Intellectual Property Appellate Board

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OA/33/2015/PT/KOL

TUESDAY, THISTHE 25thDAY OF AUGUST, 2020

HON'BLE SHRI JUSTICE MANMOHAN SINGH **CHAIRMAN**

HON'BLE DR. ONKAR NATH SINGH **TECHNICAL MEMBER (PVPAT)**

1. **UNIVERSITY OF MIAMI.**
   1400 NW, 10TH AVENUE SUITE 906, MIAMI,
   FLORIDA 33136, USA

…APPLICANT/APPELLANT

(Represented by: Ms. ArchanaShanker and Ms.Gitika Suri)

Versus

1. **THE CONTROLLER OF PATENT**
   (ASST. CONTROLLER OF PATENTS)
   THE PATENT OFFICE, BOUDHIK SAMPADA
   BHAWAN, CP-2 SECTOR V, SALT LAKE CITY,
   KOLKATA – 700 091

…RESPONDENT

(Represented by –None)

ORDER

HON'BLE SHRI JUSTICE MANMOHAN SINGH, CHAIRMAN

1. The present appeal under Section 117Aof the Indian Patents Act is filed against the orders dated 27th February 2015 passed by Respondent no. 1 being the Controller of Patents under Section 15 of the Indian Patents Act, erroneously rejecting the Appellant's Indian Patent Application No. 2090/KOLNP/2006(hereinafter referred to as **IN'2090**).

2. Facts

a) A PCT application no. PCT/US2005/001581 (published as WO 2005/069916) was filed by the Appellant on 21st January, 2005 and was titled as "*Topical Co-enzyme Q10 Formulations and Methods of Use Thereof*".

b) The said international application filed under the PCT claims priority from US patent application no. 60/538,319 dated 22nd January, 2004.

c) The Appellant filed a national phase application in India under Rule 20 of the Patent Rules, 2003 within 31 months from the date of priority. The national phase application was filed on 25th July, 2006.

d) The application was published under Section 11A of the Indian Patents Act on 18th May, 2007.

e) The Respondent No. 1 issued the first examination report on 05th May 2010. The Appellant prepared and filed a response to the first examination report on 2nd May 2011. The due date for placing the application in order for grant under Section 21 of the Indian Patents Act expired on 05th May 2011.

f) After approximately one year from the last date of filing a response to the first examination report, a hearing notice was issued by the Respondent No. 1 appointing a hearing in the matter on 22nd August, 2012.

CLAIM OF INVENTION OF IN'2090 BY THE APPELLANT

3. The present invention is directed to pharmaceutical composition comprising co-enzyme Q10 and the method of using co-enzyme Q10 for treatment of cancer, selective reduction of cancer cell growth, induction of apoptosis in cancer cells and inhibition of tumor mediated angiogenesis.

The claims as originally filed were directed to the following:-

1. A composition comprising CoQ 10 and a pharmaceutically acceptable carrier.

8. A method of treating a cancer patient, comprising: administering to a patient in need thereof, a composition comprising a therapeutically effective amount of Coenzyme Q10; contacting a tumor cell with the composition resulting in the lysis of the tumor cell; thereby treating the cancer patient.

16. A method for inhibiting tumor cell growth in a subject, the method comprising administering to the subject a pharmaceutical composition comprising CoQ 10.

20. A method of inducing apoptosis in a tumor cell, the method comprising administering a pharmaceutical composition comprising coenzyme QIO.

30. A method of inhibiting angiogenesis in a tumor, the method comprising contacting a tumor with a pharmaceutical composition comprising coenzyme Q10.

33. A kit comprising: Coenzyme Q10, phospholipon 90, glycerol, butylatedhydroxytoluene (BHT), ethanol, medium chain triglycerides (MCT), and lavender.

3.1 The compositions described in the specification were topically administered (refer Page 2, 4 and 12 for instance) or could be administered by parental delivery for example via intravenous injection (Page 14, 15 for instance).

3.2 As claimed in the application as filed the composition comprises*CoQ 10 and a pharmaceutically acceptable carrier.* In a preferred embodiment of the invention co-enzyme Q10 was formulated in a liposomal formulation, having liposomes as a carrier.

3.3 The composition comprises 0.01% to about 30% w/w of co-enzyme Q10 and preferably 1% to 25%. A composition of co-enzyme Q10 comprising a lipid has also been exemplified in the specification. The composition exemplified in the specification is disclosed on page 12 and comprises Phospholipon 90G (American Lechitin, Stanford, CT), Phospholipon 90H (American Lechitin, Stanford, CT), Glycerol, Butylatedhydroxytoluene (BHT), Ethanol, Medium Chain Triglycerides (MCT), lavender (Sigma-Aldrich, St. Louis, MO) and Coenzyme Q10 (Pure Prescriptions, San Diego, CA). A protocol for preparing the composition is also provided on the same page.

4. The claims were revised during prosecution and the method of treatment claims were deleted in response to the objection of the Controller, the composition claims were revised and limited to be directed to liposomal composition for the treatment of cancer comprising 0.01 to 30% w/w co-enzyme Q10 and a liposome for topical and intravenous administration. Therefore, the claims pending before the controller were narrower in scope than the originally filed claims and based on the subject matter disclosed and exemplified in the original specification.

ADVANTAGES/EFFECTS FO THE COMPOSITION CLAIMED

5. Applicants' specification as originally filed describes experiments in which the inventors proceeded to analyze the effects of Coenzyme Q10 on various cell types. In these studies, the inventors observed that when Coenzyme Q10 is delivered to normal cells in culture; it does not cause cell death, and, in fact, enhances their

growth. However, when the Coenzyme Q10 is delivered to cancer cells, it inhibits cell proliferation and causes cell death, e.g., by inducing apoptosis and/or cell lysis.

The specification further demonstrates that a topically administered composition comprising Coenzyme Q10 and a lipid is effective in the treatment of cancer. These studies are briefly summarized below.

Inhibition of Cell Proliferation by Coenzyme Q10 in Panel of Cancer Cell Lines

5.1. Applicants' specification as originally filed describes a series of experiments in which a panel of human cancer cell lines, including a melanoma cell line, a squamous carcinoma cell line, four different breast adenocarcinoma cell lines, a hepatocellular carcinoma, an osteosarcoma cell line, and a prostatic adenocarcinoma cell line, as well as control cells (human neonatal fibroblasts and human neonatal keratinocytes), were treated with Coenzyme Q10 over a range of concentrations *in-vitro*. The effect of Coenzyme Q10 on the proliferation of cells was assessed by determining cell number in the treated samples as compared to the vehicle control samples (see, e.g., Example 1 at pages 42-48). The results of these experiments show that Coenzyme Q10 treatment results in a statistically significant inhibition of growth of the cancer cells (see Figures 1-4, 6, 9, 10 and 15-27), and a statistically significant increase in the proliferation of non-cancer control cells (see Figures 7 and 8).

5.2 The effect of Coenzyme Q10 on cells was also assessed by analyzing the induction of apoptosis in treated cells as compared to vehicle control using both an Annexin-VPE assay and mitochondrial membrane dye assay (see, e.g., Example 1, page 42, line 15 through page 43, line 10; and Example 4 at page 49). The results of these experiment show that Coenzyme Q10 selectively induces apoptosis, i.e., inhibits growth, in a range of different human tumor cells as compared to control fibroblasts (see Figure 5) and, further, induces apoptosis in human prostatic adenocarcinoma cells (see Figure 28).

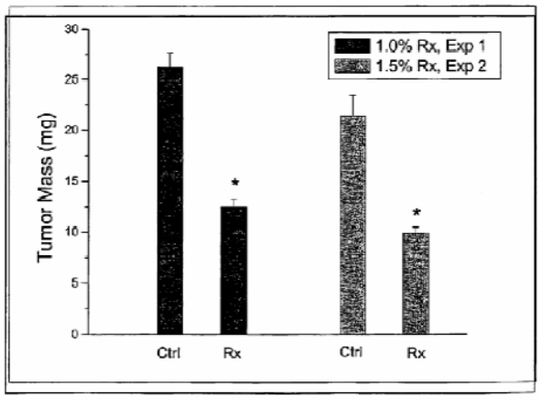
Topical Administration of Coenzyme Q10 in the Treatment of Melanoma in Mouse Model

5.3. Consistent with the foregoing results obtained *in-vitro*, Applicants' specification as originally filed also describes an experiment in which each of eight mice were inoculated with melanoma cells to generate tumors (see Example 3 at pages 48-49 of the specification). The treatment group was treated daily with Coenzyme Q10

(either 1.0% or 1.5%) in a lipid containing formulation for 30 days. The tumors from the treatment group (four mice) and control group (four mice) were then excised and the mass of the tumors was determined. The results of this experiment demonstrate a striking and statistically significant reduction in tumor mass in the mice treated with Coenzyme Q10 as compared to control mice (see, e.g., Figures 11-13 and, in particular, Figure 14, of the application).

5.4. Specifically, Figure 13 is a photograph showing the dramatic difference in size of tumors excised from the Coenzyme Q10 treated mice as compared to control mice. Figure 14, reproduced below (as amended in an Amendment Under Article 34 filed in priority international PCT Application PCT/US2005/001581 on December 13, 2005), is a graphical representation of the results showing that the average tumor mass decreased by 52.3% and 54.0% in the 1.0% and 1.5% Coenzyme Q10 treatment groups, respectively, as compared to the control.

Effect of Topical CoQ10 on SKMEL28 Tumor Mass in Nude Mice



5.5. The foregoing experimental results obtained ***in-vivo*** demonstrates the striking effect of **administration of a topical composition** comprising Coenzyme Q10 and a lipid (e.g. a liposomal composition) to inhibit the growth of a tumor.

5.6. These studies demonstrate the efficacy of a composition comprising Coenzyme Q10 and a lipid in treating (in particular by topical administration) a number of cancer types.

2. ***Formulation of Coenzyme Q10 with a Lipid Enhances Delivery of Coenzyme Q10 into Cells***

5.7. The composition of the present invention demonstrates improved uptake of Coenzyme Q10 into cells when delivered in a lipid containing formulation as compared to a non-lipid containing formulation.

5.8. Various cancer cells were plated and treated with a known concentration of Coenzyme Q10, either in an isopropanol formulation or a lipid containing formulation. After 24 hours, the cells were collected and the amount of Coenzyme Q10 per cell was determined. Exemplary results for a study from one cancer cell line are shown in the table below:

Treatment	**pM CoQ10/cell**
Untreated	38
50 μM CoQ10; isopropanol formulation	37
100 μM CoQ10; isopropanol formulation	45
50 μM CoQ10; lipid formulation	227
100 μM CoQ10; lipid formulation	717

5.9. Little or no change in the amount of Coenzyme Q10 per cell was observed after contacting the cells with the Coenzyme Q10 isopropanol formulation (38 vs. 37 or 38 vs. 45 pM Coenzyme Q10 per cell). However, the amount of Coenzyme Q10 delivered per cell was significantly increased by a lipid formulation comprising Coenzyme Q10 and a lipid, resulting in nearly a six-fold increase or nearly a 19-fold increase in the concentration of Coenzyme Q10 per cell as compared to a control cell depending on the concentration of Coenzyme Q10 used.

These results demonstrate the significantly enhanced delivery of Coenzyme Q10 into cells using a lipid formulation of the invention.

5.10. Drug development is a cumbersome process taking anywhere between 10-15 years for a lead compound tested *in-vitro* inlaboratory to be approved and be sold as a commercial product in the market. During the research the following stages have to be passed for a commercial drug product to reach the market.

1. Drug research - a target molecule is identified and then a promising molecules/lead compounds that can become a drug for that target is discovered. The lead compound goes through series of test and those that survive the initial screening are further optimized.

2. Pre-clinical testing – This involves testing (in lab and on animals) the optimized lead compound to determine if the drug is effective and safe for testing on human.

3. Clinical trials – The compound that are found to be safe for testing on human are then tested on first the healthy volunteers (phase 1), followed by testing on small group of patient (phase 2) then testing on large group of patients (phase 3).

4. New drug application and approval – once the clinical trials were over and after analyzing the clinical trial a new drug application for approval may be filed by a company.

5.11. Discovery and development of new medicine is a long and complicated process in which the results obtained in step 1 are further verified, elaborated and confirmed at every subsequent step of drug development.

5.12. A Patent application is usually filed at an early stage - usually after step one, or step one and two have been conducted and a promising drug candidate(s) has been identified. This is essential to freely conduct further studies on potential drug candidates and prevent the information regarding the research to be in the public domain.

6. It is stated that in the present case too, the effectiveness of coenzyme Q10 in the treatment of cancer, and the effectiveness of using a lipid containing composition, were identified, studied in laboratories and on animal bodies. As these results were quite promising, a patent application covering the method of treatment using coenzyme Q10 and a lipid containing composition of coenzyme Q10 which was found to be quite effective were filed in India along with other countries. As the method of treatment of claims were not permissible in India, the same were withdrawn from the patent office. The composition claims that were in particular directed to liposomal composition were maintained.

The example elaborated above in Para's 15 to 21, which were disclosed in the specification clearly and completely describes an embodiment of the composition and its effectiveness in treating cancer which was studied *in-vitro* and on animals. These results were further confirmed in various pre-clinical and clinical stages that were subsequently done after the filing of the patent application. These studies simply elaborated, reinforced and confirmed the properties and effects of co-enzyme Q10 and its lipid containing formulation that were identified in the patent application itself. They have been provided as a support to the subject matter disclosed and claimed in the present application. The post filing studies provided are as follows:-

Post-filing Studies Provide Data Demonstrating Inhibition of Tumor Cell Growth and Treatment of Cancer Using an Injectable Coenzyme Q10 Composition in Xenogeneic Tumor Models

7. The affidavit of efficacy of a composition for intravenous administration comprising Coenzyme Q10 and a lipid in the treatment of cancer has been provided in the affidavit of Niven R. Narain filed in the present proceedings has been placed on record.

It is alleged that in each of the studies, human tumor cells of the appropriate type were injected into immunocompromised mice to establish pancreatic, lung, liver, colon, or breast tumors. Mice having palpable tumors were typically divided into four groups:

1. Control
2. Coenzyme Q10 (4%)-lipid composition
3. FDA approved treatment for the specific cancer type
4. Combination therapy of the Coenzyme Q10-lipid composition and the FDA approved treatment for the specific cancer type

Mice were monitored at least for survival. In all of the studies, treatment with the composition comprising Coenzyme Q10 and a lipid administered by injection was effective in prolonging survival as compared to control animals, and was at least as effective in prolonging survival as the approved treatment. In fact, in most tumor models, the composition comprising Coenzyme Q10 and a lipid administered by injection was more effective in prolonging survival than the approved treatment. Further, in all of the tumor models, a combination treatment with a composition comprising Coenzyme Q10 and a lipid administered by injection and the FDA approved treatment further extended survival of the mice beyond either treatment alone.

These studies further demonstrate the efficacy of a composition comprising Coenzyme Q10 and a lipid administered by injection in treating a number of cancer types.

4. Post-filing Phase 1 Clinical Trials Provide Data Demonstrating Inhibition of Tumor Cell Growth and Treatment of Cancer in Humans Using Topical and Injectable Coenzyme Q10-Lipid Compositions

Based on the results from the animal studies discussed above, Phase 1 clinical trials in humans were performed to assess primarily the safety and, as a second goal, the efficacy of compositions comprising Coenzyme Q10 and a lipid for topical and intravenous administration. Details related to the clinical trial of the topical composition comprising Coenzyme Q10 and a lipid for the treatment of squamous cell carcinoma are summarized below. Details related to the clinical trial of intravenously administered Coenzyme Q10 and a lipid for the treatment of cancer are also provided herein below.

4.1. Topical Administration of Coenzyme Q10 in a Lipid-Containing Composition in the Treatment of Squamous Cell Carcinoma in a Human Clinical Trial

8.The efficacy of lipid- containing Coenzyme Q10 topical formulation has also been further elaborated and provided by the affidavit of John P. McCook filed before the Respondent No. 1.

9. The Declaration of John McCook is related to the results from a six week human clinical trial for the treatment of squamous cell carcinoma using a topical Coenzyme Q10 formulation. In the study, 23% of the 34 enrolled patients had a complete clinical response, defined as a negative histological assessment for squamous cell carcinoma, after 6 weeks of treatment. Of the 27 subjects who completed the trial and met all of the inclusion criteria, 18% were found to have a complete clinical response after 6 weeks of treatment. Further results are provided in the Declaration.

These affidavit results from the post-filing date human clinical trial further demonstrate the efficacy of topically administered Coenzyme Q10 in treating a tumor, specifically squamous cell carcinoma which was already demonstrated in the specification.

4.2. Intravenous Administration of Coenzyme Q10 in a Lipid-Containing Composition in the Treatment of Advanced Tumors in a Human Clinical Trial

Finally, the results from an interim analysis of a Phase 1 human clinical trial to assess the safety of an intravenous formulation comprising Coenzyme Q10 and a lipid are provided herein. These results demonstrate the safety and efficacy of a composition for intravenous administration comprising Coenzyme Q10 and a lipid for the treatment of cancer.

Trial Design

10. A Phase I clinical trial was performed to determine the toxicity of Coenzyme Q10 in subjects with advanced tumors with the secondary goal of determining efficacy of treatment of cancer with a formulation comprising Coenzyme Q10 and a lipid. An interim analysis was performed in the study on 31 participants, all having stage III or IV tumors refractory to multiple prior chemotherapy regimens. The cancer subtypes of the patients participating in the trial were the following: 3 stage IV pancreatic cancers; 3 stage IV uterine sarcomas; 3 stage IV myxoidliposarcomas; 3 stage IV leiomyosarcomas; 2 stage IV chondrosarcomas; 2 stage IV osteosarcomas; 2 stage IV angiosarcoma; 1 stage IV adenocarcinoma of colon; 1 stage IV squamous cell of cervix; 1 stage IV squamous cell of tonsil; 1 stage IV papillary thyroid; 1 stage IV adenoid cystic; 1 stage IV synovial cell sarcoma; 1 stage IV malignant fibrous histiocytoma; 1 stage IV desmoplastic sarcoma; 1 stage IV hepatocellular carcinoma; 1 stage IV spindle cell sarcoma; 1 stage III cholangiocarcinoma; 1 stage IV appendiceal carcinoma; and 1 stage IV pleiomorphic sarcoma.

The lipid-containing Coenzyme Q10 formulation was administered intravenously over 4 hours x 3 days per week x 4 weeks per cycle.

Result

The clinical trial revealed that;

Coenzyme Q10 lipid-containing formulation is very well tolerated at the tested dosages;

Two patients showed at least a minor response, i.e. a reduction of tumor size;

The median progression free time of the patients was two months.

It is stated in view of the advanced disease stage of all of the subjects and the fact that the primary goal of a Phase I trial is to demonstrate safety, these results are considered successful, as explained below.

Low Dosages

Phase I clinical trials are primarily conducted to evaluate safety of the therapy, to determine a safe dosage range and to identify side effects. Evaluation of the treatment efficacy is not among the main objectives of Phase I trials. In fact, high efficacy cannot be expected because, in order to determine the safe dosage range, the trial is carried out relying on a dose-escalation design. This means that the treatment of the patients is initiated with very low dosages. Subsequently, dosage is increased in small steps until a maximum tolerated dose (MTD) is reached. In nearly all instances, the therapeutic effect

of a drug is directly related to the administered dosage. This interim analysis provides preliminary results for lower dosages.

All of the patients participating in the trial were severely ill patients that are very difficult to treat. In particular:

All patients suffered from rapidly progressing disease;

All but one of the patients suffered from Stage IV disease, i.e. the final stage of cancer with metastasis at distant sites of the body, which is most difficult to treat and which has the worst prognosis;

All participating patients had undergone multiple prior chemotherapeutic regimens which were not effective or ceased to be effective after a period of treatment.

Stage IV patients with distant metastasis are the patients with the worst prognosis, for whom in many cases a standard therapy does not even exist. The patients participating in this trial were in such poor condition at the beginning of the trial that even a relatively short progression free time period must be seen as a meaningful achievement. Moreover, for the individual patient this progression free time caused by the treatment with Coenzyme Q10 represents a great benefit because of the very low remaining life expectancy at this stage of cancer.

The foregoing results of the Phase I clinical trial further evidence the advantageous effect of the ability of Coenzyme Q10 lipid-containing composition to treat cancer.

11. The objection raised by the Respondent No. 1 in the hearing notice were as follows:-

i) Title of the application not being precise.

ii) The objection relating to inventive step in view of the documents US20020039595 and US20020156302 under para 3 of the first examination report being maintained.

iii) Claims fall under Section 3(d) and 3(e) of the Indian Patents Act.

Objection with regard to novelty of the invention in view of the documents, Kokawa et al., US6582723 and US20020156302 in para 5 of the first examination report being maintained.

iv) Claims 47 to 79 not being supported by the specification.

v) Additional claim fee required for claims added.

vi) Additional fee required for additional pages added.

vii) Form-3 should be filed in the correct format.

12. The hearing in the matter was adjourned and later on appointed and attended on 2nd August, 2013. Eight objections as above were conveyed in the hearing letter and as mentioned in the order of the Respondent No. 1, the major objections were on the ground of novelty/inventive steps under Section 3(d) and Section 3(e) of the Indian Patents Act.

A further discussion was appointed by the Respondent No. 1 and vide e-mail of 18th January, 2014, it was confirmed that the same would be attended on 7th February, 2014.

Submissions for the hearing were filed on 24th January, 2014 and 28th January 2014 and the case was discussed at length with the Respondent No. 1 on 7th February 2014.

13. Affidavits of the experts namely **Niven R. Narain** and **John P. McCook** in support of the application were filed along with the submissions. Subsequent to the hearing, on 27th February, 2014 the original executed copies of the affidavits of the two experts in support of the application were filed at the patent office.

14. After the hearing, on 27th February, 2015 the Respondent no. 1 issued a one page order rejecting the application on the following grounds:-

i) Use of liposome as carrier of active drug molecules is already known in the art. The proposed revision of claim, combining the carrier liposome with active drug molecule, Coenzyme Q 10 and evidence for enhancement of activity (as proposed by further documents) are beyond the scope of 'invention' as described in the complete specification as on record.

ii) Further technical results or post filing data cannot be included in the descriptive part of the complete specification as it is not allowable as per section 59 of the 'Act.

iii) Applicant did not incorporate the further experimental results in the specification by way of amendment within stipulated time period. At this stage, inclusion of major technical data and change of direction of the invention is not acceptable and merit of the invention has to be decided based on the disclosure as on record.

iv) As per present disclosure, specification lacks in technical data for enhancement of efficacy or synergism. Therefore, the 'invention' cannot be acknowledged to involve inventive step [as per section 2(1)(j)] and also not patentable under section 3(d) of the 'Act.

v) The revised claim as drafted fall u/s 3(i) [method of treatment] of the 'Act and thus, not allowable.

To comply with the Section 8(1), the Appellant had filed Form-3 on various occasions including on 25th July, 2006, 20th October 2006, 25th December, 2011, 2nd September 2013 and 22nd July, 2013. The appellant had also filed Section 8(2) details at the office of Respondent No. 1.

Details with regard to the prosecution of corresponding EP application **5711599.0** were filed alongwith the response to the first examination report. Further details covering details with regard to many countries counting into thousands of pages were also filed on 22nd July, 2013 and 2nd September 2013.

15. Violation of the principles of Natural justice - No objection under Section 3(i) raised in the hearing notice.

Respondent No. 1 incorrectly rejected the patent application in the order dated 27th February 2015 on the ground that Section 3(i) of the Indian Patents Act when the Respondent No. 1 did not even raise an objection under Section 3(i) of the Indian Patents Act in the hearing notice dated 11th July 2012. It is against the principles of natural justice that an application be rejected without communicating an objection to the Appellant as required under Section 14 of the Indian Patents Act. This was clearly an error made by Respondent No. 1.

16. Violation of the principles of Natural justice - the reasons for refusal are not clear.

it is stated on behalf of appellant that the respondent no. 1 in a one page order wherein the reasons for rejection have been given only in two paragraphs rejected the present application on the grounds of lack of inventive step, Section 3(d), Section 3(i), claims not being supported by the specification, without elaborating on any of the grounds of rejection. It is a well establish legal principle under patent law as also held by the Hon'ble IPAB in the decisions like ORDER No.08/2014 that the refusal decision by which the rights of the applicant be refused has to be a speaking order. The details regarding the grounds for refusal, and how those grounds are established on the subject matter claimed have to be elaborated in the order. In the absence of such a speaking

order, there is a flagrant violation of the principles of the natural justice and also the principles of law established in the country.

17. Claims do not relate to method of treatment and do not fall under Section 3(i) of the Act.

The claims of the present application are directed to a pharmaceutical composition which has been clearly defined with its components in the claim. The claims are not directed to a method of treatment and therefore cannot fall under Section 3(i) of the Indian Patents Act.

The use of expression treatment in the claim does not render a claim falling under Section 3(i) of the Indian Patents Act. The expression "*composition for the treatment*" has been used in the preamble of many claims which have been granted by the office of Respondent No.1 and is only a way of defining the composition and in no way the claimed composition can be a method performed by a physician for treatment of disease. There are plenty of compositions claimed wherein the composition is defined in the preamble with the disease/condition that is being ***treated*** with the composition.

The objection of Section 3(i) on composition claims therefore shows non-application of mind by the Respondent No. 1 and is a clear error apparent on face.

Claims do not fall under Section 2(1)(j) of the Act.

18. From the decision of the Respondent No.1 it is not clear as to which documents have been considered by the respondent No.1 in holding that the impugned application lacks inventive step and why said application lacks inventive step.

19. It is a matter of record that the claims of the application are directed to pharmaceutical compositions for topical or intravenous administration comprising Coenzyme Q10 (CoQ10) and a liposome. The composition can be prepared, for example, as suspensions or emulsions. The applicants' specification provides experimental data demonstrating that these pharmaceutical compositions are effective in the treatment of cancer, e.g., the compositions decrease tumor cell growth and decrease angiogenesis. Results from *in-vitro* and in-vivo studies demonstrate enhanced delivery of Coenzyme Q10 into cells using a lipid containing composition and the efficacy of Coenzyme Q10 lipid containing compositions in treating cancer in both animal models and in humans.

The surprising advantages of the claimed pharmaceutical composition and the treatment of cancer using such a composition are neither taught nor suggested by the cited art.

The hearing notice did not identify claims that have been identified as lacking inventive step or novelty in view of the cited documents and, therefore, in the absence of a clear indication, the cited references are being addressed for all the claims and the applicant has articulated arguments in relation to the said prior art documents which neither destroys novelty or inventive step of the claimed invention.

I. D1 US2002/0156302 the explanation on behalf of appellant

20. D1 fails to teach or suggest each and every element of the claimed invention. Specifically, D1 provides no teachings related to compositions comprising Coenzyme Q10 in the recited amounts and a liposome, or the advantages of such a composition as provided in the instant application. D1 also fails to teach or suggest the use of a pharmaceutical composition comprising Coenzyme Q10 and a liposome for topical or intravenous administration for the treatment of cancer.

D1 is directed to ***methods of stereo specific synthesis*** of Coenzyme Q10, not to compositions for, or methods of, treatment of cancer using Coenzyme Q10. Paragraph 0037 of D1 teaches that "[o]ral administration is favored over parenteral administration due to the very low solubility of coenzyme Q10 in excipients compatible with is parenteral administration."

Therefore, based on the teachings of D1, one of skill in the art would expect that Coenzyme Q10 could ***not*** be formulated for topical or intravenous administration, as claimed.

20.1. Therefore, D1 neither teaches nor suggests the claimed compositions comprising ***Coenzyme Q10 and a liposome*** for ***topical or intravenous administration***.

In paragraph 0039, D1 teaches that

compositions for topical administration can be prepared by dissolving or suspending ***coenzyme Q 10 in vegetable oils*** such as corn oil, canola oil, or soy bean oil, lecithin, glycerol, glycerylfurole, Tween 80 or other derivatives, suspending agents or diluents. After the addition of suitable carriers and formulation aids to such solutions or suspensions, the compositions can be forwarded as pastes, creams, ointments, gels, lotions, unguents.

20.2. Thus, D1 teaches formulation of Coenzyme Q10 in ***vegetable oils***. Liposomes form in ***aqueous*** solutions, ***not oils***. Therefore, the ***oil-based*** Coenzyme Q10 formulations of D1 would not include liposomal compositions as claimed. Therefore, D1 neither teaches nor suggests the claimed compositions comprising a ***liposomal*** composition comprising Coenzyme Q10 and a ***liposome*** for topical or intravenous administration.

20.3. D1 discloses that Coenzyme Q10 is associated with the treatment of a number of diseases, particularly cardiovascular disease. D1 does not disclose the ***treatment of cancer*** with a composition comprising Coenzyme Q10 and a lipid for topical or intravenous administration. The Learned Controller's attention is directed to various portions of the specification of D1, reproduced below, to support this assertion. Specifically, the specification of D1 states:

[0007] [Coenzyme Q10] is used successfully in ***treating*** ischemic ***heart disease, chronic heart failure***, toxin induced ***cardiomyopathy, hypertension*** and ***hyperlipidemia***.… [C]oenzyme Q10 is found in high concentrations in healthy hearts and at low levels in people with congestive failure [*sic*] leading to the suggestion that supplementation with the Coenzyme would be of help in the ***treatment of heart disease***. (emphasis added)

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[0009] In addition to its helper role in the release of energy, Coenzyme Q10 serves as an ***antioxidant***, neutralizing free radicals that cause potentially irreversible damage to cells, tissues, and organs Coenzyme Q10 is also believed to strengthen the immune system, so as to provide antibacterial and antiviral activity (including HIV)…. Among the increasing number of pharmacological uses ***ascribed to Coenzyme Q10 are anticancer (in particular breast cancer) activity***, in the ***treatmentof periodontal disease, diabetes, Parkinson's, Alzheimer's, Huntington's disease and to help counteract the aging process***.

20.4. As above, in paragraph 0007, D1 teaches treatment of heart disease using Coenzyme Q10. In paragraph 0009, D1 teaches pharmacological uses ascribed to Coenzyme Q10 include treatment of periodontal disease, diabetes, Parkinson's, Alzheimer's, Huntington's disease. Notably, D1 fails to teach treatment of cancer, even after teaching treatment of many other diseases.

20.5. D1 instead reports that an "anticancer activity" has been ascribed to Coenzyme Q10, and that such activity is related to Coenzyme Q10 being an antioxidant.

Therefore, the skilled person when reading the teachings of D1 in relation to cancer would not be led to believe that Coenzyme Q10 has potential therapeutic activity for treating cancer, but rather that the "anticancer activity" ascribed to Coenzyme Q10 is a preventative or protective activity.

20.6. The skilled person would recognize that a number of other pharmaceutical uses have been suggested, i.e., ascribed, but not demonstrated for Coenzyme Q10, based on its activity as an antioxidant. Based on this antioxidant property, it is stated that Coenzyme Q10 has been ascribed "anticancer activity", and not that it could be used for the *treatment* of cancer. Indeed, the skilled person would not consider a molecule that has been ascribed an anticancer activity generally based on its antioxidant properties as necessarily being useful for treating cancer.

In view of the above, the applicant submits that D1 does not render the claimed invention as lacking in novelty or inventive step, since the documents failed to teach each and every element of the claimed invention or even suggest the same.

In addition to the foregoing, Applicants further submit that the claimed composition provides surprising advantages that could not be expected from the teachings of D1, i.e., the usefulness of a composition comprising Coenzyme Q10 and a liposome in the treatment of cancer. Applicant submits that the skilled person, at the time of the invention, would have had neither the motivation, nor a reasonable expectation of success, to modify the teachings of D1 to arrive at the instantly claimed invention, specifically pharmaceutical compositions comprising Coenzyme Q10 and a liposome, and the use of the composition for treating cancer, at least because D1 provides no experimental results to support any of the long list of alleged activities asserted in the specification, let alone for treatment of cancer. Accordingly, D1 fails to destroy the inventiveness of the claimed invention.

D2 <u>US2002/0039595-comments on behalf of the appellent</u>

21. D2 is generally directed to an oral liposomal delivery system (see, e.g., the title of D2). Specifically, D2 is directed to "liposome encapsulated gel caps for oral administration" of essentially any biologically active agent including "drugs, nutritional supplements, vitamins, minerals, enzymes, hormones, proteins and polypeptides" (abstract). D2 does not teach simply a preparation of a liposomal composition to be used for any route of administration, but rather requires "the incorporation of a fluid liposome dispersion into a gelatin based capsule" (first sentence of the description of the invention, paragraph 13, emphasis added).

Therefore, the skilled person would recognize that the D2 reference is directed to a liposomal composition in a gelatin capsule for oral delivery and not topical or intravenous delivery.

21.1. In regard to Coenzyme Q10, at paragraph 0023, D2 teaches a "*Co-Enzyme Q10 LipoCap Formulation*" containing purified water, phospholipon 90H, cholesterol, Vitamin E, Coenzyme Q10, potassium sorbate, and propylene glycol. At paragraph 0024, D2 teaches that the mixture is "*injected into the open-end of a soft gelatin capsule then sealed with tweezers*," i.e., is prepared for oral administration.

21.2. Moreover, D2 teaches the particular advantages of phospholipon 90 and cholesterol compositions for oral administration. Specifically, D2 teaches that

liposomes can be mechanically stabilized using certain phospholipids, e.g. phospholipon 90H, and cholesterol at an optimum molar ratio of 2:1. The optimum ratio is expected to vary with the specific phospholipid selected. This stability can protect the liposome from GI degradation. (paragraph 0016, emphasis added)

Therefore, one of skill in the art would conclude, based on the disclosure of D2 that Coenzyme Q10 can be prepared in a liposomal composition for oral administration and that such compositions are useful to stabilize the liposome to protect the liposome from GI degradation. There is no teaching or suggestion that the composition comprising Coenzyme Q10 should be administered by a non-oral route in which Coenzyme Q10 is not contacted with the GI tract, e.g., topical or intravenous administration.

21.3. There is no teaching or suggestion that the composition of D2 comprising Coenzyme Q10 would be useful for the treatment of any disease or condition. Thus, D2 provides no teaching or suggestion that a composition comprising Coenzyme Q10 can be used for the treatment of cancer.

Accordingly, D2 fails to destroy the inventiveness of the claimed invention.

Kokawa et al.,reply on behalf of appellant

22. D3 provides no teachings whatsoever related to specific Coenzyme Q10 compositions, let alone compositions comprising Coenzyme Q10 and a liposome as required by the claims. Further, D3 provides no teaching or suggestion that a composition of Coenzyme Q10 as claimed possesses a therapeutic anticancer activity.

22.1. D3 reports that cancer and chemotherapeutic agents, such as cyclophosphamide (CPM), result in depression of immunological function. D3 further reports that immunopotentiators can be useful to overcome such immunosuppression caused by chemotherapeutics. Counterproductively, however, immunopotentiators can also reduce metabolic activation of "masked" chemotherapeutic agents, such as CPM, thereby decreasing their level in the blood. D3 reports that administration of "coenzyme Q10, a physiological activator of the electron transfer system in mitochondria" may promote metabolism of the chemotherapeutic agent, CPM. D3 does not teach or suggest that Coenzyme Q10 itself functions as a chemotherapeutic agent, but instead that Coenzyme Q10 promotes metabolism of (masked) chemotherapeutic agents, such that those masked chemotherapeutic agents can then exert their anti-cancer effects.

22.2. D3 teaches that;

"*CPM activation was depressed in the YS-bearing rats and the depression was markedly intensified by [the immunopotentiators] PSK or OL-432 administration. Phenobarbital… or coenzyme Q10… administration could mitigate the depression of the blood levels [of CPM] caused by the immunopotentiators, and the combination of phenobarbital and with coenzyme Q10 could recover the blood levels [of CPM] up to those of YS-bearing control rats, or even higher.*"

(emphasis added)

22.3. D3 thus reports that a combination of phenobarbital and coenzyme Q10 promotes metabolism of a chemotherapeutic agent, CPM, by counteracting the suppression of that metabolism by the immunopotentiators PSK and OL-432. Therefore, the skilled person when reading D3 would not expect that Coenzyme Q10 itself, in the absence of a primary (masked) chemotherapeutic agent in combination with an immunopotentiator, would have any utility in treating cancer.

Based on the above teachings of D3, it is evident that there is no teaching or suggestion in D3 that Coenzyme Q10 displays a therapeutic anti-cancer effect itself, i.e., that Coenzyme Q10 would have any affect whatsoever in the absence of a masked chemotherapeutic agent and an immunopotentiator. Accordingly, the skilled person would have had no reasonable expectation of success, based on the teachings of D3, to arrive at the claimed invention, a topical or

intravenous composition comprising Coenzyme Q10 and a liposome for treating cancer.

In view of the foregoing, it is evident that D3 fails inventiveness of the claimed invention.

D4 <u>US6582723, the submission on behalf of appellant</u>

23. D4 is generally directed to a composition comprising

a ***combination*** of specific ***nutrients*** that help to prevent, protect and neutralize cancer cells which appear in the body…The three ***essential*** components ***work together to synergistically*** prevent and fight malignancy by boosting the body's immune system (col 1, ln 19-31, emphasis added).

23.1 D4 is directed solely to "nutrients" which would be recognized by the skilled person as being formulated for oral administration, not for topical or intravenous administration as claimed.

23.2. D4 teaches that the three ***essential*** components work ***synergistically***. The American Heritage Dictionary (Houghton Mifflin Company, c. 1976) defines "essential" as follows:

1. Constituting or part of the essence of something; basic or ***indispensable***;

and "synergism" as follows:

1. Biology. The action of two or more substances, organs, or organisms ***to achieve an effect of which each individually is incapable***.

Therefore, the skilled person reading D4 would not expect that individual components of a composition containing "three essential components that work together synergistically" would individually be capable of producing the alleged effect of the combination.

23.3. D4 contains no data at all to support even the alleged effects of the combination. Therefore, even if D4 did teach that Coenzyme Q10 itself could treat cancer, which it does not, the teachings could not be considered to demonstrate that Coenzyme Q10 itself, in the absence of the other essential components could be used for the treatment of cancer. One of skill in the art thus would have no reasonable expectation based on the teachings of D4 to arrive at the claimed invention.

23.4. In summary, none of the cited references, either alone or in combination, teach or suggest a composition comprising Coenzyme Q10 for topical or intravenous administration as claimed. It follows that, none of the references teach or suggest the demonstrated advantages of the claimed topical and intravenous lipid containing compositions, including increased cellular uptake of Coenzyme Q10 as compared to a non-lipid containing composition. Moreover, none of the references teach or suggest the use of Coenzyme Q10 itself for the treatment of cancer, and therefore no combination of any of the references destroy the novelty or inventiveness of the claimed invention.

23.5. The results provided in the specification and the declarations provided clearly demonstrate the surprising advantages of the claimed compositions comprising Coenzyme Q10 and a lipid in both the delivery of Coenzyme Q10 to a cell and in the treatment of cancer. These results could not have been expected from the teachings of the cited art above. The said results, particularly on page 2 point no. 5 of Niven R. Narain shows that the formulation of Coenzyme Q10 with a lipid increases cellular uptake of Coenzyme Q10 as compared to formulation of Coenzyme Q10 in a composition not containing a lipid. These observations provide a possible mechanism contributing to the demonstrated efficacy of the topically administered, lipid containing Coenzyme Q10 formulation in the treatment of cancer in a xenogeneic mouse model as provided in the specification.

23.6. The controller has therefore completely erred in holding that the invention lacks inventive step. The respondent has erred further in not elaborating on how the invention lacks inventive step, i.e., in view of which documents it lacks inventive step.

The specification supports the efficacy and synergism of claimed composition

24. The Controller has clearly erred in holding that the application does not provide any data in support of synergism and efficacy of the claimed composition. As elaborated above in Para 15 to 22, the specification clearly supports and provides data which not only elaborates on the efficacy of the claimed composition but also on how the ingredients provided in the composition act synergistically to produce the desired results.

25. The appellants filed affidavits of the experts namely Niven R. Narain and John P. McCook providing details of synergism and efficacy of the claimed composition. The affidavits explain the non-obviousness of the present application, the details of the data presented in the specification and the conclusion that can be drawn thereto, the further clinical data that has been generated in respect of the subject matter claimed and disclosed etc. Similar affidavits have been filed by the applicant in other jurisdiction and have been considered by the patent offices. However, there is not even a whisper of such affidavits and the data, or the details provided therein in the order of the Controller dated 27th February, 2015.

26. In complete disregard of the evidence on record filed by the appellants, the Controller rejected the present application. This is clearly an error by Respondent No. 1 and it is a complete violation of the principles of natural justice.

Violation of legal principle laid down by the Hon'ble IPAB – Composition claims do not fall under section 3(d)

27. The Respondent No. 1 erred in holding that the claims of the present application fall under Section 3(d) of the Indian Patents Act without elaborating on how Section 3(d) is applicable to the present composition claims. It has been clearly been established in **order no. 173 of 2013** by the Hon'ble IPAB that composition claims do not fall under Section 3(d) of the Indian Patents Act. Paragraph 84 of the Order of the Hon'ble IPAB is reproduced herein below:-

The section explained that a mere discovery of which is not to be considered as an invention if it is a new form of a known substance, new property of new use of known substance or a known process or the use of a known process, machine or apparatus. But this discovery would be considered as an invention if the new form results in enhancement of known efficacy of that substance and so on as described in the section. The explanation to the section enumerates various derivatives of the known substance which shall be considered to be the same substance unless, there is significantly different in therapeutic efficacy. Therefore all the forms of the known substance that are mentioned are derivatives of the known substance which could be salts, esters, ethers and so on. Combination is also mentioned here. The respondent had argued that this cannot be considered as a form of a known substance. The respondent is right. This is invention is a combination of Brimonidine and Timolol. The applicant perhaps wants us to consider it either as a

derivative of Brimonidine or as a derivative of Timolol. It is not a derivative. The combination mentioned in the Explanation can be only mean a combination of two or more of the derivatives mentioned in the Explanation or combination of one or more of the derivatives with the known substance which may result in a significant difference with regard to the efficacy. A combination of two active drugs like Brimonidine and Timolol cannot be considered derivatives of each other. ***This ground is rejected.***

28. Neither the hearing notice nor the order explained precisely what is the "known" substance vis-à-vis which enhanced efficacy had to be shown. The hearing notice also failed to explain how section 3(d) would apply to the present case. There are various case laws vide which the Hon'ble IPAB has made it amply clear that the Controller is duty bound to give reasons in any order being passed and in case no reasoning is found in the order and it is very vague , it deserves to be set aside.

The Respondent No. 1 was not correct in holding that the composition claims fall under Section 3(d) of the Indian Patents Act and further erred in not giving reasons for the same.

Filing of additional data

29. The applicant has filed extensive data and also clinical trial results to support the patentability of the present invention. In this regard, it is submitted that the said data has been present in the form of affidavits and elaborates on the data in the patent specification which, in itself, contains extensive experimental details clearly establishing that the composition comprising Coenzyme Q10 and lipid has improved efficacy and surprising advantages in the treatment of cancer.

30. Respondent No. 1 was not correct in disallowing said additional data as the filing of said additional data is permissible. Reliance in this regard is placed on the following cases:-

Genetics Institute, LLC. Vs. Novartis Vaccines And Diagnostics (655 F.3d1291)

Our law is equally clear that every property of a claimed compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness. Knoll Pharm. Co. v. Teva Pharms. USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004) ("There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent

*application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack."). For those reasons, we have held that evidence of unexpected results may be used to rebut a case of prima facie obviousness even if that evidence was obtained after the patent's filing or issue date. Id. ("**Evidence [of unexpected results] developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application.");***

In re Khelghatian, 53 CCPA 1441, 364 F.2d 870, 876 (1966) - holding the claimed invention non-obvious in view of post-filing evidence of an unexpected property not disclosed in the specification, **while noting that the evidence "[wa]s directed to that which *'would inherently flow'* from what was originally disclosed.**

Knoll Pharmaceuticals Company, Inc. Vs. Teva Pharmaceuticals USA, Inc. [367 F.3d 1381)

"Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application. It is not improper to obtain additional support consistent with the patented invention, to respond to litigation attacks on validity. There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity."

The claims are supported by the application as filed

31. The respondent no. 1 is not correct in holding that the claims as presently claimed are not supported by the original specification and beyond the scope of the subject matter originally disclosed. The original claims were directed to a composition of coenzyme Q10 and other pharmaceutically acceptable carrier, which can also be a lipid, e.g., forming a liposome, as defined in the dependent claims. The composition containing lipids and coenzyme Q10 has been clearly defined as a preferred embodiment on page 2, 12 of the description and has been exemplified further in example 3 provided in the specification.

The efficacy of the composition has also been studied and demonstrated, the details of which has been explained in the declarations and above in paragraph 15 to 47. It would therefore be incorrect in stating that the composition as presently claimed is beyond the scope of what was originally disclosed in the patent application. The claims

have only been limited to a particular embodiment. Data supporting the invention claimed obtained by further research and clinical data has been provided as supporting evidence. A limited scope of claims, which claim an embodiment of the initial claims, an embodiment which has been exemplified in the specification cannot be held to be beyond the scope of what was originally filed.

32. More than five years have been passed, the respondent have failed to file the counter affidavit. No one appeared when the appeal was heard. No written argument was filed by the respondent. We have gone the record as well as the facts stated in the appeal. The said facts and legal issues are not rebutted on behalf of respondent. It appears to us that the impugned order has been passed without considering the law application in the facts of the present case.

33. The respondent No.1 has failed to consider the facts and evidence produced by the appellant. merely vague order has been passed.

34. The respondent No.1 was wrong in rejecting the application as the same is a breakthrough invention for treatment of cancer, an embodiment of which is being studied at the clinical stage for treatment of cancer.

35. The claims are novel and also inventive in view of the cited documents and completely supported by the specification as originally filed. Filing of additional documents, data and evidence in support of the invention, to overcome the objection raised and to attack a specific objection is something which is allowed under the Patent Law of not only India but also other foreign jurisdictions. Nothing has been discussed in the impugned order. We have not understood, how the respondent has taken the contrary view of the same invention which has been recognized in other countries of the world. The respondent is bound give valid reason fi contrary is taken. The said reason aremissiong. The reason given in the impugned order contrary to law.

36. In view of the impugned order dated 27th February 2015 passed by the Respondent No. 1 is set aside. The patent be granted forthwith. The appeal is allowed.

37. No costs.

-Sd/- **-Sd/-**

(Dr. Onkar Nath Singh)
Technical Member (PVPAT)

(Justice Manmohan Singh)
Chairman