White Paper Re: Developing multi-centre international PBM trials
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Rationale:

This document arises from discussions held at the joint Arlington 2014 WALT/NAALT meeting and San Diego 2017 NAALT meeting.

Outline of this White Paper:

1) Why is translational research needed in PBM?
2) What is the proposal? How to enact it?
3) What is the next step?

1) Why is translational research needed in PBM?

Translational research should occur in a coordinated fashion in order to ensure the rigour of the findings and the value of the outcomes for implementation in clinical settings. Translation occurs through an ordered process, from basic science (T0, pre-clinical and animal studies) to proof of concept Phase 1 human trials, to Phase 2 (T1) and Phase 3 (T2) controlled trials in patients, through to T3 Phase 4 clinical trials, and lastly to T4 population level outcome research.

In a comprehensive database of PBM publications (Heiskanen)[1] the following data demonstrates the breadth of laboratory and clinical trials:

- 1080 human studies (incl. 510 randomized studies, of which 220 were double-blind and 80 were single-blind. There are also 28 crossover studies and 8 multi-centre trials, though this might be underestimated. These 1080 papers include also 100 case reports or case series.)
- 1170 animal studies (incl. 800 rat studies, 220 mouse studies, 90 rabbit studies)
- 620 *in vitro* studies
- 130 systematic reviews (incl. 54 meta-analyses)
- 280 narrative reviews
- 60 editorials/guest editorials

Given the significant mis-match in human multi-centre trials versus other studies, it would seem reasonable to suggest the PBM research community has not satisfactorily navigated the translational landscape; and there would be several clinical research gaps that require addressing, or promising new fields of research that should be addressed in a systematic way in order to convince skeptics of the field.

In some areas of PBM research, the evidence in clinical trials is not as convincing as results produced in animal trials. This view is shared by others and evidenced in systematic reviews and meta-analyses e.g., the role of PBMt in clinical pressure ulcer treatment has not received as much attention (Machado et al, 2017) as the role of PBM in animal wound healing (given the high number of studies that have investigated PBMt in various models of induced wounds in animals).

Proponents of PBM therapy would agree that the publication and dissemination of results of rigorously designed and well-controlled translational clinical trials would assist in making the case for PBMt as a low cost, non-invasive, non-pharmacological intervention that has the potential to address some of the most urgent health issues of our time[2]. Select groups of researchers have been on the journey of systematic translation of findings from bench-top and animal studies and developing the work in to and conducting clinical trials (e.g., Leal Junior, Lopes-Martins and Bjordal in muscle performance; Eells and colleagues in macular degeneration; Lyons and colleagues in multiple sclerosis). However, human clinic trials are expensive to run, and require teams of researchers with complementary skills and knowledge that can be difficult to bring together. Such knowledge includes appropriate clinical trial design relevant to PBM. An example of how this factor can be important, is the recent tendency to use the human participant as their own control, either through cross-over designs or using the contralateral side as the control. Such clinical design features are problematic in PBM research due to the known abscopal or systemic effects that have been reported since the earliest days of PBM research (i.e., Mester et al, 1985). To eliminate remote effects as a confounding factor in human clinical trials, large numbers of participants may be required and so the

[1] https://docs.google.com/spreadsheets/d/1ZKl5Me4XwPj4YgJCBes3VSCJjiVO4XI0tIR0rbMBj08/edit#gid=0
[2] Including pain control and the opioid crisis

costs of carrying out such trials increases exponentially especially when specific diagnostic features are not adequately controlled (e.g., in wound healing) or where the target site for PBMt is not adequately identified (e.g., knee osteoarthritis).

In order to address some of the above factors, and to put clinical researchers in touch with biomedical researchers, a workshop at the joint Arlington 2014 WALT/NAALT meeting was held; and two workshops had been planned for NAALT2017 in San Diego: (1) how to conduct clinical research with Dr Phil Gabel and Dr Liisa Laakso; and (2) with Prof Janis Eells and Dr Liisa Laakso which was to consider how to promote translational research. Although these workshops were cancelled, some discussions were held at an invitation-only event with the outcome being this white paper.

The main purpose of the San Diego meeting was to come to some agreement on the feasibility of identifying and forming international multidisciplinary research teams to apply for grant funding to conduct multi-centre, international clinical trials of PBM in areas of agreed greatest need. The basis for doing so, was that if numerous centres were involved in the research, fewer participants would need to be recruited at each site (thus putting the research within reach of each trial centre) yet collectively, the numbers would more likely to reach an acceptable level of statistical power.

It was noted that those invited to attend the San Diego meeting had either a university affiliation and/or extensive experience in clinical trials. Those with clear industry affiliations were not included at the time to avoid issues of potential conflict of interest. It is recognized that it is not possible to undertake PBM research without some level of industry support, but perceived conflict of interest needs to be managed carefully so that it does not obscure the outcomes of future clinical research. The need to obtain non-industry funding from competitive research grant funding bodies is therefore imperative, and although industry partners will need to be included in future others such as statisticians, physicists, engineers and publishers should also become partners as plans progress.

2) What is the proposal? How to enact it?

At the San Diego NAALT 2017 meeting, the invitees were in general agreement that there is a need for multi-centre trials although there will be difficulties in setting up such trials (including ethics, funding).

A range of questions was posed, and some outcomes of the discussions were recorded by the Chair, as follows.

Questions:

- What needs to happen in preparation for conducting clinical translational trials?
- Are the areas of need obvious? Are there any strategic funding priorities we can link into?
- Is a stock-take of clinical applications necessary? How could we do this?

To progress with multi-centre trials, two matters need to be decided:

(a) **Where is the evidence**; and

(b) Where is the best chance of success?

The following areas were considered most likely **targets** for multi-centre trials as they had strategic priority in different regions of the world:

- Diabetic wounds
- Neurodegenerative and brain conditions
- Cancer treatment-related side effects; and wellness in cancer survivorship
- Muscle (including cardiac muscle) and preserving function in older adults / preventing falls
- Pain

In each field, there is a need for **some smaller clinical trials** to begin with to assist in deciding what PBM parameters work and what protocols are best to move forwards with.

From amongst the invitees at the meeting, several **PBM researchers** were identified as having expertise +/- interest in the target fields. Others would need to be identified and an expression of interest might be necessary. Such individuals would form **working groups** to start communications regarding commencement of international groupings willing to progress the identified fields of research as multi-centre international trials. A **lead researcher** would be needed for each field to coordinate each group's activities, and those involved would need to be prepared to contribute.

The trials will need **simple protocols** that can be easily and repeatably applied at each site.

The disease or condition targeted needs to have a good outcome **scale** that is measurable; and a protocol that has a **reasonable chance to succeed**. Researchers need to be able to show that we can work together so strategically, it would be useful for partners with mutual interests to **start working and publishing together as soon as possible**.

As discussions progress, decisions will need to be made regarding the PBM device/s to be used in the trials (based on evidence and **parameters** of interest) before going to industry. It will be important to ensure that research is based on **PBM alone** (rather than combined therapies) to confirm PBM efficacy.

Multi-centre trials will need **significant funding** (including industry funding) – some ideas were proposed.

As the planning progresses in each priority area, **sources of funding will need to be identified**, and groups can commence making funding applications as their work progresses.

> [One strategy that may be required is that a small study is completed at one site to demonstrate success and feasibility, and then application for approval in other sites can be commenced. Such results may already be evident and might form the basis of further work.]

As results become known the groups may be able to develop **clinical treatment guidelines** and **consensus statements** for the strategic areas.

3) What is the next step?

It was agreed that Dr Liisa Laakso would develop a White Paper (this document) to promote further discussions and planning.

The White Paper will form the basis of an editorial in the journal Photobiomodulation, Photomedicine and Laser Surgery in 2019.

The White Paper has been produced for delegates at WALT2018-Nice to consider and discuss its contents at the pre-conference workshop entitled "***Clinical Trials Consortia:*** *Moving towards international, multi-centre PBM trials*" to be held on Wednesday October 3, 2018 from 3:30pm to 5pm.
Interested parties are invited to attend.

If parties are unable to attend the above session, they should make known their comments and interest in being part of multi-centre trials, and contact:

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