Sona Gold Nanorods: The Ideal Nanoparticle for Photothermal Cancer Therapies?

Exploring the Context for Sona Nanotech's Toxin-free, Bio-compatible Gold Nanorods

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Glossary

Gold Nanorod(s)	**GNR(S)**	**Nanometer**	**nm**
Cetyltrimethylammonium Bromide	**CTAB**	**Near Infrared**	**NIF**
Gold Nanoparticle(s)	**GNP(s)**	**Mercaptopolyetheleneoxide**	**PEG-Thio**
Pegylation	**PEG**	**Real Time *in-vivo***	**RTiV**

Introduction

Sona Nanotech Inc. (Sona) conducts ongoing research to validate and further understand the biocompatibility and efficiency of its technology both of which are key to enabling important nanomedical advancements. Of particular interest is the ability to insert gold nanorods (GNRs) into cancerous tumours, then apply light energy to them, generating heat and killing nearby cancerous cells. This is a well-known and scientifically proven application of nanotechnology, though one not yet commercialized.

Sona's recent research has included a small animal study to confirm the expected biocompatibility of Sona GNRs and one evaluating their efficiency in generating heat from applied light.

While gold nanorods possess unique attributes, such as optoelectronic properties, thermal conductivity and surface plasmon tunability suitable for *in-vivo* applications, the biocompatibility of GNRs has been the subject of intense scientific scrutiny since their creation due to the standard practice of using cetyltrimethylammonium bromide (CTAB), a known toxic chemical, in their production.

Given this general concern, many investigations have been conducted to assess CTAB's toxicity, impact on cellular uptake, circulation, and distribution of GNRs within organs. Conventional wisdom suggests that the process of washing GNR's produced with CTAB or coating them with PEG (Polyethylene Glycol) either eliminates or reduces its risk significantly. However, what is clear, is the undisputed detrimental effects that any residual CTAB would have on cells, leading us to question the safety of using any material that has been produced with toxic CTAB for *in-vivo* applications.

Sona's proprietary GNR production process does not utilize CTAB, thereby eliminating this concern when using Sona GNRs *in-vivo*. Sona uses its own proprietary surfactant blends, called Gemini and Omni for production and these surfactants possess drastically different and non-toxic physicochemical characteristics when compared to CTAB. This unique attribute alone positions Sona GNRs as a prime candidate for use with *in-vivo* biomedical applications such as photothermal therapy, drug delivery and cell imaging.

CTAB TOXICITY ISSUES

CTAB is a well-known toxic cationic surfactant and is used for the shape directed growth of gold nanorods. CTAB remains suspended in solution and fixed on the surface of GNR's, even after rigorous centrifugation. Of significant concern to its presence for *in-vivo* applications is its well-known tendency to destroy animal cells and its ability to enter cells with or without GNRs present.

Regarding cell entry, two common active mechanisms have been studied: CTAB's interaction with the phospholipid bilayer that destabilizes the cell membrane and the catalytic action of a CTAB by-product CTA+ which quenches the enzyme ATP Synthase, reducing energy in the cell causing damage to mitochondria and inducing apoptosis (i.e. cell death).

RESEARCH ON SONA GNRS

As part of its ongoing research program, Sona has undertaken various studies with partners at leading institutions involved in cutting edge nanotechnology research. Recent studies include a confirmatory investigation into Sona GNRs' biocompatibility in a mouse model and an evaluation of their photothermal properties, including their efficiency at generating heat from a tuned light source.

SONA GNR'S BIOCOMPATIBILITY

The small animal study was conducted using a cohort of 12 healthy female BABL/c mice and showed no sign of toxicity following the Sona GNRs dose used in the study. Mice were dosed with 1nm and 13nm concentrations of Sona's Gemini and Omni 850nm GNRs that had both been surface functionalized with 10kDa Poly-ethylene Glycol (PEG) to aid in cell entry and *in-vivo* stability. Throughout the study, mice were weighed roughly every two days after gold nanorod administration until the experimental endpoint 14 days later. During the two-week period, no abnormalities in weight change were observed, as shown in Figure 1 below**:**

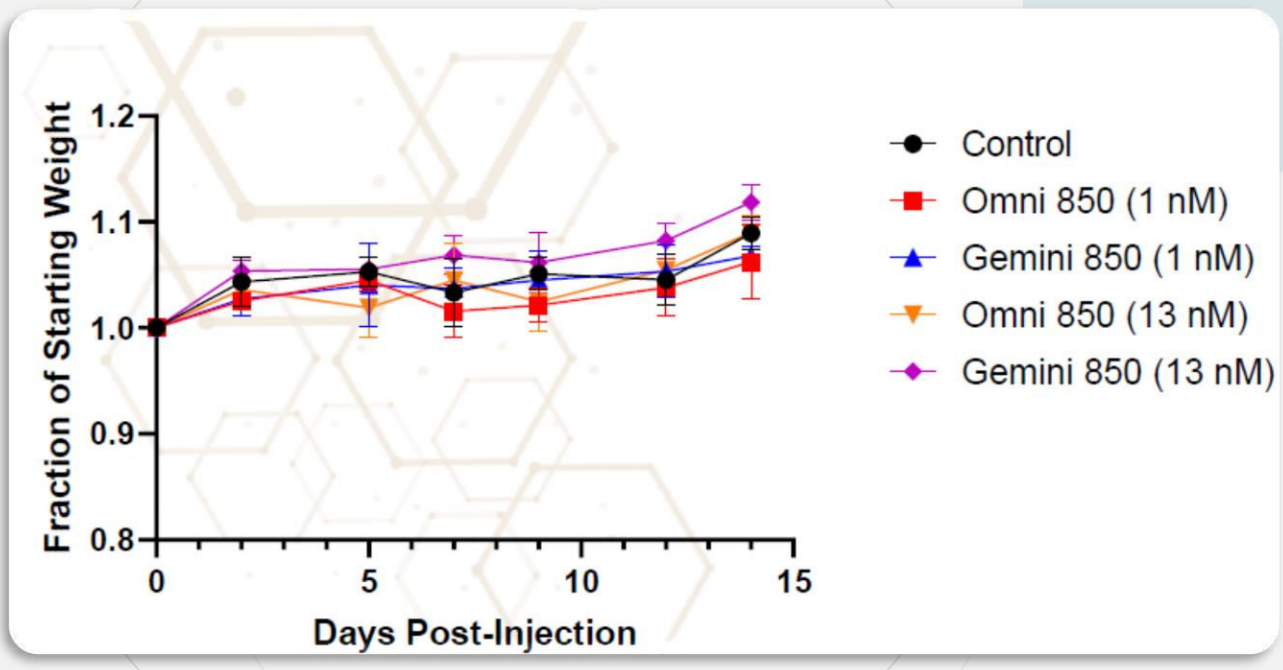

Figure 1. Weight changes in BALB/c mice after intravenous administration of gold nanorods. Data are reported as mean ± s.d. (n=3 per group).
Two weeks after gold nanorod administration, blood was collected in EDTA-coated capillary tubes for Hematology analysis across 15 different assays including total white blood cells, total red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total platelets, mean platelet volume, red cell distribution width, total neutrophils, total lymphocytes, total monocytes, total eosinophils and total basophils. (See Appendix 1)

Serum from this blood was collected, stored at -80°C and analyzed for nine different cardiovascular and liver biomarkers including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, total cholesterol, HDL cholesterol, LDL cholesterol, total triglycerides and glucose. (See Appendix 2)

All hematology and clinical chemistry values for the gold nanorod-treated mice were within the normal range with no toxicity observed for the dose concentrations used in this study, as was expected given the absence of CTAB from Sona's proprietary and patent-pending production process.

SONA GNRs EFFECTIVENESS FOR PHOTOTHERMAL THERAPY

One of the merits of using GNRs for photothermal therapies is their unique ability to be highly tuned to resonate at a specific wavelength by altering their size specifications during production. This attribute provides high functionality with commercially available light sources, such as near-infrared lasers and LED lights.

Near infra-red light, with resonance between 650nm and 1450nm, is commonly used to heat GNRs *in-vivo*, and can pass through tissue with a minimal loss of power. Tuned GNR's with wavelengths of ~850nm, in the middle of the therapeutic window, are therefore ideal for use in photothermal therapy.

In another recent study, Sona's 850nm Gemini and Omni GNRs were compared to an 850nm gold nanorod produced using CTAB and assessed with a laser tuned to the same longitudinal surface plasmon resonance (LSPR) of all nanorod samples (850nm). Optical densities of each sample were matched at ~ 1.1 in water, placed into a quartz cuvette at room temperature (~25°C) and exposed to a laser for 1800 seconds (30 minutes). The temperature of the solution was monitored over this period.

Both Gemini and Omni gold nanorods showed energy transfer equivalence to CTAB nanorods. Each nanorod type gradually increased the temperature of the solution at the same rate with no meaningful difference in their abilities to heat their respective solutions observed.

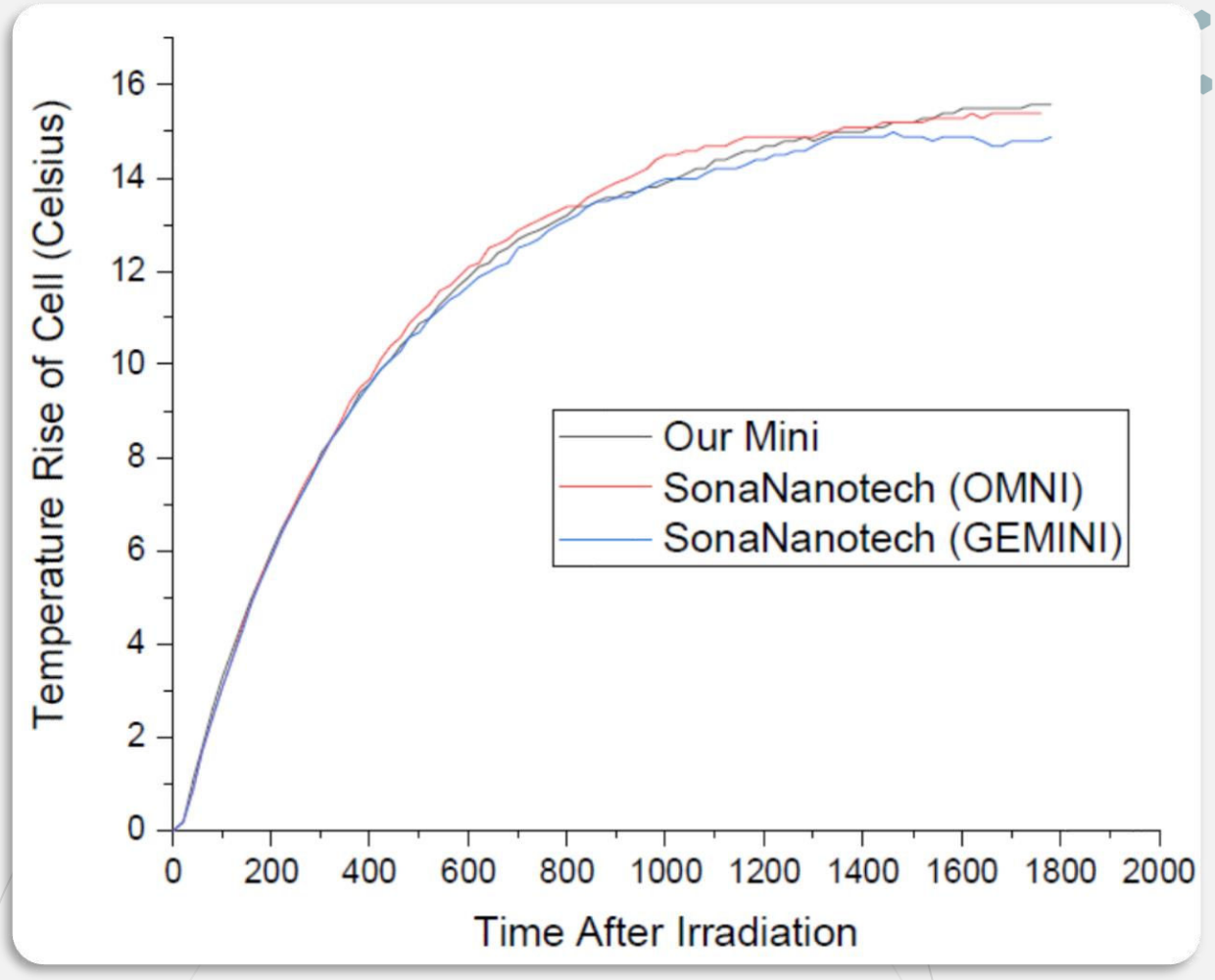

Figure 2. Temperature delta increases of GNR solutions over time

For all samples, a temperature delta plateau of 15°C was reached after ~1200 seconds (20 minutes). See Figure 2 above. This plateauing in temperature was likely due to the concentration of the nanorods in solution and the consistent power output of light produced by the laser. Both of these parameters could be manipulated to increase or decrease the temperature delta over a set period, indicating a highly controllable and tunable process to selectively create conditions for either hyperthermia or ablation of cells, the two commonly used approaches to destroy cancer cells. This capability is understood to be essential for permitting either of these two types of photothermal therapies to be conducted.

Further studies will be conducted using Sona GNRs to evaluate their effectiveness in photothermal therapies in both in-vitro tissue models and *in-vivo* animal studies, including various tumor and non-tumor models.

CONCLUSIONS

Sona's toxicity studies have shown Sona GNRs to be biocompatible while Sona's photothermal studies have shown them to be as efficient at generating heat from light as other GNR that used CTAB in their production.

These conclusions suggest that Sona GNRs have the potential to play a critical role in advancing nanotechnology medical applications, in which efficacy and safety are equally important, due to their functionality and unique biocompatibility properties. Further studies will aim to ensure Sona GNR's biological and physiological compatibilities to help catalyze advancements in these fields.

Key Takeaways

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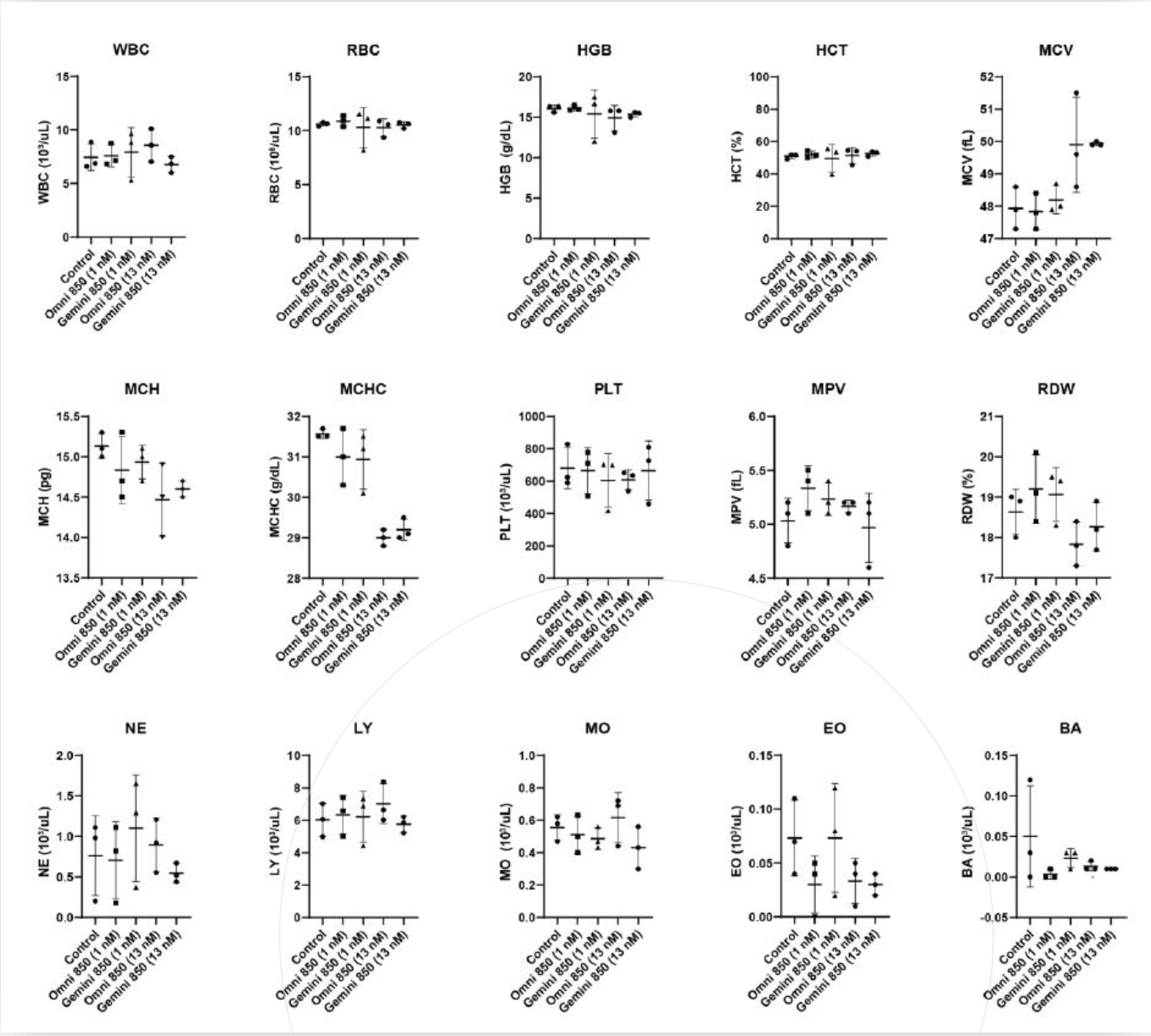
- CTAB-based nanoparticles should not be used for *in-vivo* applications as residual CTAB remains in solution and would be toxic to human cells.
- Sona GNRs generate no signs of toxicity in small animals in diluted and concentrated dose regimes.
- Sona GNRs induce heat transmission to its surrounding solution at the same rate and capacity as a CTAB-based gold nanorod.
- Sona GNR's are a prime candidate for use in photothermal therapy due to their optical properties, heat generating efficiency and unique biocompatibility.

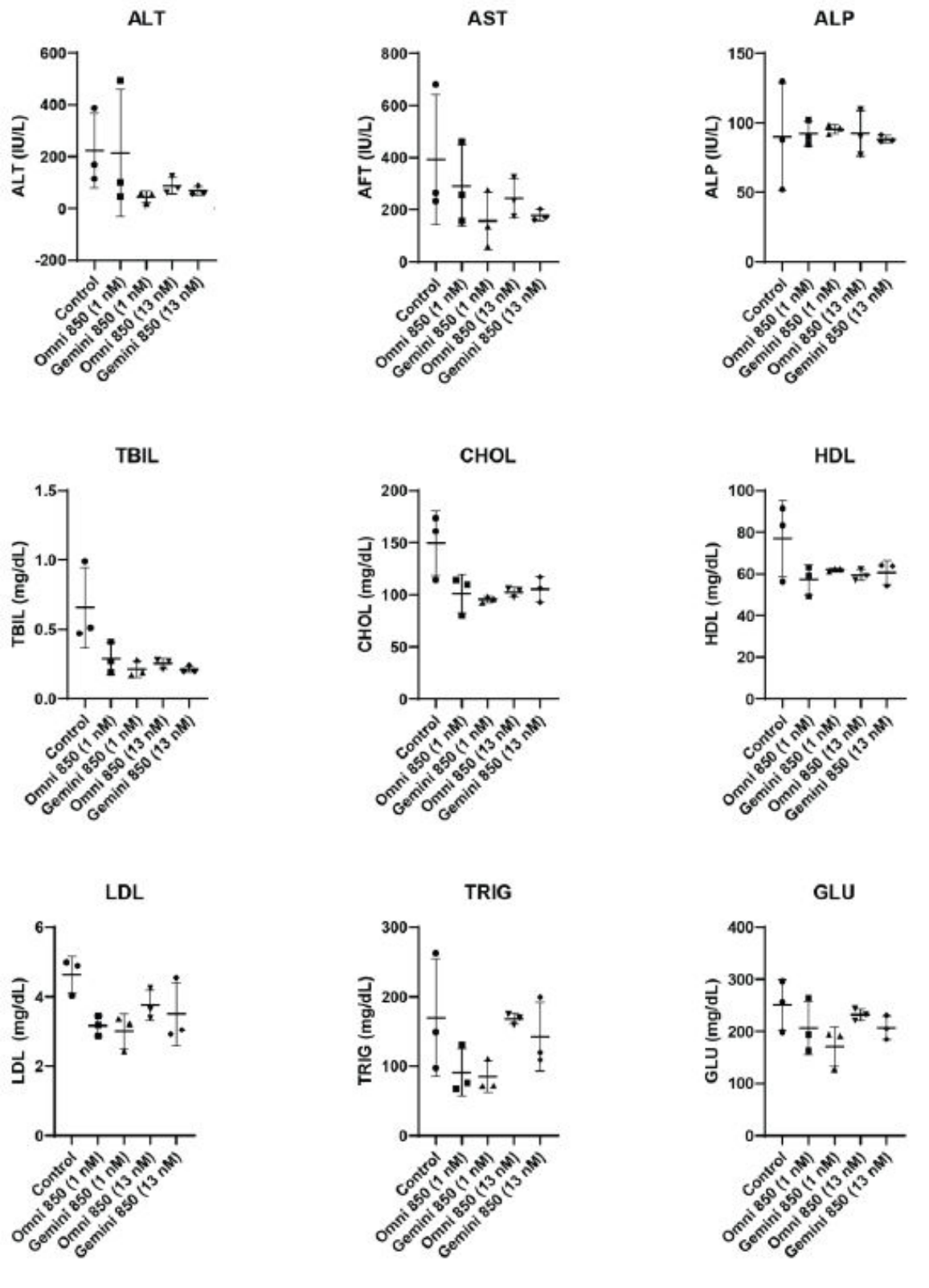
APPENDIX 1 - HEMATOLOGY AFTER GOLD NANOROD ADMINISTRATION



Data are reported as individual measurements along with the mean ± s.d. (n=3 per group).

Abbreviation note: WBC = total white blood cells, RBC = total red blood cells, HGB = hemoglobin, HCT = hematocrit, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, PLT = total platelets, MPV = mean platelet volume, RDW = red cell distribution width, NE = total neutrophils, LY = total lymphocytes, MO = total monocytes, EO = total eosinophils, BA = total basophils.

APPENDIX 2 - CLINICAL CHEMISTRY AFTER GOLD NANOROD ADMINISTRATION



Data are reported as individual measurements along with the mean ± s.d. (n=3 per group). Abbreviation note: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, TBIL = total bilirubin, CHOL = total cholesterol, HDL = HDL cholesterol, LDL = LDL cholesterol, TRIG = total triglycerides, GLU = glucose.

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MSDS Cetyltrimethylammonium Bromide (CTAB), www.columbuschemical.com