

September 2019

Responses to issues raised in “Questionable activities of UK company Celixir, by Patricia Murray”

Overall, we believe that the misunderstanding arises from Professor Murray’s inability to access our considerable, confidential information concerning the nature of our cells and how we manufacture them under Good Manufacturing Practice (GMP). We are also concerned that she does not have access to the considerable information submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) as part of our Clinical Trial Authorisation (CTA).

We have taken the decision, based on our considerable experimental data, to test our allogeneic immunomodulatory progenitor (iMP) cells in human patients at the Royal Brompton Hospital in London (hereafter the “Brompton study”). We are confident that these iMP cells are novel, patent protectable (and patented in some countries) and have the potential to reverse the effects of ischaemic heart failure. We are capable of reproducibly producing batches of iMP cells under GMP. The MHRA has reviewed and approved all of the considerable and confidential documentation relating to the Brompton study. The same is true of the CRO supporting the study. Our founders, investors, collaborators and partners all support us in our endeavours after a careful review of our data.

1. Background relating to Celixir’s clinical trials

We can confirm that we did use our iMP cells in the 2012-2013 study that took place at the AHEPA Hospital, Thessaloniki, Greece (hereafter the “Greek study”). This is explained in the 2016 Anastasiadis paper¹.

2. Questions relating to Celixir’s proprietary cell type, ‘iMPs’

We are developing two proprietary cell types, namely progenitor cells of mesodermal lineage (PMLs) and iMP cells. Both cell types are tissue engineered from mononuclear cells (MNCs). The MNCs can be derived from either peripheral blood or bone marrow. This is explained in the PML patent application² and the iMP patent application³.

PMLs were originally engineered from peripheral blood by Dr Ina Laura Pieper during her Celixir (Cell Therapy Ltd) sponsored PhD. At the time, they were believed to be similar to mesenchymal stem cells (MSCs) and so were called PB-MSCs. Since Celixir sponsored Dr Pieper’s PhD, we were entitled to use her data and images in our patent applications and promotional material and Dr Pieper has never

¹Anastasiadis et al., J Cardiovasc Transl Res. 2016 Jun;9(3):202-13

²<https://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20130110&DB=&locale=&CC=WO&NR=2013005053A2&KC=A2&ND=1>

³<https://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2015189587A1&KC=A1&FT=D&ND=&date=20151217&DB=&locale=>

questioned this. This cannot represent plagiarism. After the PML and iMP patent applications were filed, Dr Pieper was allowed to publish her work⁴. Dr Pieper chose to keep her original title for the cells, namely PB-MSCs.

When filing the PML and iMP patent applications, we chose to rename the two PB-MSC cell types as PMLs and iMP cells to distinguish them from other cell types, especially MSCs. We also took the view that they are progenitor cells rather than stem cells and labelled them as such. We could not go back in time and remove previous references to stem cells and have struggled to prevent third parties from using such a common and well-recognised term.

We are confident that the PMLs and iMP cells are different from one another. For instance, the production of iMP cells takes longer (15-30 days³) than the production of PMLs (14 days or less²). The different production methods result in different phenotypes. A thorough comparison of the marker expression profiles in the PML² and iMP³ applications confirms this fact. The cells look the same under a microscope because they are both derived from MNCs and are produced in similar (but different) ways. We can relate the phenotypes of the cells to their putative mechanisms of action and this information has been reviewed by our partners, including Alliances Bioscience and Daiichi Sankyo.

PMLs and iMP cells are not MSCs. They are not produced using standard protocols for isolating MSCs. We have reviewed dozens of references relating to MSC isolation and none of them disclose our method of culturing MNCs in our proprietary, supplemented culture medium.

With regards to IP, any novel and non-obvious product is potentially patentable. We are confident that the PMLs and iMP cells are novel and non-obvious. Several established and recognised Patent Offices understand this and have granted patents relating to our cells.

We acknowledge that Figure 5 in the PML application shows data generated by an unconnected group in the US⁵. This was brought to our attention in April 2019. A careful review of the facts and events before the PML application was filed showed it was a genuine mistake on our part and not intentional. It resulted from a referencing error. We immediately took steps to have the offending data removed from all our patents and applications and reached out to the authors to apologise and explain our position.

The removal of the data in Figure 5 from the PML patents/applications does not affect the patentability of the PMLs. The inclusion of pre-clinical animal data in a patent application is not a prerequisite for the granting of a patent. Patent applications are typically filed at the beginning of development (when limited and normally only *in vitro* data are available) and so it is rare that they include any animal data. The key requirements are (1) sufficient data confirming the cells are new and (2) sufficient information concerning how the cells are made. Both are clear from the PML application² without the animal data in Figure 5.

⁴<https://www.ncbi.nlm.nih.gov/pubmed/28245527>

⁵<https://stemcells.journals.onlinelibrary.wiley.com/doi/full/10.1002/stem.103>

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3. Issues relating to trial NCT01753440, undertaken in Greece 2012-2013

The PB-MSCs produced by Dr Pieper from Welsh donors were not used in the Greek study. The study used iMP cells produced in an accredited Greek laboratory¹.

We initially isolated PMLs and iMP cells (called PB-MSCs at the time) from peripheral blood. The peripheral blood iMP cells (PB-MSCs) were analysed and, as noted, the data formed the basis of the iMP patent application³. Before the Greek study, we switched to using bone marrow MNCs to tissue engineer the iMP cells⁶. We have extensive data confirming we can make the same iMP cells from both sources.

The 2016 Anastasiadis paper¹ confirms the iMP cells used in the Greek study were derived from bone marrow. Table 1 of the 2016 paper is taken from the patent application³ (which used peripheral blood derived iMP cells/PB-MSCs) as the data are representative of iMP cells and the paper does not state the data relate to bone marrow derived iMP cells.

We are allowed to include Dr Pieper's images of PMLs (PB-MSCs) in our promotional materials because we sponsored her PhD. The videos never stated these cells were derived from bone marrow. We cannot see how this contradicts the clear statement in the peer-reviewed 2016 Anastasiadis paper that the cells were derived from bone marrow.

We also cannot see how the use of Dr Pieper's images suggests that the iMPs used in the Greek study were the PB-MSCs isolated by Dr Pieper from Welsh donors. The 2016 Anastasiadis paper¹ is correct when it says they were not. We did in 2011 amend our REC application concerning the Welsh PB-MSCs to refer to therapeutic use, but this was to keep our options open (as was our prerogative). This does not mean the Welsh cells were used in the Greek study. Professor Murray acknowledges this, as she has said, "*This change to the patient information sheet **suggests** that at some point between 14/12/2010 and 17/11/2011, Celixir decided that they **might** like to use the cells derived from the blood of myocardial infarction patients as a therapy in other patients.*" (emphasis added).

We did not need approvals from the Research Ethics Committee (REC), MHRA and Human Tissue Authority (HTA) because the iMP cells were manufactured in Greece¹ and so were under the governance of the National Organisation for Medicines (NOM). Professor Murray is correct that our GMP facility in Greece received its licence after the Greek study. The cells for the Greek study were not manufactured in our facility but were manufactured by an accredited Greek laboratory.

The trial results were published in the 2016 Anastasiadis paper¹. The peer reviewers agreed that the IMPs "*improved myocardial contractility and perfusion of nonvascularized territories resulting in a significant reduction in left ventricular scar area at 12 months after treatment*" (abstract). Professor Westaby likely did not get an opportunity to discuss CABG as he had only 17 seconds in a promotional video to discuss the trial results.

⁶Confidential IMPD

We agree with Professor Jeremy Pearson's comments regarding bypass and this is why the Brompton study will be double blinded and placebo controlled. We also appreciate that many similar studies to the Greek study and our proposed Brompton study have failed. We note that mesenchymal precursor cells (MPCs) are different from our iMP cells and have a different mechanism of action. The results in the 2016 Anastasiadis paper¹ have been peer reviewed and it is our prerogative to continue to test the iMP cells (should the MHRA agree, which it does).

We did not sponsor the Greek study. Only 11 patients were recruited, and all data were recorded, analysed and published.

Finally, we are comfortable with the affiliations of the co-authors in the 2016 Anastasiadis paper¹. Ajan Reginald was studying for a MSc in Experimental Therapeutics at the University of Oxford at the time of publication and matriculated in 2014 and graduated in 2017. Professor Sir Martin Evans was a member of Cardiff University at the time. Dr Sabena Sultan has taken steps to have her affiliation corrected.

Nancy Piouka prepared/manufactured and harvested the iMP cells for all of the 11 patients in the Greek study at the accredited laboratory¹.

The Greek co-authors of the 2016 Anastasiadis paper¹ chose to cite the gold standard Cochrane review to describe the field (Cochrane Database of Systematic Reviews, 4, CD007888; reference 10 in the second paragraph of the Introduction of the 2016 paper) rather than their earlier paper. It is also noteworthy that the earlier study did not suggest scar reduction following treatment. The earlier Greek study also used autologous cells.

Allogeneic iMP cells have several advantages over autologous cells (e.g. <https://www.futuremedicine.com/doi/10.2217/rme.09.64>) and this is why we have decided to continue developing our allogeneic iMP cells.

4. Issues relating to the forthcoming trial NCT03515291 at the Royal Brompton Hospital

We manufacture the iMP cells under GMP⁶. The full process was included in the Investigational Medicinal Product Dossier (IMPD) as part of our CTA and approved by the MHRA. Our Greek GMP facility is licensed for the production of advanced therapy medicinal products (ATMPs). The facility is located in Greece for commercial reasons, including Greece being in the European Union.

The iMP cells are modified because the cells change from MNCs to iMP cells^{3,6}. There is no isolation step to remove the iMP cells from a heterogenous population⁶. The qualification of starting materials, full manufacturing process, in process testing and final release specification by a QP have been reviewed and approved by the MHRA⁶.

We now have a clinical trial agreement in place with the Royal Brompton Hospital.

5. Response of organisations to concerns and FOI requests relating to Celixir's activities

The concerns and FOI requests led to the Brompton study being put on hold and being reviewed by the MHRA and Health Research Authority (HRA). The MHRA have our extensive data package and dossier. We have subsequently received confirmation that a MHRA review was done and the approval remains in place and no halt to the clinical trial is required.

6. Celixir's subsidiary companies, funders and supporters

As described in the accounts, the payments Ajan Reginald received from Elixir Inventions were for confidential IP and approved by the independent remuneration committee of the Celixir Board and satisfactorily reviewed by the auditors.

We believe it is standard business practice for founders and investors to promote the company in which they have a declared interest.

7. Conclusion

The MHRA approved our CTA after careful review of qualification of starting materials, full manufacturing process, in process testing and final release specification by a QP. With respect, Professor Murray has not seen any of this information. After a subsequent review following Professor Murray's concerns and FOI requests, the MHRA remain satisfied by our dossier and that the Brompton study should proceed. The independent experts from the Royal Brompton and the Royal Free have also reviewed the detailed information and found Professor Murray's accusations to be baseless.

The primary role of the MHRA is safety. It has a duty to address the benefit and risk. They do this with full disclosure from the Sponsor (in this case Celixir). We have interacted with both the CHMP and the FDA and have compiled the dossier with their advice. The MHRA reviewed our CTA submission (twice) and is satisfied that the Brompton study can proceed.

We have implemented compliance processes in accordance with the European Clinical Trial Directive, the European Good Clinical Practice (GCP) Directive and International Committee of Harmonisation (ICH) and also implemented manufacturing processes in accordance with the European GMP Directives and ICH. The Contract Research Organisation (CRO) supporting the Brompton study have reviewed and approved all of the documentation relevant to the study, including the MHRA approval.