To: The Editor, Stem Cell Research and Therapy  
From: Prof Heidi Abrahamse  
Date: 18 August 2013  
Title: Lung Cancer Stem Cells and Low Intensity Laser Irradiation (LILI): A Potential Future Therapy?  
Authors: Anine Crous and Heidi Abrahamse

CORRECTIONS TO MANUSCRIPT: MS: 6868544491024586

Dear Dr Tuan

Please find below detailed corrections as made to the above manuscript on recommendation of the reviewers.

REVIEWER 1

1. Page 3, Lung Cancer: The following sentence is contradictory "These modifications occur as a result of genetic sequence or epigenetic alterations, where modification is seen in gene activation or proteins, but does not affect the gene sequence itself [8,9]." The authors state that there is alterations in the genetic sequence, but then go on to say that the gene sequence is not affected.
   Corrected: These modifications occur as a result of genetic sequence or epigenetic alterations, where modification is manifested in gene activation or expression of proteins [8,9].

2. Page 14, Line 10 and 14 and Page 15 line 17: The abbreviation ROS should be used, it has already been written out in full on page 3.
   Corrected: Page 14, Line 10 and 14 and Page 15 line 17, the abbreviation ROS is now used as it has been already written out in full as reactive oxygen species on page 3.

3. Reference 55 is missing a volume number.

4. Are all the journal references used in this paper from journal supplements as indicated?
   Corrected: All supplements were corrected.

5. The number of references used is 63, this exceeds the journal limit of 50.
   Corrected: Number of references in text 50, number of references in edited table 9.

6. Figure 1: The arrow leading to increased ATP needs to be aligned.
   Corrected:

7. Since a number of abbreviations has been used in the paper, a list of abbreviations after the conclusion would be useful.
   Corrected: Abbreviation list now included in manuscript
**Abbreviations**

CSCs, cancer stem cells; SCs, stem cells; LILI, Low Intensity Laser Irradiation; ATP, adenosine triphosphate; PDT, photodynamic therapy; PS, photosensitiser; ROS, reactive oxygen species; CT, computed tomography; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ESCs, embryonic stem cells; ASCs, adult stem cells; TICs, tumour initiating cells; HH, Hedgehog; NCI, National Cancer Institute; mW, milliwatts; W/cm², watts per centimetre squared; mW/cm², milliwatts per centimetre squared; nm, nanometres; lambda, λ; HeNe, Helium-Neon; cAMP, Cyclic adenosine monophosphate; mRNA, messenger ribonucleic acid; ATPase, adenosine triphosphatase; cell-SELEX, Systematic Evolution of Ligands by Exponential Enrichment; NIRF-I, near-infrared fluorescence imaging.

**REVIEWER 2:**

1. **I would recommend to provide further discussion on the effect of LLLT on the normal cells and effect on malignant cells, and discuss the difference between the two.**
   **Corrected:** Inserted on pg 12, final paragraph: A study conducted by Al-Watban and Bernard, (2011), on normal and malignant cell lines consisting of the following: embryonic (3 T3, CCI-226 mouse embryonic fibroblast), human skin fibroblasts (HSF), Chinese hamster ovary cells (CHO) and neoplastic cells (RIF-1 and EMT-6), were treated with LILI in order to determine the laser dose for the different stimulatory or inhibitory effects while keeping all cell lines at similar conditions. They concluded that there is dose-dependency for cell growth to laser treatments and that the extent of cellular proliferation is influenced by the type of cells involved. Normal cells showed biostimulation exploiting stem cell expansion and differentiation. Malignant cells also indicated increase in proliferation suggesting that LILI has the capability to induce further cell growth of neoplasms; nonetheless LILI also induced cell bio-inhibition at higher energy outputs implicating the use of LILI to destroy malignant cells. This study showed that the optimum biostimulatory dose at a wavelength of 632.8 nm is at 180 mJ/cm² and bioinhibitory doses were from 420–600 mJ/cm² using cumulative doses [5].

2. **Formal changes: Please include a list of abbreviations.**
   **Corrected:** Abbreviations added, see reviewer 1.

I trust these corrections will meet with your approval.
Thank you for your support.

Sincerely,

Prof. Heidi Abrahamse