deactivate endotoxicity for an early prevention of sepsis caused by gram-negative bacterial infection.





	d-spacing (Å)
(1) LPS-alone	4.19
(2) LPS + SAuNC-A	4.19
(3) LPS + SAuNC-H	4.03
(4) LPS + SAuNC-M	3.85
(5) LPS + SAuNC-E	3.54

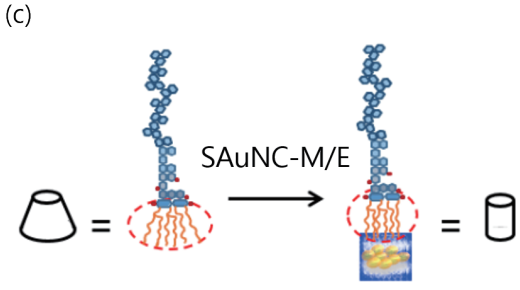


Fig. 1: Measurement of CMC and *d*-spacing for LPS in the absence and presence of various SAuNC. The top panels (a) show scattering intensities as a function of *q*, which are signals from nascent LPS aggregates (micelles or vesicles) at varied concentrations, in the absence or presence of SAuNC of four types. (b) Measurement of *d*-spacing of lipid A in the presence of various SAuNC. The table summarizes the *d*-spacing under each condition. (c) A simple model representing the packing density of lipid A in the presence of either SAuNC-M or SAuNC-E. [Reproduced from Ref. 1]

The endotoxin known as lipopolysaccharide (LPS), which can be obtained from gram-negative bacterial cell walls, is a potent inflammatory activator to induce immunological responses. The dangerous biological outcomes of endotoxicity, including excessive inflammation and even impaired immunity that can lead to potentially fatal sepsis and shock, are understood to be strongly associated with the molecular conformation of lipid A of a lipopolysaccharide (LPS) through its influence on the binding affinity of the natural host-guest interaction between the endotoxin (*i.e.*, LPS) and the toll-like receptor 4 (TLR4)-MD2 complex. In biological environments the conformation of lipid A is, however, prone to form a smaller packing density because the LPS can spontaneously aggregate.

Using small-angle X-ray scattering (SAXS) and grazing-incidence wide-angle X-ray scattering (GIWAXS), Shu-Yi Lin (National Health Research Institutes) and her co-workers found two specific sub-nanometer gold clusters (SAuNC-M and -E) that can efficiently block endotoxin activity by targeting lipid A and compacting its intramolecular hydrocarbon chain-chain distance (*d*-spacing).[1] Direct evidence showed an increased critical micelle concentration (CMC) of LPS; the *d*-spacing values of lipid A decreased from 4.19 Å to either 3.85 Å or 3.54 Å (**Fig. 1**), indicating increased packing densities in the presence of sub-nanometer gold clusters. In terms of biological relevance, the concentrations of key pro-inflammatory NF-κB-dependent cytokines, including plasma TNF-α, IL-6 and IL-1β, and CXC chemokines, in LPS-challenged mice showed a noticeable decrease. The treatment of anti-endotoxin gold nanoclusters was demonstrated to prolong significantly the survival duration in LPS-induced septic mice (**Fig. 2**), which would effectively protect patients from systemic inflammatory response syndrome (SIRS), septic shock and sepsis-induced lethality. Lin and her co-workers hope that this finding will be translated into industry to address the clinical problem (**Fig. 3**). (Reported by Shu-Yi Lin, National Health Research Institutes)

This report features the work of Shu-Yi Lin and her co-workers published in Nano Lett. ***18****, 2864 (2018).*

TLS 23A1 IASW – Small/Wide Angle X-ray Scattering

- SAXS, GIWAXS
- Soft Matter, Biomedical Materials, Medicine

Reference

1. F.-H. Liao, T.-H. Wu, Y.-T. Huang, W.-J. Lin, C.-J. Su, U.-S. Jen, S.-C. Kuo, S.-Y. Lin, Nano Lett. **18**, 2864 (2018).

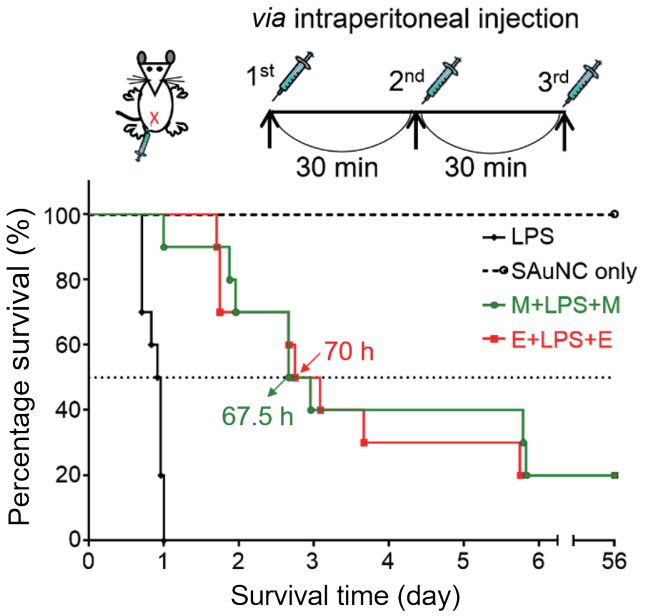


Fig. 2: Rates of survival of mice with LPS-induced sepsis (25 mg/kg BW) subjected to treatment with SAuNC of two kinds (75 mg/kg BW). The dashed line represents the half-percentage survival. M and E indicate SAuNC-M and SAuNC-E, respectively. [Reproduced from Ref. 1]

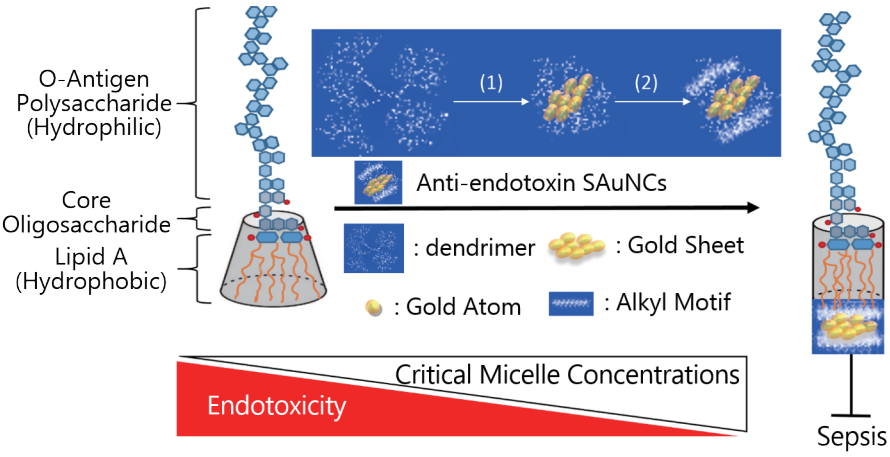


Fig. 3: Simple model representing the possible correlation between the packing density of lipid A of LPS and sepsis progression in the presence of SAuNC. The blue rectangle indicates the formation of a sub-nanometer gold cluster inside a dendrimer, in which steps 1 and 2 include the synthesis and alkyl-motif modification of gold nanoclusters, respectively, to form anti-endotoxin SAuNC. Please note that the conformation of lipid A is depicted as being conical (left side) and then cylindrical (right side) in shape to correlate with the change of CMC as well as the difference in endotoxicity. [Reproduced from Ref. 1]