Transfection in Moderna Patent Litigation

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1. **Abstract**

Classical physics allows the atom to have heat capacity at the nanoscale, the conservation of heat proceeding by a change in temperature. However, simple QED based on the Planck law of quantum mechanics denies the atoms in nanoparticles (NPs) the heat capacity to conserve heat by a change in temperature, the consequence of which is ~80 nm lipid NPs conserve heat by creating UVC radiation. Patients tested positive for Covid-19 are therefore proposed to be given single intravenous injections of NPs in saline, the NPs emitting UVC to inactivate *in vivo* a limited number of Covid-19 virions that then act as the antigens to elicit immunity to the remaining virions currently in the patient's body, as well as to future Covid-19 infections. Indeed, simple QED is patentable as an *in vivo* Covid-19 vaccination; whereas, Moderna's patent based on the *surprising discovery* that non-lamellar lipid structures somehow produce charge in transfecting mRNA across cell walls is not patentable. However, the NPs may enter the brain and damage neurons and DNA, but with low level NP induced UVC intensity the NP induced damage is expected to be minimal. CDC testing to determine low level NP doses is requested.

Keywords: Covid-19, Quantum Mechanics, Planck law, Nanoparticles.

2. Introduction

Even before Covid-19 pandemic, Moderna attempted [1] to invalidate a US patent owned by Arbutus Biopharma because of similarity with the delivery of their mRNA-1273 vaccine. The Arbutus patent relates to lipid nanoparticles (NPs) having mRNA to allow the human body to *in vivo* produce therapeutic proteins. Indeed, Moderna in 2011 began study of various lipid NP delivery systems, one of which belonged to Arbutus. But Moderna did not work with Arbutus, and instead worked with Acuitus, a small spin-off of Arbutus. Recently, the U.S. Patent and Trademark Office (USPTO) rejected [2] the Moderna argument, but Moderna is expected to appeal the decision.

The issue in the Moderna/Arbutus dispute was the delivery of mRNA in a vaccine to a cell with a solid lipid nanoparticles (NPs). Vaccines usually deliver the antigen to a cell inside hollow spherical NPs. Moderna uses a solid NP to carry the mRNA on its surface that codes for whatever antigen is to be delivered to the cell.

Specifically, Moderna argued: the present invention is "patentably new" based on the *surprising discovery* that by controlling the lipid composition, a stable novel non-lamellar lipid nanoparticle (i.e., SNALP) can be produced. In contrast, prior art describes a lamellar lipid structure. However, the USPTO disagreed citing Atlas Powder, 190 F.3d at 1347 and Titanium Metals, 778 F.2d at 780, 782. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.”

In effect, the *surprising discovery* of Moderna that controlling the lipid composition a non-lamellar SNALP can be produced does not make the inherent characteristic of the prior art patentable by Moderna. Moderna is expected to appeal.

3. Background

Moderna claimed the *surprising discovery* that lipid complexes form three-dimensional solid nanostructures relate to transfection efficacy describing the efficiency of delivering the mRNA through a cell wall. In 2003, the lipid complexes comprised NPs of spherical lipid nanostructures [3] with mean sizes between 50 and 1000 nm.

Since then, the NP size has been reduced to sub-100 nm levels. Fig. 1 shows mixing DNA with liposomes containing PEG produces [4] electron-dense CL–DNA NPs (solid arrow) coexisting with cationic liposomes (dotted arrow). CL = cationic liposomes. Scale bar-100 nm

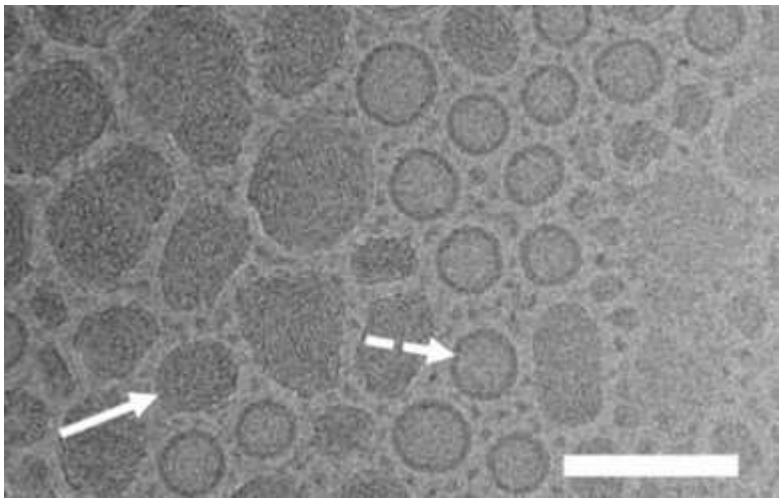

Figure 1. CL-DNA and cationic liposomes

The significance of the discovery [5] of the structure of CL-DNA complexes was highlighted by the finding that the structure of CL-DNA complexes affects their charging function. Indeed, the structure of lipid NPs as non-viral vectors in gene therapy explains how positively charged lipids electrostatically bind negative charged nucleic acids.

The basic lipid transfection structures comprise charged lamellar and inverted hexagonal. For hexagonal structures, transfection efficiency is independent of the membrane charge density. Lamellar lipid structures are shown [5] to evolve into inverted hexagonal shapes, but the evolution of the inverted hexagonal shape to a charged spherical shape was not presented. Thus, an alternate transfection mechanism, which is independent of membrane charge must dominate the interaction with cell walls.

4. Alternative Mechanism

Lipid NPs as non-viral vectors to introduce genetic material, e.g., mRNA into cells are not as effective as viral vectors. Because of this, it is instructive to consider the transfection of a viral vector across the cell wall as the conceptual upper bound of lamellar and inverted hexagonal non-viral structures evolving to spherical lipid NPs.

In this regard, the spherical Covid-19 virion as a viral vector is chosen to transfection of genetic material by lipid NPs. The Covid-19 virion is generally thought to enter the cell upon binding to Angiotensin converting enzyme II (ACE2) receptors. However, the Covid-19 symptom of the loss of smell is expressed even though the ACE2 receptors are not expressed [6] in olfactory neuron cells. In mouse models, genetically engineered human

ACE2 receptors in the nose exposed to SARS-CoV virus were found in the brain and not in the lung, suggesting ACE2 receptors are not necessary for the virus to transfect the cell wall. The question is,

How does the Covid-19 virion transfect a neutral charged cell wall?

Absent ACE2 receptors, the path to the brain suggests [7] the Covid-19 virion expresses a source of EM radiation, a source based on simple QED theory. Like transfection by charged [8] nano-needles, the EM radiation removes electrons from the virion to charge the body and spikes positive. Fig. 2 depicts [7] the Covid-19 body to emit long wavelength UVB (~320 nm) to initiate cytokine storms while the spikes emit EUV (~ 50 nm) radiation to burrow through cell walls.

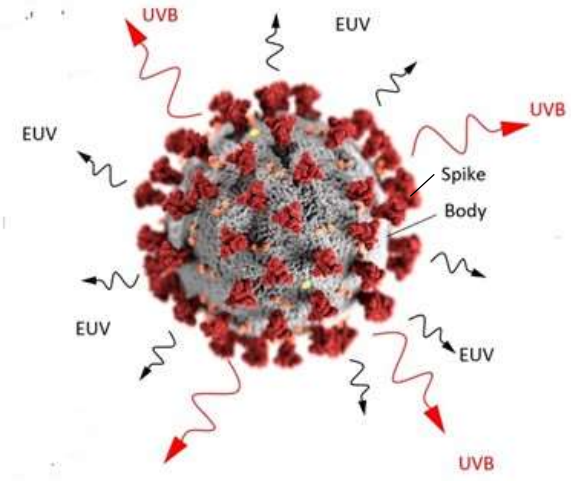

Fig.2 EM radiation from Covid-19 virion.

5. Purpose

The purpose of this paper is to present the simple QED theory of nanoscale heat transfer to explain how NPs can produce UV radiation within the human body. To illustrate, the Moderna lipid nanocarrier of mRNA injected intravenously is shown to be a source of UV radiation that by inactivating some of Covid-19 virions within the body of a patient already tested positive creates the antigens *in vivo* that elicit Covid-19 immunity to inactivate remaining in the body. Unlike Moderna, the mRNA is not necessary to elicit immunity - only the lipid NP to produce UV is important. However, UV radiation may also damage DNA, but in the short time necessary to disinfect a limited number of Covid-10 virions to elicit immunity, DNA damage is minimal and recoverable by DNA repair mechanisms. Developed over the past decade, simple QED is proposed as an *in vivo* vaccination avoiding long FDA approval times necessary in pandemic infections.

6. Analysis

The simple QED enhanced UVC radiation emitted from lipid NPs powered by heat in blood and tissue at normal body temperature illustrates the ease at which Covid-19 is disinfected as shown in Fig. 3.

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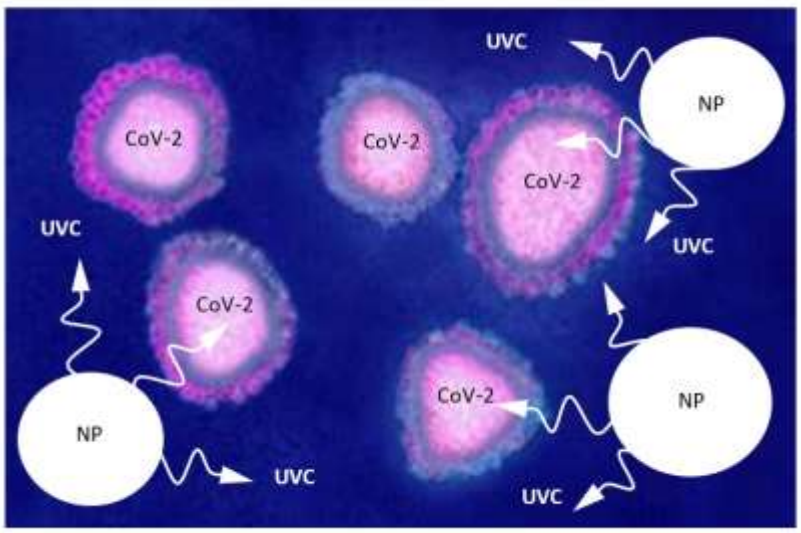

Fig. 3. UVC disinfection of Covid-19 by lipid NPs

Simple QED is a nanoscale heat transfer process based on the Planck law [9] of quantum mechanics (QM) differing significantly from that of classical physics in that the Planck law denies atoms in nanostructures the heat capacity to change temperature upon the absorption of heat. What this means is heat transfer without changes in temperature precludes the Fourier law of heat conduction commonly used in nanoscale heat transfer. Similarly, the Stefan-Boltzmann law for radiative heat transfer depending on temperature is not applicable to nanostructures. Although valid at the macroscale, the Fourier law and Stefan-Boltzmann equation are invalid at the nanoscale. Molecular Dynamics (MD) simulations [10] based on classical physics thought to provide an understanding of the atomic response to thermal disturbances assume atoms in nanostructures have temperature. Although MD is valid for periodic boundary conditions, extension to discrete nanostructures is not. Researchers need both new theory and computational procedures to be developed to understand nanoscale heat transfer from NPs in nanomedicine.

Simple QED is a method of nanoscale heat transfer analysis that conserves heat with the emission of EM radiation instead of temperature. QED stands for quantum electrodynamics, a complex theory based on *virtual* photons advanced by Feynman [11] and others. In contrast, simple QED is a far simpler theory based on the Planck law that requires the heat capacity of the atoms in nanostructures to vanish allowing conservation to proceed by the creation of *real* photons comprising EM waves that stand within and across the nanostructure.

Unlike electron level quantum states, simple QED quantum states are size dependent based on the dimension of the nanostructure over which the EM waves stand. By classical physics, the kT heat capacity of the atom is independent of the EM confinement wavelength λ, where k is the Boltzmann constant and T absolute temperature. QM differs as the heat capacity of the atom decreases under EM confinement $\lambda < 200$ microns, and at the nanoscale for $\lambda < 100$ nm, the heat capacity may be said to vanish. The Planck law at 300 K is illustrated in Fig. 4.

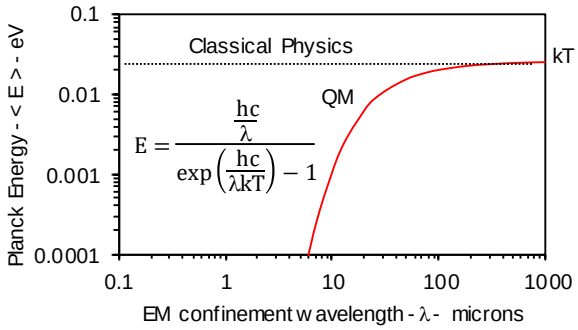

Fig. 4: Planck law of the Atom at 300 °K
In the inset, E is Planck energy, h Planck's constant, c light speed, k Boltzmann's constant, T temperature, and λ the EM confinement wavelength

EM confinement occurs by the high surface-to-volume (S/V) ratio of nanostructures that requires the heat Q to almost totally be confined in the surface, the surface heat itself as EM energy providing the brief EM confinement necessary to create EM waves standing across the internal dimension d of the nanostructure. For heat (or light) having wavelength $\lambda < d$, the absorption occurs over the incident face of the particle. However, for small particles $d << \lambda$, the light fully immerses the particle to be absorbed uniformly over the full surface. Fig. 5 illustrates $\lambda >> d$ with light (yellow) immersing the NP and absorbed in penetration depth δ over the full NP surface.

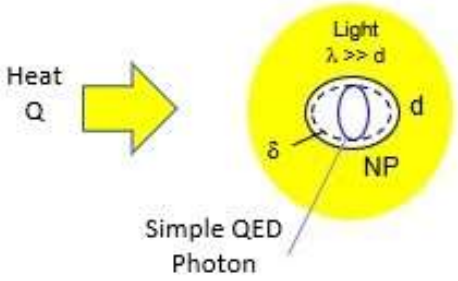

Fig. 5. Heat Q (or light) absorbed in full NP surface

Confinement of the light Q while creating the UVC standing wave requires EM confinement at least equal to the Planck energy E of the light. The pressure P acting on the surface is given for bulk modulus B and volume strain ΔV/V by, $P = B \cdot \Delta V/V = 6 \cdot \delta \cdot B/d$. But $P = E / V = 6E/\pi d^3$ giving $\delta = Q/\pi B d^2$. For an 80 nm NP with bulk modulus $B \sim 2x10^9$ N/m^2, the absorption depth δ of a single UVC photon is δ ~ 20 fm - a small but necessary depth to confine the absorbed heat Q = E to the geometry of the standing wave.

Simple QED absorbs heat Q in the NP surface given by the penetration δ depth. Unable to conserve the surface heat by a change in temperature, conservation requires the creation of simple QED radiation, the time τ to create the standing wave, $\tau = 2d/(c/n)$. The Planck energy $E \sim h/\tau = hc/2nd$ depends on the refractive index n of the NP to correct for the velocity c of light within the NP. The simple QED Planck energy E is quantized by the dimension d of the NP that defines the half-wavelength λ/2 of the nanostructure. Fig. 6 illustrates the standing EM radiation in a spherical NP of diameter d, but NP atoms still follow their quantized electron energy levels.

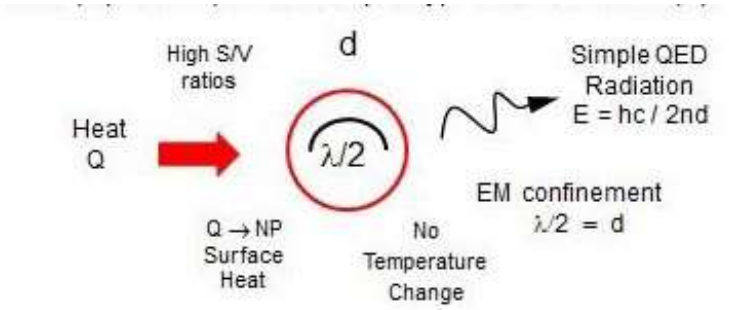

Figure. 6: Planck Energy of EM Radiation

In a rectangular NP with different dimensions of width, thickness, and length there are 3 simple QED quantum states corresponding to the different dimensions of the NP. However, only the minimum dimension is important as by Fermat's principle, the absorbed heat is dissipated in minimum time. Continuous variation in internal nanostructure dimensions produces a broadband spectrum of simple QED dissipated in continuous QED quantum states. Historically, the notion of size dependent quantum states is not found in the literature.

Classically, all atoms in the NP at equilibrium have temperature T equal to the bath temperature. In terms of the Boltzmann constant k and the number N of atoms, the total LNP thermal energy U is,

$$U = \frac{3}{2} NkT$$

However, by the Planck law the N atoms do not have kT energy. Instead, simple QED conserves the energy U that otherwise would occupy the 80 nm LNP by creating standing EM radiation across the NP diameter d as shown in Fig. 6.

The molecular weight of lipid meibomian C44H56O2 is 616 and the number Nm of molecules is, $Nm = (\rho V/616)\cdot Av$, where volume $V = \pi d^3/6 = 2.68 \times 10^{-22}$ m^3, density $\rho = 1000$ kg/m^3 and Avagadro's number $Av = 6.023 \times 10^{26}$ mols/kg-mol. Hence, $Nm = 2.62 \times 10^5$. For 102 atoms/molecule, N = 102 Nm = 26.7 million atoms → U ~ 1 MeV. For $E = hc/\lambda$ at λ = 248 nm, E ~ 5 eV, the NP creates about 200,000 UVC photons upon equilibrating with the 300 °K thermal bath temperature

However, the UVC photon must be created promptly, say < 5 fs. What this means is the UVC photon cannot be created from body temperature surroundings. Much higher bath temperatures are required. To classically create the UVC photon, the required temperature T is, $T = E/1.5k \sim 37{,}000$ °K.

But high temperatures are not necessary for NPs under high EM confinement. Indeed, once the heat Q is absorbed in the penetration depth δ = 20 fm of the NP, the creation time τ of the UVC photon $\tau = 2d/(c/n) \sim 0.85$ fs < 5 fs < 5 fs and acceptable.

7. Discussion

The simple QED radiation induced in the Covid-19 virion body and spikes including lipid NPs proposed for the 'The Nanoparticle Treatment' from thermal energy in the surroundings is summarized in Table 1.

Table 1
Simple QED Energy and Wavelengths

	Covid-19 Body	Covid-19 Spike	Nanoparticle NP
Material	Coronavirus	Coronavirus	Lipid
Diameter d (nm)	100	15	80
Refractive Index n	1.6	1.6	1.55
Wavelength λ (nm)	320	48	248
Planck E (eV)	3.88	26	5

The simple QED Planck energy E and wavelength λ are based on the NP diameter d and refractive index n. The Covid-19 body diameter d varies from 80 - 120 nm [12] with 100 nm being the average for the coronaviridae family. Like SARS, the Covid-19 spikes are globular proteins d ~ 15 nm in diameter [13] attached to the virus body by a narrow stalk.

Regarding the index n of the virus, available data is not clear. Even so, the index in the UV or EUV is required, but only data is available in VIS, e.g., n = 1.42 at λ = 830 nm [14]. Optical fringe measurements [15] show a maximum index n ~ 1.8 with the average of variations across the virus body taken n ~ 1.6. The index n of the spikes could not be resolved [16] and is also taken at n ~ 1.6. The index n ~ 1.55 of the lipid NP described above in relation to the Planck energy E in the compression induce upon the absorption of the 250 nm photon was extrapolated from data [12] at 400 nm.

Recall EUV (< 200 nm), UVC (200 to 280 nm), UVB (280 to 320 nm), and UVA (320 to 400 nm). The Coronavirus body emission (320 nm at long wavelength UVB) and spikes (48 nm in the EUV) while the NP emits (~248 nm near the 254 nm UVC peak). It is noted the Coronavirus body emission increases toward the UVC peak for NP diameters < 80 nm.

7. Conclusions

The Moderna patent based on a *surprising discovery* of non-lamellar lipid structure was properly rejected by the USPTO as not patentable. Moreover, Moderna's inference that charge is somehow produced in non-lamellar lipid structures is invalid.

Simple QED produces charge depending on the size of NPs < 100 nm formed by lipid structures independent of lamellar or non-lamellar phases, the charge produced by EM radiation removing electrons to produce positive charge.

Like the Moderna patent based on a *surprising discovery* of non-laminar lipid structures, simple QED charging based on the theory of the Planck law is also not patentable as scientific theories are not patentable. But applications of scientific theories are patentable. Hence, charging of NPs by simple QED should be patentable.

The Planck law allows ~80 nm lipid NPs to produce UVC radiation that disinfects the Covid-19 from the heat at body temperature, a significant difference with classical physics that predicts the lipid NP only acquires body temperature.

Regarding Covid-19 disinfection, simple QED produces UVC from lipid NPs using only the thermal energy of the surrounding blood and tissue.

In the manner of an *in vivo* Covid-19 vaccine, the NP treatment of UVC disinfection of a patient tested positive by a single intravenous injection that inactivates a limited number of live virions to produce the inactivated virions that act as the antigen to elicit immunity to inactivate the remaining virions in the body, including future Covid-19 infections.

The FDA is recommended to approve UVC disinfection of Covid-19 in vaccinations of ~ 80 nm lipid NPs in small quantities. In the blood stream, the disinfection would be rapid. NPs entering the brain may damage neurons and DNA. Nevertheless, the temporary low UVC levels make risks minimal by allowing DNA recovery by repair systems.

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