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A Theoretical Mechanism for the Action of SONG-Modulated Laser Light on Human Very Small Embryonic-Like (hVSEL) Stem Cells in Platelet Rich Plasma (PRP)

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Abstract

It has previously been shown that human very small embryonic-like (hVSEL) stem cell proliferation occurs rapidly when hVSEL stem cells in platelet rich plasma (PRP) are exposed to Strachan Ovokaitys Node Generator (SONG)-modulated laser light. The surface antigens Oct 3/4, SSEA4 and CXCR4 in the lineage negative (Lin-) compartment were assessed using flow cytometry. Of these three markers, it is known that CXCR4 may be blocked from binding to flow cytometry antibodies by its antagonist ligand, the Endogenous Peptide Inhibitor of CXCR4 (EPI-X4). In this theoretical manuscript, we focus on possible novel methods of unblocking CXCR4 by SONG-modulated laser light to make it readily available for binding by flow cytometry antibodies. We propose that the SONG-modulated red laser penetrates the minor pocket of CXCR4 and thus disrupts the hydrogen bonds and salt bridges binding CXCR4 to EPI-X4. A quantum-mechanical description of the laser interaction with the hydrogen atoms of the hydrogen bonds and salt bridges provides an atom-level illustration of the forces producing stem cell proliferation effects in vitro. This is a novel description of the mechanism of action of SONG-modulated laser light on stem cell antigens at the quantum level which may have wide implications in stem cell biology and regenerative medicine.

Introduction

Our previous research has shown the presence of human very small embryonic-like (hVSEL) stem cells in platelet rich plasma (PRP), which were exposed to Strachan Ovokaitys Node Generator (SONG)-modulated (5 mW, 670 nm) red laser light. SONG modulation of laser light cancels the central wavelength band of the laser output in a process described as non-fringing destructive interference. The remaining upper and lower wavelength bands create a beat frequency pattern of sparse nodes of constructive interference which represents the physical visible light that remains. Modulation of this complex wave form pattern results in a rapid traverse of these nodes that can reach pulse repetition frequencies at intervals as rapid as sub-femtosecond. The destructive interference and sparseness of the nodes reduces the flare at the surface of the tissue interface[1]. The laser light was adjusted through optical phase conjugation to a power of 1 mW output for 3 minutes. The resultant laser-exposed hVSEL stem cells were then assessed for cell proliferation using flow cytometry. Those hVSEL stem cells exposed to laser light were shown to have an increase in proliferation compared to controls[1]. In this theoretical paper, we provide a quantum mechanical model to explain these observations.

Human very small embryonic-like (hVSEL) Stem Cells

hVSEL stem cells are pluripotent stem cells found in peripheral blood and most tissues, and represent

a unique and readily available source of stem cell for regenerative medicine procedures[2,3]. Other authors have also confirmed the presence of hVSEL stem cells in peripheral blood and that these cells may be envisioned as "cellular paramedics" that are involved in immune surveillance or tissue and organ rejuvenation[4].

It is generally agreed that hVSEL stem cells are a population of epiblast-derived cells created during embryonic gastrulation which further highlights their important role in normal physiology as well as their role in rejuvenation and longevity[5]. The possible role of hVSEL stem cells in disease modulation is under intense study, including research on cardiovascular disease[6], neurogenesis[7], Crohn's disease[8] and even reproductive biology[9]. Given this background, it is clear that hVSEL stem cells play an important role in both normal physiology and disease. An enhanced understanding of how we may improve the biological potential of these cells by using modulated laser light will lay the groundwork for future exciting collaborations between healthcare scientists and quantum physicists to develop a unified understanding of cell biology at the finite level. This paper contains reference to terminology used in quantum physics which may be unfamiliar to some readers. This quantum physics terminology is explained in "***Supplementary Material - Appendix A***" to assist those readers who are not quantum physicists.

Biology of the CXCR4 antigen

The Endogenous Peptide Inhibitor of CXCR4 (EPI-X4) is the antagonist ligand of the C-X-C Motif Chemokine Receptor 4 (CXCR4)[10]. This naturally occurring peptide, originating from the fragmentation of albumin, binds to the CXCR4 antigen mostly by interacting in the minor pocket of CXCR4 through its N-terminal residues, inhibiting G-protein signaling to the associated cells[11]. There have been several EPI-X4 derivatives reported[12] and their IC50 (half maximal inhibitory concentration) values show that N-terminal residues of EPI-X4 are crucial for binding to CXCR4 ***(see Supplementary Material - Appendix A)***[13]. It has subsequently been shown that the NTER-IN configuration (N-terminal of EPI-X4 inside the binding pocket of CXCR4) plays a pivotal role in CXCR4/EPI-X4 binding. Furthermore, only seven EPI-X4 residues played any significant role in this binding, four of which (all positively charged) interact through the minor pocket of CXCR4[14], forming three salt bridges and one hydrogen bond.

Salt bridges are electrostatic and hydrogen bonding interactions between oppositely charged residues. Whereas hydrogen bonds can combine (as in water) to create a major force, individual bonds are weak and easily broken. The distance between the residues participating in a salt bridge is important, being less than 400 picometers (pm)[15]. Amino acids greater than this distance apart do not qualify as forming a salt bridge, and salt bridges undergoing thermal fluctuations continuously break and reform their hydrogen bonds[16].

In addition to the positively charged N-terminal salt bridges and hydrogen bonds, the negatively charged EPI-X4 residue L16 (C-terminal Leu) interacting with the CXCR4 residue K271 (Lys) has a destabilizing effect. However, chemical elimination of L16 showed little effect on the binding of EPI-X4 to CXCR4, demonstrating that the first three salt bridges and the hydrogen bond are the major agents of the binding (Table 1). The last two of the seven significant interactions, V11 and T15 of EPI-X4 interact with E25 and R30, which comprise the β-strand of CXCR4, and provide some small additional binding stabilization (Table 1). The chemical elimination of EPI-X4 residue L1 or K7 almost completely eliminates receptor binding[17].

EPI-X4, originating from albumin fragmented in the acidic conditions of embryonic gastrulation[18], binds to and dysregulates the CXCR4 expressed by hVSEL stem cells. This protects the salt bridges and hydrogen bonds (Table 1) in the minor pocket of CXCR4 from thermal fluctuations, thereby maintaining hVSEL stem cell quiescence[19].

The *prima facie* evidence of rapid proliferation of hVSEL stem cells in PRP *in vitro* demonstrates that the SONG-modulated red laser light is penetrating into the minor pocket of CXCR4, interrupting the salt bridges and the hydrogen bonds (Table 1). This breaks the CXCR4/EPI-X4 binding and exposes CXCR4 to labelled antibodies in the subsequent flow cytometry analysis. The important question which results from these observations is by what mechanism does such a low-intensity, SONG-modulated red laser light disrupt the CXCR4/EPI-X4-complex hydrogen bond and salt bridges within the minor pocket of CXCR4?

Table 1. EPI-X4/CXCR4 residues and bonds.

EPI-X4 Residue	CXCR4 Residue	Bond Type	Effect
L1 (N-terminal Leu)	D97 (Asp)	Salt Bridge	Main Stabilizing
K6 (N-terminal Lys)	D187 (Asp)	Salt Bridge	Main Stabilizing
K7 (N-terminal Lys)	D262 (Asp)	Salt Bridge	Main Stabilizing
R3 (N-terminal Arg)	H281 (His)	Hydrogen Bond	Main Stabilizing
L16 (C-terminal Leu)	K271 (Lys)	Salt Bridge	Minor Destabilizing
V11 (Val)	E25 (β-strand Glu)	Hydrophobic	Minor Stabilizing
T15 (Thr)	R30 (β-strand Arg)	Hydrophobic	Minor Stabilizing

Abbreviations: CXCR4, C-X-C Motif Chemokine Receptor 4; EPI-X4, Endogenous Peptide Inhibitor of CXCR4.

Generalized Quantum Mechanical Description of the Hydrogen Bond

The process which associates the interaction of modulated laser light with the relevant quantized energy levels of hVSEL stem cells and the related laser-induced turbulence and heating is fairly complex. It would nevertheless be a useful starting point to provide a simple quantum mechanical model which captures the essential features of this interaction.

For a hydrogen bond, the dimensionally reduced Hilbert space has two interacting diabatic states ***(Supplementary Material - Appendix A)*** that can be denoted as $(D - H, A^-)$ and $(D^-, H - A)$. The former represents a product state of the electronic states of an $A-$ ion of a D-A bond in the absence of the acceptor. The difference between the two states arises from the transfer of a proton from the donor towards the acceptor and back again.

The Hamiltonian ***(Supplementary Material - Appendix A)*** for the two diabatic states has matrix elements that depend on the D-H bond length r, the donor-acceptor separation R, and the angle ϕ, which describes the deviation from linearity (Figure 1).

The effective Hamiltonian describing the two interacting diabatic states has the form:

$$H = \begin{pmatrix} V_D(r) & \Delta_{DA}(R,\phi) \\ \Delta_{DA}(R,\phi) & V_A(r^*) \end{pmatrix}$$

where $V_D(r)$ and $V_A(r^*)$ constitute the Morse potential ***(Supplementary Material - Appendix A)*** for the system, and $r^* = \sqrt{R^2 + r^2 - 2rR\cos\phi}$ is the length of the A-H bond (Figure 1).

The diabatic states are coupled via the off-diagonal matrix element:

$$\Delta_{DA}(R,\phi) = C\cos\phi\,\frac{R - r\cos\phi}{r^*}$$

where R, r^* and ϕ are as defined above, and C is a scalar whose components may vary with the chemical identity of the hydrogen bond donor and acceptor atoms.

As the system under description has two interacting diabatic states with two bonds, D-H and H-A (which are highly anharmonic), a simple, single harmonic potential will not suffice. The Morse potential can be used to better determine the diabatic states by describing each state independently.

For each case, $j = D$, where A denotes the donor D-H bond and acceptor H-A bond, respectively.

The Morse potential ***(Supplementary Material - Appendix A)*** is:

$$V_j(r) = D_j\left[e^{-2a_j(r-r_{0_j})} - 2e^{-a_j(r-r_{0_j})}\right]$$

where D_j is the binding energy, r_{0_j} and a_j) are constants denoting the equilibrium bond length

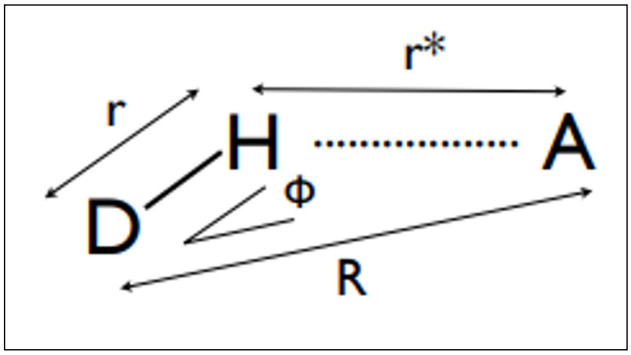

Figure 1. Definition of geometric variables for a hydrogen bond between a donor (D) and acceptor (A). Legends: r is the D-H bond length; r* is the A-H bond length; R is the donor-acceptor separation. The angle ϕ describes the deviation from linearity, upon which the strength of the bond is directly related (the strongest bonds occur when ϕ is at zero and $R = r + r^*$).

and the decay constant, respectively. D_D and D_A and denote the proton affinity of the donor and acceptor, respectively.

The energy of the stationary, interacting diabatic states determined by the above Hamiltonian can be calculated using the time-independent Schrödinger equation ***(Supplementary Material - Appendix A)***:

$$H|\Psi(x)\rangle = E|\Psi(x)\rangle$$

where E is the energy of the system and Ψ is the wave function. ***(See Appendix A)***[10].

The fluctuations in energy values E for the diabatic states of the system are illustrated in Figure 2.

There is an energy barrier between the donor and the acceptor that drops as the donor-acceptor distance decreases. At the lowest energy levels, the hydrogen atom will be more strongly connected to the donor, so it is most likely to be found on the donor side of the energy barrier but is delocalized on the length scale about 20-30 pm apart[20]. As the donor-acceptor distance R decreases and the energy barrier draws closer to the zero-point energy levels of the system, the hydrogen will be found more centrally, but delocalized as before. Increases in temperature will weaken hydrogen bonds, inducing greater thermal motion. The length and therefore the strength of a hydrogen bond is exquisitely sensitive to temperature and pressure. Hydrogen bonds are generally so weak that their internal energy is directly related to their strength, with the equilibrium bond distance controlled by a combination of both thermodynamics and quantum mechanics. Single hydrogen bonds are likely to form weak or low-barrier bonds, but still fall within the $R < 400$ pm required to qualify as a salt bridge.

SONG-modulated laser effects on hydrogen bonds and salt bridges in CXCR4/EPI-X4 binding

Figure 3 illustrates how the delocalization of the hydrogen atom on either side of the energy potential curve of weak and low-barrier bonds is likely to be found at either its ground state energy E_0 or at its first excited state E_1. If, at any time, the hydrogen atom can be energized from E_1 to E_2, the hydrogen atom will be even more strongly bound to the donor atom, dissociating it still further from the acceptor atom. The energy required to achieve this, would need to be 1.9 eV ***(Supplementary Material - Appendix A)***.

The light emitted from a laser is quasi-monochromatic with a small spread in wavelengths around the central wavelength (spectral width). Lasers emit light that is highly directional and emitted as a relatively narrow beam. The SONG-modulated laser light is further focused by destructive and constructive interference patterns potentially enabling deeper penetration with far fewer "scattering" effects. The receptor (the hydrogen atom) responds to excitation from the transmitter (the laser), and the transmitter is an amalgam of single atoms, each one excited singly, each one producing its own energy wave. Every reaction at the receiver is in response to a single atom excitation at the source (the transmitter). As the light is at the lower-energy red end of the spectrum of visible light,

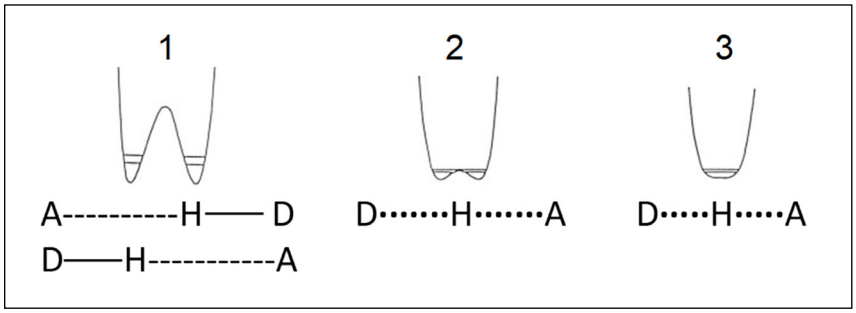

Figure 2. Hydrogen Bond Energy Barriers. 1) Weak bonds (R >260 pm). There is a large potential barrier, and so the tunnel splitting are a small fraction of the energy spacings. The hydrogen is firmly attached to either the left-hand or right-hand donor and is more loosely bonded to the acceptor. There is an energy barrier between the two possible positions of the hydrogen, with the zero-point energy levels shown as horizontal lines. 2) Low-barrier bonds (R=240-260 pm). The zero-point energy is comparable to (but less than) the potential barrier. There is still a visible tunnel splitting of the two lowest levels. 3) Strong bonds (R≤240 pm). The ground state lies above the barrier or there is no barrier.

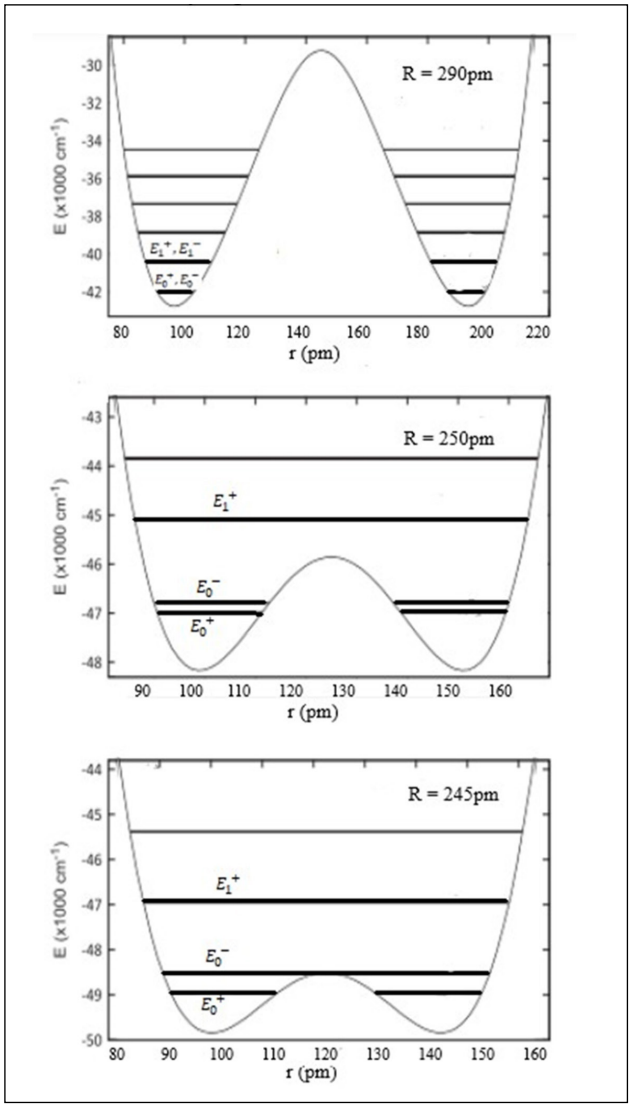

Figure 3. Potential energy curves and the vibrational energy levels. The donor-acceptor distance R is decreasing from top to bottom, from weak to moderate bonds. The energy levels shown are for hydrogen atoms. Note: The horizontal and vertical scales of the above graphs differ slightly.

each transmitter atom produces red light, which will react with any E_1-energy hydrogen atom. Increasing the intensity of the red light merely excites more single laser atoms, which cannot excite the receiver hydrogen atoms any higher than from E_1 to E_2. While it will react with particles in the general *in vitro* environment, most likely yielding some small insignificant thermal effect, the SONG laser as discussed above will penetrate the minor pocket of CXCR4. The red SONG laser, at 670 nm, will supply precisely the energy to interact with the hydrogen bonds and therefore the salt bridges within the minor pocket of CXCR4. Every atom at the source of the red laser light will supply the 1.9eV to every hydrogen atom it finds in its E_1, to excite into its E_2 state.

Referring again to the time-independent Schrödinger equation, the two diabatic stationary states:

$$H|\Psi_{(0)}\rangle = E_{(0)}|\Psi_{(0)}\rangle$$

$$H|\Psi_{(1)}\rangle = E_{(1)}|\Psi_{(1)}\rangle$$

Interaction with the SONG laser results in a destabilizing third state:

$$H|\Psi_{(2)}\rangle = E_{(2)}|\Psi_{(2)}\rangle$$

which constitutes a perturbation from the interrelating two-state equilibrium of the hydrogen bonds and therefore the salt bridges. No data exists on which to build a model of the turbulent conditions instigated in hydrogen bonds by laser perturbations; but if the assumption is made that only the delicate hydrogen atom is immediately affected, so that the donor-acceptor length R is maintained initially, the following elements of the Hamiltonian become the most likely perturbation variants:

r, r* and ϕ

as the Hamiltonian describing the two interacting diabatic states has the form:

$$H = \begin{pmatrix} V_D(r) & \Delta_{DA}(R,\phi) \\ \Delta_{DA}(R,\phi) & V_A(r^*) \end{pmatrix}$$

Of these, most importantly, ϕ will be increased with the extra hydrogen atom energy supplied by the SONG laser. As the strongest bonds occur when ϕ is at zero and , any initial increase in ϕ, with R initially unaffected, r and r* will both be increased (Figure 1), undermining the strength of the hydrogen bond.

The SONG-modulated stream of red-energy photons continuously penetrates the minor pocket of CXCR4, reacting with and undermining the stability of the hydrogen bonds and disrupting the electrostatic bonding of the salt bridges. The destabilized residues will also begin to affect one another, swapping thermal energy, increasing the

environmental temperature of the binding pocket. As soon as the new turbulent environment of the binding pocket breaks a hydrogen bond, the zero-point energy of that bond is released, adding still further to the destabilizing energy, increasing the temperature once more, until sufficient bonds are dismantled (Table 1) to enable the breaking of the binding of EPI-X4 to CXCR4.

Further experimental analysis of the hydrogen bond and salt bridge dismantling would be necessary to detail the processes in terms of the variables involved in the turbulence, but we offer the above as an accurate description of the elimination of the binding of EPI-X4 to CXCR4, exposing the *in vitro* hVSEL stem cells to a rapid increase of CXCR4 antigen availability for labelling by flow cytometer antibodies.

Optimal laser exposure times

A 3-minute exposure time has proven the most effective, in which the laser thermal turbulence in the minor pocket of CXCR4 maximizes the proliferation of hVSEL stem cells *in vitro*[1]. In 3 minutes, the binding of EPI-X4 to CXCR4 has been broken and the laser has become ineffective because the thermal energy of the minor pocket is comparable to that of the red-energy laser. After 3 minutes - specifically at 6 and 9 minutes - of continuous laser exposure, the CXCR4 antigens available for antibody binding have been shown to decrease[1]. A new thermal stability has become established in the minor pocket of CXCR4 as the turbulent conditions subside. In the hotter but now stabilizing conditions, the binding residues of CXCR4 and EPI-X4 are forming new bonds, the nature and binding strength of which would require further experimental analysis. However, the two adiabatic states, with the shared hydrogen atom at E_0 and E_2, allow donor/acceptor distances *(R)* and values of r, r* and ϕ to change which allow new hydrogen bonds, or indeed salt bridges to form. This demonstrates some significant re-binding effect across the CXCR4/EPI-X4 complex[1].

Conclusions

The observation that SONG-modulated laser light stimulates proliferation of hVSEL stem cells (in terms of CXCR4 expression) illustrates how exchanges of energy at the quantum level initiate biological processes. The response of hVSEL stem cells to the SONG-modulated laser light is a quantum effect and can only be properly described on a quantum level. This demonstrates not only how quantum mechanics can describe biological effects, but how quantum effects could be harnessed to purposely initiate and even control biological processes. Quantum energies and relationships are complex, involving such concepts as uncertainty and probability, the exclusion principle, entanglement, spin and polarization. Some, if not all, of these are continuously in operation in the atoms and molecules that constitute all cells, creating many fundamental questions in cell biology, optical and quantum physics. SONG-modulated laser light may have similar effects on other cells and tissues and if the initial observations are correct then we need a clear understanding of the mechanism of action between laser light and living cells. In this paper we have started to develop some of the first ideas and concepts which may be relevant, especially those interactions which occur at the molecular and quantum levels. Bringing together cell biology and quantum physics may enable extremely significant future developments in the understanding of normal physiological and disease states in addition to groundbreaking therapeutic technology.

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Conflict of Interest:
John Brindley and Peter Hollands have no conflicts of interest to disclose. Todd Ovokaitys is the CEO of Qigenix.

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