Intellectual Property Office

BL O/980/22

09 November 2022

PATENTS ACT 1977

APPLICANT	Sistemic Scotland Limited
ISSUE	Whether patent application GB 1900893.7 complies with Section 1(1)(b)
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 Patent application GB 1900893.7 ("the application") entitled "*Cell Contamination Assay*" was filed on 22 January 2019 in the name of Sistemic Scotland Limited ("the applicants"). It claims priority from two earlier-filed patent applications, GB 1801035.5, filed on 22 January 2018, and GB 1809337.7, filed on 6 June 2018. The application was published on 24 July 2019 as GB2570404 A.

2 There have been a number of rounds of correspondence between the examiner and the attorney representing the applicant, throughout which, the examiner has maintained that the claimed invention does not involve an inventive step as required by Section 1(1)(b) of the Patents Act 1977 ("the Act").

3 Given the failure to resolve this issue, the applicants requested to be heard in their attorney's letter of 1 March 2022. The matter came before me for a decision based on all the papers on file. Dr Rowena Dinham acted as assistant to the Hearing Officer on this case.

The Invention

4 The invention relates to methods for determining the level of undifferentiated pluripotent stem cell (PSC) contamination in cell therapy products. Stem cell-derived therapies are increasingly showing promise in the treatment of many human diseases, and these cells may be derived from adult stem cells or pluripotent stem cells. Of these two stem cell types, pluripotent cells are more versatile as they can differentiate into all cell types in the human body, whereas adult cells are already committed to a certain cell lineage.

5 PSCs can either be embryonic stem cells (ESCs), or induced pluripotent stem cells (iPSCs), but regardless of their origin, both are known to present challenges for use in a clinical setting. The first of these is that, like any cell-based product, there is the possibility of excessive proliferation of these cells, resulting in the formation of a

tumour in the patient. The second is unique to PSCs, and concerns the potential for any undifferentiated cells to give rise to a teratoma in the patient; indeed one of the most commonly used assays for PSCs is the 'teratoma' assay performed on nude mice. When PSCs are differentiated into their desired cell type, they are no longer pluripotent and hence are no longer able to form a teratoma. Not all PSCs in a sample may differentiate, and therefore any residual PSCs contaminating a sample may subsequently lead to a teratoma formation in the patient.

6 The invention therefore provides an assay for the determination of the degree of undifferentiated PSC contamination s in a PSC-derived cell population for use in cell therapy. The method entails assaying a sample of the PSC-derived cell population for the presence of non-coding microRNAs (miRNA) that are known to be differentially expressed in PSCs. Detection of these miRNAs gives an indication of the degree of contamination of the sample by PSCs, with a low level of detection being indicative of a low level of contamination. Of the miRNAs that are known to be differentially expressed in PSCs, the assay of the invention detects levels of miRNAs selected from the miR-302 cluster, i.e. one or more of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p, and hsa-miR-302d-3p ('). The use of the miR-302 cluster provides an assay where the contamination level by PSCs is fewer than ten PSCs per one million cells of the sample.

7 The assays used to detect the levels of the miRs necessarily use a quantitative PCR, such as real time quantitative reverse transcription PCR (qRT-PCR), digital PCR (dPCR) or droplet digital PCT (ddPCR). These are all commercially available assays known for the detection of low levels of target material. According to Example 4 and Figure 4, the use of qRT-PCR is able to detect between 100 and 10 iPSCs in 1 million derived mesenchymal stem cells (MSCs), the qRT-PCR assay performed according to standard manufacturers protocols. Examples 5 and 6 (and Figures 5 and 6) show the detection of levels of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p, and hsa-miR-302d-3p using ddPCR. The description states that the ddPCR assay is more sensitive than the qRT-PCR assay. However, I note again that qRT-PCR and ddPCR are each known, commercially available assays.

8 Whilst the description does state that the ddPCR assay was '*developed and optimised in a manner that would be understood by and within the capability of the person skilled in the art'* (by optimising for RT cDNA synthesis and cDNA and primer concentration), there is nothing further that suggests what this optimisation might be. On this basis, I will assume that the ddPCR assay used is in line with standard protocols with no adaptations that are beyond those expected when tailoring an assay to a specific substrate. As such, whilst the use of these quantitative PCR assays are an important means to detect the levels of the miRNAs, it would appear that the invention does not require any modifications to these assays beyond the knowledge of the skilled person.

The Claims

9 The latest set of claims, filed on 30 July 2020, consists of 19 claims, with five independent claims; claims 1, 15, 16, 17 & 19, which are set out below:

> 1. *A method for determining the presence and/or level of contamination by PSC contaminants in a PSC-derived cell population for further use, the method comprising*

assaying a sample of the PSC-derived cell population against one or a panel of two or more pre-determined miRNAs known or determined to be differentially expressed in PSC contaminants, which one or a panel of mi-RNAs comprises one or more miRNAs selected from hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p and, hsa-miR-302d-3p,

wherein the step of assaying the sample of the PSC-derived cell population comprises:

treating and analyzing the sample to measure a level of the one or a panel of two or more pre-determined miRNAs by quantitative RT-PCR, digital PCR or droplet digital PCR; and

determining therefrom the presence and/or level of contamination by PSC contaminants in the sample, wherein the method is configured to determine whether the level of contamination by PSC contaminants meets the criterion of ten or fewer PSC contaminant cells per one million cells of the sample.

15. *Use of miRNA expression data or expression profiles for one or a panel of two or more pre-determined miRNAs known or determined to be differentially expressed in PSC contaminants, which are selected from hsa-miR-302a-3p, has-miR-302b-3p, hsa-miR-302c-3p and, hsa-miR-302d-3p, to determine whether the level of contamination by PSC contaminants meets the criterion of ten or fewer PSC contaminant cells per one million cells of a PSC-derived cell population for further use by measuring a level of the one or a panel of two or more pre-determined miRNAs by quantitative RT-PCR, digital PCR or droplet digital PCR and determining therefrom the presence and/or level of contamination by PSC contaminants in the sample.*

16. *A kit comprising one or two or more PCR primers each comprising a nucleotide sequence characteristic of a pre-determined miRNA known or determined to be differentially expressed in PSC contaminants, which one or a panel of mi-RNAs comprises one or more miRNAs selected from hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p and hsa-miR-302d-3p, for use in quantitatively determining the amount or expression level of the corresponding one or two or more miRNAs in a sample of PSC-derived cells.*

17. *A method for detection of contamination by PSC contaminants in a PSC-derived cell population to a level of ten or fewer PSC contaminant cells per one million cells of PSC-derived cell population, the method comprising*

amplifying and measuring by quantitative RT-PCR, digital PCR or droplet digital PCR the levels of cDNA molecules comprising nucleotides complementary to a target miRNA known or determined to be differentially expressed in PSC contaminants,

which target miRNA is one or a panel of mi-RNAs comprising one or more miRNAs selected from hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p and, hsa-miR-302d-3p, which cDNA molecules are derived from miRNA extracted from a sample of the PSC-derived cell population.

19. *A method of producing a PSC-derived cell population for use in cell therapy, the method comprising:*

inducing differentiation of pluripotent stem cells (PSCs) into derived cells to provide a PSC-derived cell population;

taking a sample of the PSC-derived cell population

subjecting the sample to the method of any one of claims 1 to 14 to determine the presence and level of PSC contaminants in the cell sample in dependence of determination of presence and level of PSC contaminants being at or less than a pre-determined contamination level,

characterizing the PSC-derived cell population as suitable or available for cell therapy; and

optionally administering the PSC-derived cells to a patient in need thereof.

10 Claim 1 is essentially a claim to a screening process - it detects levels of PSC contaminants in a PSC-derived population. The PSC-derived population is not produced by this method.

11 Claim 18 relates to a PSC-derived population determined by the method of claims 1-14 and is, in essence, a so-called “reach through” claim. Such claims relate to products that can be identified, but not modified, by the method of the invention, and as such may “reach through” to products that have not yet been identified. These claims are usually objected to on the grounds that they are speculative and place an undue burden on the skilled person to carry out the invention across the entire scope of the claims.

12 I note that the examiner has not raised an objection to claim 18 during the course of the prosecution, and I do not intend to address this here as it will not have bearing on my assessment of the inventive step of the invention. Instead, should I find the application to possess the necessary inventive step, I shall remit it to the examiner for this point to be addressed.

13 Similarly, claim 16 is a ‘kit’ claim comprising primers suitable for use in such a method and will have different limiting features to that of the method claims. This has not been independently addressed during the prosecution, other than as part of the general inventive step arguments against the method claims, and therefore the novelty or inventive step considerations of this claim in light of the cited prior art will not necessarily be the same as those for claim 1. Again, I will not address this here but will remit to the examiner should I find the method claims inventive.

14 I also note that claim 19 'optionally' has the step of administering the PSC-derived cells to the patient. In his first and second examination reports, dated 4th February 2019 and 29 October 2020 respectively, the examiner raised an objection to this and the corresponding section of the description. The applicants agreed to address this issue when an agreement had been reached over the allowability of the claims. Obviously with no such agreement reached, this matter also will remain outstanding should I find the application inventive.

15 As this is a decision on the papers, it would not be appropriate for me to draw a conclusion on the inventive step of claims 16 and 18, or the allowability of claim 19 in light of the administration step without any input from the applicants at this point. Consequently, I will only decide whether claims 1-15, 17 & 19 are inventive in light of the cited prior art, and if I find that they do possess the required inventive step, I will remit the application to the examiner to address the outstanding matters outlined in paragraphs 11-13 above.

The Issues To Be Decided

16 The issue for me to decide is whether the invention as claimed (while taking account of the related matters referred to in paras 11-13 above) involves an inventive step as required under section 1(1)(b) of the Act.

The Relevant Law

17 Whether or not an invention involves an inventive step is the concern of section 1(1)b and section 3 of the Act.

18 Section 1(1)(b) of the Act reads as follows:

> *1(1). A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say:*
>
> *(a) …;*
> *(b) It involves an inventive step;*
> *(c) …;*
> *(d) ….*

19 Section 3 of the Act, entitled 'Inventive Step' reads:

> *An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of Section 2(2) above (and disregarding Section 2(3) above).*

20 Section 2(2) of the Act, which refers to the state of the art, reads:

> *The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything*

else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way.

21 The approach to assessing inventive step is the structured approach found in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59 ("*Windsurfing*") as modified by Jacobs LJ in *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588 ("*Pozzoli*"). This approach, referred to as the "Windsurfing/Pozzoli" test involves the following steps:

> *(1)(a) Identify the notional "person skilled in the art"*
> *(1)(b) Identify the relevant common general knowledge of that person;*
>
> *(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;*
>
> *(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;*
>
> *(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?*

22 According to section 125(1) of the Act, the claims are interpreted as they would be understood by the skilled person in light of the description and any drawings in the application as filed, i.e.:

> *For the purposes of this Act an invention for a patent for which an application has been made or for which a patent has been granted shall, unless the context otherwise requires, be taken to be that specified in a claim of the specification of the application or patent, as the case may be, as interpreted by the description and any drawings contained in that specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly.*

Arguments and analysis

23 During the course of the prosecution, the examiner has cited a number of documents that he considers render the invention as claimed obvious. The weight placed upon these documents, and the subsequent arguments surrounding inventive step has varied throughout the examination process. In his second examination report, dated 29 October 2020, the examiner introduced *Kuroda et al* (*PLoS One, Vol 7, 2021 "Highly sensitive in vitro methods of detection of…" Article No. : e37342*) and considered that the claims lacked an inventive step in light of this document, when read in combination with the common general knowledge of the skilled person. Whilst his arguments in his third examination report, dated 27 October 2021, focussed on an alternative document (*Parr et al*, cited therein), the examiner revisited his arguments, and those of the applicant prior to the issue of the pre-hearing report, at which point he returned once again to *Kuroda et al* as this closest prior art. Five further documents,

first cited in his examination report of 29 October 2020, were also referred to in the pre-hearing report. My assessment of inventive step will therefore focus upon the following six documents (D1-D6) as listed in the pre-hearing report dated 2 August 2022:

> D1: PLoS One, Vol.7, 2012, *Takuya Kuroda, et al*., "Highly sensitive in vitro methods for detection of...", Article No.: e37342
>
> D2: Biochem. Biophys. Res. Comm., Vol.417, 2012, *Kuo Chic-Hao, et al*., "A novel role of miR-302/367...", pp.11-16
>
> D3: Stem Cell Rep., Vol.4, 2015, *Zhang Zhonghui, et al.*, "MicroRNA-302/367 cluster...", pp.645-657.
>
> D4: Comp. Biochem. Physiol., Part D., Vol.16, 2015, *Chen Liang, et al.,* "Evolutionary conservation and function...", pp.83-98
>
> D5: Open Biol., Vol.5, 2015, *Gao Zeqian, et al*., "The miR-302/367 cluster...", Article No.: 150138.
>
> D6: Stem Cells Dev., Vol.18, 2009, *Wilson, K. D. et al.*, "MicroRNA profiling of...", pp.749-758

24 To determine whether the present application has an inventive step over the prior art, I will follow the approach set out in *Windsurfing/Pozzoli* above.

Step 1(a): Identify the notional 'person skilled in the art'

25 Much of the disagreement between the examiner and the applicants has been around the identification of the person skilled in the art (and their common general knowledge). It is widely accepted that the skilled person may in fact be a team of individuals, and both the examiner and applicants agree that the skilled person in this case is broadly a team of scientists comprising a molecular biologist and a biologist concerned with cell therapy treatments. The disagreement between them lies in the degree of specialism of the biologist concerned with cell treatment. In the opinion of the examiner, it would be reasonable that the scientists involved in the skilled team would include those concerned with cell therapy treatments derived from PSCs, and he points out that the description states that PSCs are becoming an increasingly popular way of producing cell therapy treatments. However, the applicants disagree on this point - they argue that the increasing popularity of a field does not affect the identity of the skilled team, and that by defining the skilled team as '*concerned with cell therapy treatments derived from PSCs*', the examiner is being too specific and risks that the statutory question of obviousness is judged through the eyes of an over-qualified and/or expert-like team.

26 I am not convinced by the arguments from the applicants that the team set out by the examiner would be over-qualified or expert-like. It is well established that the skilled person would have the ability to make routine workshop developments and that they would have read literature relevant to their field. As pointed out by Arnold J in *Mylan*[1],

[1] *Mylan and Actavis v Warner-Lambert* ([2015] EWHC 2548 (Pat)

at [113]), a "*patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used….".* As I have identified above, the present application is directed to methods for the detection of undifferentiated PSC contaminants in cell products derived from PSCs, and therefore the skilled would have a practical interest in this particular field.

27 In their agent's letter of 1 March 2022, the applicants consider that the skilled person '*must be someone who is directly involved in producing the product in question. A therapist, such as a medical doctor, would not be directly involved in carrying out the invention and so would not be a member of the skilled team'*. Again, I am not convinced by this argument, and I think it is useful here to refer to the reasoning of Jacob LJ in *Schlumberger Holdings Ltd*[2], where the skilled person needed to perform the invention[3] would be different to the skilled person needed for obviousness. The applicants' position appears to conflate these two scenarios in pointing out that a therapist/ medical doctor would not be directly involved in *carrying out* the invention, rather than whether they would be part of the skilled team used for the assessment of inventive step. Therefore, whilst this argument might be true for what skills are required to perform the invention, I do not agree that this is the case for determining who the skilled person is when assessing obviousness. As Jacob LJ stated (at [65]), when assessing obviousness:

> "*In the case of obviousness in view of the state of the art, a key question is generally "what problem was the patentee trying to solve?". That leads one in turn to consider the art in which the problem in fact lay. It is the notional team in that art which is the relevant team making up the person skilled in the art…"*

28 He goes on (at [71]-[73]) to consider the facts of the case in hand: did each expert see, from their own perspective, that they had a solvable problem, and would it be obvious to them to consult the other? Put another way, '*was the marriage obvious to either notional partner?*'.

29 If I apply this approach to the present application, the problem that the patentee is trying to solve is the contamination of cell therapy products derived from PSCs by residual undifferentiated PSCs. This would be the problem faced by the biologist concerned with cell therapy treatments, and they would necessarily be aware of this drawback of the use of PSC-derived products in therapy. In looking to address this problem, they would seek out the knowledge of a molecular biologist to help identify the degree of contaminating cells. Conversely, the molecular biologist involved in the differentiation of PSCs to target cells would be well aware of the therapeutic potential of these cells and would turn to a biologist concerned with cell therapy treatments with a knowledge of PSC cells in order to ensure that the products would be suitable for therapeutic use. Therefore, paraphrasing the words used by Jacob LJ in

---

[2] *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS, [2010] RPC 33*

[3] *The skilled person is seeking to perform the invention based on the information in the application as filed i.e. to meet the requirements of support and sufficiency under section 14 of the Act – see IPO Manual of Patent Practice, paragraphs 14.64 – 14.66.1.*

Schlumberger Holdings Ltd[2], the marriage would indeed be obvious to both notional partners.

30 The applicants in their letter of 16 August 2022 considered that the examiner was applying *ex-post facto* analysis when defining the skilled person, and that their approach '*does not seek to pursue or be expected to lead to a particular outcome'*. However I find this at odds with the assessment of inventive step in general, which as I stated above is based upon the problem that the patentee is trying to solve. The skilled person would recognise that there was a problem and would use their abilities to find a solution to it. That solution may or may not be the same as that identified by the application in hand, but, regardless, it would be an outcome that the skilled person would expect to pursue. This is not *ex-post facto* analysis; this is established doctrine in the assessment of inventive step.

31 Therefore, I am in agreement with the examiner that the notional person skilled in the art would be a skilled team comprising a molecular biologist and a biologist concerned with cell therapy treatments derived from PSCs.

Step 1(b): Identify the relevant common general knowledge of that person

32 Along with the identification of the person skilled in the art, there is also disagreement around the common general knowledge (CGK) of this skilled person. The Intellectual Property Office's (IPO) Manual of Patent Practice[4] (see paragraph 3.29) reminds us that "*common general knowledge can, perhaps, be summarised as part of the mental equipment or mental toolkit needed so as to be competent in the art concerned. It is what makes the person skilled"*.

33 Laddie J (as he then was) explained CGK in *Raychem*[5] (see page 40, line 27-40):

> *"The common general knowledge is the technical background of the notional man in the art against which the prior art must be considered. This is not limited to material he has memorised and has at the front of his mind. In includes all that material in the field he is working in which he knows exists, which he would refer to as a matter of course if he cannot remember it and which he understands is generally regarded as sufficiently reliable to use as a foundation for further work or to help understand the pleaded prior art. This does not mean that everything on the shelf which is capable of being referred to without difficulty is common general knowledge nor does it mean that every word in a common textbook is either. In the case of standard textbooks, it is likely that all or most of the main text will be common general knowledge. In many cases common general knowledge will include or be reflected in readily available trade literature which a man in the art would be expected to have at his elbow and regard as basic reliable information"*.

---

[4] *The Manual of Patent Practice (MOPP) explains the Intellectual Property Office's (IPOs) practice under the Patents Act 1977 - see* Patents: Manual of Patent Practice - GOV.UK (www.gov.uk)

[5] *Raychem Corp's Patent [1998] RPC 31*

34 More recently, in *Teva*[6] (at [60]), Sales J affirmed that in the age of the internet and digital databases, searches of these databases are routine and part of sharing information in the scientific community. He went on to add that:

> "…*if there is sufficient basis … in the background CGK relating to a particular issue to make it obvious to the unimaginative and uninventive skilled person that there is likely to be – not merely a speculative possibility that there may be – relevant published material bearing directly on that issue which would be identified by such a search, the relevant CGK will include material that would readily be identified by such a search"*.

35 Nevertheless, CGK should be distinguished from what is considered to be the state of the art, and so a concept well-known to a few experts or within certain organisations would not necessarily be accepted as CGK unless it can be shown to be known to and accepted by the large majority of those skilled in the art. Aldous LJ in *Beloit*[7] *(No.2)* (at page 494, line 20-31) pointed out that:

> *"It has never been easy to differentiate between common general knowledge and that which is known by some. It has become particularly difficult with the modern ability to circulate and retrieve information. Employees of some companies, with the use of libraries and patent departments, will become aware of information soon after it is published in a whole variety of documents; whereas others, without such advantages, may never do so until that information is accepted generally and put into practice. The notional skilled addressee is the ordinary man who may not have the advantages that some employees of large companies may have. The information in a patent specification is addressed to such a man and must contain sufficient details for him to understand and apply the invention. It will only lack an inventive step if it is obvious to such a man. It follows that evidence that a fact is known or even well-known to a witness does not establish that that fact forms part of the common general knowledge. Neither does it follow that it will form part of the common general knowledge if it is recorded in a document".*

36 In their agent's letter dated 1 March 2022, the applicants refer to the judgment of Kitchin LJ in *HTC*[8] (at [66]), where, referring to the Windsurfing/Pozzoli test, he stated "*Step (1)(b) involves identifying the relevant common general knowledge relied upon and doing so with some precision".* He goes on to emphasise the importance of this in an obviousness attack **based solely upon CGK**, and further refers to the judgment of Floyd J in *Ratiopharm*[9] (at [156]) where he sets out important considerations when basing an obviousness attack **solely on CGK**. However, in the present case, the obviousness attack is not solely based on CGK, and whilst I agree that it still plays an important part in the assessment of inventive step, I do not feel that the precision

---

[6] *Teva UK Limited & Anor v AstraZeneca AB [2014] EWHC 2873 (Pat)*

[7] *Beloit v Valmet (No.2)* [1997] RPC 489

[8] *HTC Europe Co. Ltd v Apple Inc* [2013] RPC 30

[9] *Ratiopharm GmbH v Napp Pharmaceutical Holdings Ltd* [2009] RPC 11

required in the identification of what is CGK in the present case is the same. Floyd J sets this difference out quite neatly in *Ratiopharm*[9], where he states:

> "…*in the present case it is admitted that "the existence of oxycodone" was common general knowledge. But the dispute here is not about whether a skilled person knew about oxycodone. The real dispute is about what oxycodone was used for. If the skilled person has not used oxycodone as an alternative to morphine for oral administration for moderate to severe pain, it becomes difficult to argue that it would occur to him to use oxycodone in the course of deciding on a controlled release formulation for use in such circumstance".*

This makes a clear distinction between what is CGK for general purposes (i.e., the existence of oxycodone) and how CGK needs to be more precise if that is the only basis of an obviousness attack (i.e., whether the skilled person would have used oxycodone for the treatment of pain).

37 During the course of the prosecution, the examiner has made several assumptions around what would form part of the CGK. The wording of this has changed throughout the course of the prosecution (and indeed is different again for the pre-hearing report), but the substance has remained the same and therefore the arguments from the applicants still apply. I will take each of these assumption in turn:

(i) *Residual, undifferentiated PSCs need to be identified and removed prior to the use of the cells in therapy, otherwise treatment can give rise to teratomas or other neoplasms*

38 In support of this statement, the examiner refers to the description of the application, which states that this is a known challenge of stem cell therapies. He also refers to two further documents (D7 and D8) which he first cited in his examination report dated 29 October 2020, which I have listed below:

> D7: Sci. Reports, Vol. 6, 2016, *Parr, C. J. C. et al*., "MicroRNA-302 switch…", Article No.: 32532
>
> D8: Sci. Reports, Vol.6, 2016, *Garitonandia, I. et al*., "Neural stem cell tumorigenicity..", Article No.: 34478

39 The applicants on the other hand argue that none of the documents cited by the examiner as demonstrating CGK provide sufficient evidence that this statement does form part of the common general knowledge. In particular, they argue that a skilled team concerned with cell therapy treatments would not be aware of specific regulatory requirements and as such this would not form part of their CGK.

40 I'm not entirely sure what the applicants mean by '*specific regulatory requirements*' in their arguments, but I will assume that in this context this relates to the safety of PSC-derived products, and the fact that residual undifferentiated PSCs in a clinical sample can give rise to teratomas and other proliferative diseases. I admit that I was a little surprised that the applicants argued that this would not be CGK. A well-known test for pluripotency is the formation of teratomas by cells implanted into SCID mice, and whilst this is not a clinical test, any skilled person working with PSCs with an intention to find a therapeutic use would be aware of this. They would also be aware that not

all PSCs in a sample will differentiate into their target cell, and that there would therefore be a risk of residual PSCs in a differentiated cell sample. However, I do not think that the extent of this risk would necessarily form part of the CGK, in other words how may contaminating cells would give rise to teratomas or other neoplasms, and this would be regardless of whether the team comprised cell therapists (as asserted by the examiner) or biologists concerned with cell therapy treatments (as asserted by the applicants). Nevertheless, given that the presence of PSCs in a cell sample does inherently pose a risk, in my opinion the skilled person would know that having as few contaminating cells as possible in a sample would be the most suitable for any potential therapeutic use. Again this is regardless of whether the team comprises therapists or merely biologists with an interest in cell therapy.

41 I therefore agree with the examiner that the skilled person (who as I have explained above is a team) would, within their CGK, be aware that PSCs transplanted into a patient would pose a teratoma or neoplastic risk, that not all PSCs in a sample will differentiate into the target cell and would understand that in order to minimise the aforementioned risks, having as low a number of PSCs as possible in a sample would be preferable. D7 and D8 do generally discuss this, and I think are representative of this broad aspect of the CGK. However, I do not consider that the skilled person would know what the upper limit of PSCs in a transplant sample would be, and whilst assays to detect and estimate the number of residual undifferentiated cells are available, as in D7 and D8, I think that it would indeed be a stretch to consider that the skilled person would know how many PSCs in a sample would be deemed to be clinically safe and within regulatory requirements. Therefore I do not consider that this specific aspect would form part of the CGK, and again this is regardless of whether the skilled team included cell therapists or biologists.

42 Consequently, I agree with the examiner that, in this case a skilled team would know that the identification and removal of residual undifferentiated PSCs is required before cells can be used in therapy, because failure to do so could result in teratoma or neoplasm formation.

(ii) *Methods to identify PSC contaminating cells using specific markers on PSCs are well known to the skilled man*

43 The applicants do not appear to dispute the examiner's assertion that methods to identify PSC contaminating cells exist (and indeed the application itself lists 14 such techniques that could be used). They also agree that the claimed assay methods, i.e., qRT-PCR, dPCR and ddPCR are known to exist, but dispute the fact that the skilled team would know that they could be used to measure the expression levels of a panel of miRNAs, resulting in a sensitive method for the detection of PSC contaminants. In his pre-hearing report, the examiner has conceded this point and therefore agrees that this would not form part of the CGK. I also agree with this concession; whilst these methods *per se* would be within the skilled teams knowledge, their use as a sensitive method in detecting PSC contaminants would not necessarily form part of CGK.

44 In my view, whether or not the skilled team would use qRT-PCR, dPCR or ddPCR in the method of the present invention is not relevant for the assessment of CGK but rather is a consideration for the fourth step of the *Windsurfing/ Pozzoli* approach.

(iii) *Means to identify known microRNAs, e.g. by PCR, would also be common general knowledge*

45 This aspect of the CGK has not been disputed by the applicant and therefore I do not feel the need to elaborate other than to agree with this statement and point out that the methods used in the present application (qRT-PCR, dPCR and ddPCR) are all commercially available and apparently used according to the manufacturer's instructions (aside from the routine modifications required to adapt to a specific target).

(iv) *The miR-302 cluster is specific to pluripotent stem cells, is highly expressed in early stages of development, and then declines prior to differentiation*.

46 The examiner reassessed this assertion around CGK prior to issuing his pre-hearing report, where he concluded that this would not form part of the CGK. I agree, but with the caveat that the skilled team would know that all cells possess markers that are specific to each stage of their development, and that PSCs are known to possess a variety of markers that are specific to pluripotency.

47 Therefore, to summarise what I consider to be part of the common general knowledge (CGK) of the skilled team:

- not all PSCs will differentiate into their target cell;
- transplanted PSCs would have the potential to form a teratoma or other neoplasms, and therefore any intended therapeutic use of PSC-derived cells would seek to minimise any contamination from residual undifferentiated cells;
- methods suitable for the identification of markers on contaminating cells, such as PCR, qRT-PCR and ddPCR were known, and these can be applied to microRNAs; and
- PSCs were known to possess markers that were specific to pluripotency.

Step 2: Identify the inventive concept of the claim in question, or if that cannot readily be done, construe it

48 Before I construe the inventive concept, I will first point out that both the examiner and the applicants have provided a construction of claim 1, and not of the later independent claims. Claims 1, 15, 17 and 19 are all method claims which similarly are concerned with the detection of undifferentiated PSCs (and, in the case of claim 19, producing a PCS-derived cell population), and so the underlying inventive concept will be the same. However, as noted above, claim 16 is a product claim (to a kit) and claim 18 is a reach-through claim. The construction of claims 16 and 18 will be different, and as I have already pointed out, as I am not assessing the allowability of these claims as part of this decision, I will not construe them here.

49 The examiner initially identified the inventive concept as:

> "*a method for determining the presence or level of contamination by PSCs in a PSC-derived cell population, comprising assaying the population for*

one or more miRNAs selected from hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p and hsa-miR-302d-3p".

The applicants have a much narrower view of the inventive concept and argue that it is better construed as

"*use of quantitative RT-PCR, digital PCR or droplet digital PCR in an assay for one or more of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p in a sample of a PSC-derived cell population intended for use in cell therapy in order to determine whether the PSC-derived cell population meets the criterion of ten or fewer PSC contaminant cells per one million cells of the sample, and may be considered safe*".

50 The applicants go on to assert (in their agent's letter dated 1 March 2022) that "*it is important to formulate the inventive concept in this way for proper application of Step 4 and that by doing so the inventive concept properly includes the recognition that the specified technique is capable of not only measuring PSC contamination level but achieving the sensitivity of ten PSC cells per million by the assay for particular miRNAs' expression*". In response to this, the examiner narrowed his identification of the inventive concept in his pre-hearing report, such that it relates to:

"*a method for determining the presence or level of contamination by PSC in a PSC-derived cell population, comprising assaying the population for one or more miRNAs selected from hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p and hsa-miR-302d-3p in order to determine whether the PSC-derived cell population meets the criterion of ten or fewer PSC contaminant cells per one million cells of the sample*".

51 My first observation is around the reason for the criterion that the level of contamination by PSC contaminants is ten or fewer PCS contaminant cells per one million cells of the sample; the applicants in particular add into their identification of the inventive concept that a cell sample comprising this number of cells may be considered safe. I note that this is not a requirement of any of the claims, and rightly so, because this would be subjective and a desired result. Furthermore, I note that the applicants have provided no evidence to support this assertion, beyond the generally known assumption that the fewer the number of contaminating PSCs, the lower the likelihood of teratoma or tumour formation. I will therefore not give any further consideration to this limitation suggested by the applicants.

52 I will however consider the significance of specifying an actual level of contamination as ten or fewer PSCs per million in my discussion below.

53 My second observation is that both the examiner and applicant are apparently construing claim 1 only in identifying the inventive concept and not the remaining method claims. Whilst the broad inventive concept is the same, the difference in wording of claims 1 & 17 and 15 places a nuanced difference on the intentions of these claims, which impacts upon the construction and ultimately on the assessment of inventive step. I will therefore construe each of these claims in my discussion below.

Claims 1, 17 & 19

54 Claim 1 defines a method for determining the presence and/or level of contamination by PSC contaminants in a PSC-derived cell population, by detecting the presence of one or more of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p using qRT-PCT, dPCR or ddPCR. The claim further states that the method is '**configured to determine** (my emphasis) whether the level of contamination by PSC contaminants meets the criterion of ten or fewer PSC contaminant cells per million cells of the sample'. However, it provides no technical detail of what this configuration should be.

55 Section 125 of the Act requires that I construe the claim in light of the description, yet from what I can see there is nothing in the description that would suggest how the method of claim 1 is 'configured' to determine this level of contamination. The claim requires the use of qRT-PCR, dPCR or ddPCR to analyse the PSC sample for the presence of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p, but there is nothing in the claim itself or the description that suggests that the method involves anything other than the standard commercial protocols provided with these methods. In other words, by using one of qRT-PCR, dPCR or ddPCR to detect the presence of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p, one would inherently detect a level of contamination by PSC contaminants to a level of ten or fewer PSC contaminant cells per one million of the sample. Consequently, the result of detecting ten or fewer PSC contaminant cells in the sample would inevitably arise when using qRT-PCR, dPCR or ddPCR to analyse the PSC sample for the presence of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p.

56 As such, I construe claim 1 as a method suitable for determining the presence of PSC contaminants in a PSC-derived cell population by assaying the population for the presence of one or more of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p using qRT-PCT, dPCR or ddPCR. The method will inherently determine whether there are ten or fewer PSC contaminant cells per one million cells of the sample.

57 Claim 19 defines a method of producing a PSC-derived cell population by inducing differentiation of PSCs into derived cells and determining the presence and level of PSC contaminants using the method of claim 1. Claim 19 utilises the method of claim 1 to identify PSC contaminant cells in a sample of the PSC derived cells. Thus, the method of claim 19 encompasses the method of claim 1.

58 Claim 17 defines a method suitable for detection of PSC contaminants to a level of ten or fewer PSCs per million of a PSC-derived population. As with claim 1, the method steps require the use of qRT-PCR, dPCR or ddPCR to detect the presence of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p, and so again the use of these steps would inherently determine whether there are ten or fewer PSC contaminant cells. .

Claim 15

59 Turning now to claim 15, which defines the use of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p expression data to determine whether the

level of contamination by PSC contaminants meets the criteria of ten or fewer PSC contaminant cells per million cells of a PSC-derived cell population, by measuring these miRNA levels using one of qRT-PCR, dPCR or ddPCR.

60 The wording of this claim is such that the miRNA expression data is intentionally used to determine whether the level of contamination by PSC contaminants is ten or fewer per million cells in the sample, and this differs from the wording of claim 1 in that this measurement is an intentional part of the use of the data and not an inherent result of performing the method. It therefore follows that the construction of this claim is different to that of claim 1 as the limitation imparted by the level of contamination differs.

61 I therefore construe claim 15 as the use of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p expression data to determine whether the level of contamination by PSC contaminants meets the criterion of ten or fewer PSC contaminant cells per one million cells of a PSC-derived cell population, using qRT-PCR, dPCR or ddPCR.

Step 3: Identify what, if any, differences exist between the matter cited as forming part of the state of the art and the inventive concept of the claim or the claim as construed.

62 The examiner considers D1 to be the closest prior art in his assessment of inventive step. At this point, I should note that the applicants have not developed their arguments in relation to the relevance of this document since their submissions in their agent's letter dated 29 March 2021.

63 D1 discloses methods for the detection of residual undifferentiated PSCs in a sample of retinal pigment epithelial (RPE) cells derived from iPSCs. The introduction points out that one of the most important considerations for the use of PSCs is ensuring that the final product does not form tumours or teratomas after implantation and references earlier work that demonstrates that it is only necessary to have several hundred undifferentiated PSCs for tumours to form in mice. In light of this, the authors recognise the need to develop sensitive assays for the detection of residual undifferentiated PSCs. Put simply, this document seeks to solve the same problem as that of the present application.

64 D1 identifies the known PSC markers Oct 3/4, Nanog, Sox2 and Lin28 as being suitable candidates for identifying undifferentiated residual PSCs due to the vastly different levels of expression of these markers in PSCs when compared to the differentiated RPE cells. The remaining known PSC markers (Klf4, c-Myc, Rex1) were expressed at higher levels in the RPE cells and so deemed not suitable. The author goes on to investigate the lower level of detection (LLOD) for levels of mRNA transcripts of known PSC markers Oct 3/4, Nanog and Lin28 spiked PSCs in RPE cells using qRT-PCR. As Lin28 displayed the most promise, the authors went on to examine the specificity of Lin28 in the detection of residual undifferentiated PSCs. They concluded that qRT-PCR analysis for Lin28 detected 0.002% of residual undifferentiated PSCs (or one PSC in a sample of $5x10^4$ RPE cells/ twenty PSCs per million cells).

65 Thus, I consider that the difference between D1 and the inventive concept of the claims is (a) the use of the miRNAs: hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p to detect the PSCs, and (b) the ability to detect ten residual undifferentiated PSCs per million cells. I do not think that this is at odds with what is suggested by either the examiner or the applicants.

Step 4: Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

66 The applicants argue that there is nothing in D1 that would prompt the skilled person to use any miRNA in place of Lin28, and specifically nothing that would prompt them to choose one of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p. They argue further that even if the skilled team was aware of the role of the latter miRNAs in PSCs, there is no indication in D1 that substituting Lin28 with one or more of these would be effective, let alone be more effective than already disclosed in D1.

67 The examiner on the other hand argues that given the CGK that different cell types will have different markers that may be used as an identification means, the skilled person would be motivated to identify additional PSC markers in order to improve the assay and would consider the miR-302 cluster as a suitable candidate.

68 I agree with the examiner that the skilled person would appreciate that there are markers that are specific to PSCs that could be used to detect the presence of undifferentiated cells. I also do not think the applicants dispute this, rather they dispute the level of detection and whether the choice of marker would result in an assay that would be effective. However, as I have noted above, my construction of the claims, and specifically claims 1, 15, 17 and 19 differs from that of both the examiner and the applicant, with claim 15 having a different limitation to that of claims 1, 17 & 19. Nevertheless, the fundamental question to be asked in considering the inventive step of each of these claims is whether the skilled team would consider the miR-302 cluster as a viable candidate for the identification of residual undifferentiated PSCs. Once I have answered this question, I will go on to decide whether the invention claimed in claims 1, 17 & 19 and claim 15 involves an inventive step.

Use of the miR-302 cluster

69 As I discussed above, as part of their CGK, the skilled person would be aware of the different PSC-specific markers available in order to distinguish between differentiated and undifferentiated cells. However, the specific miR-302 cluster would not form part of this CGK, and therefore if the skilled person were to utilise this cluster in the assay of D1, they would need to seek out other documents that would direct them towards its selection as an alternative target. In his pre-hearing report, the examiner considers that the skilled person would consider the miR-302 cluster described in D2-D6 as being suitable.

70 Combining disclosures from one document with that of another is permitted in order to make an argument that a claim is obvious. However, as cautioned by Laddie J (as he

was then) in *Pfizer*[10] at [66], it must be likely that the skilled person would have considered the teaching from each together:

> "*When any piece of prior art is considered for the purposes of an obviousness attack, the question asked is "what would the skilled addressee think and do on the basis of the disclosure?" He will consider the disclosure in the light of the common general knowledge and it may be that in some cases he will also think it obvious to supplement the disclosure by consulting other readily accessible publicly available information. This will be particularly likely where the pleaded prior art encourages him to do so because it expressly cross-refers to other material. However, I do not think it is limited to cases where there is an express cross-reference. For example if a piece of prior art directs the skilled worker to use a member of a class of ingredients for a particular purpose and it would be obvious to him where and how to find details of members of that class, then he will do so and that act of pulling in other information is itself an obvious consequence of the disclosure in the prior art*".

71 This echoes the judgment of Whitford J in *Dow Chemical Company*[11], where he indicated that it is necessary to consider whether the documents are ones that the seeker of information would come across and consider together. I note that whilst the examiner has indicated that the skilled person would be aware of both sets of documents, he has not discussed whether the skilled person would in fact be minded to combine the respective teaching.

72 The IPO Manual Of Patent Practice (, at paragraph 3.43) provides some guidance around combining documents, and lists factors to consider before doing so:

a. *How the nature and the contents of the documents influence whether the person skilled in the art would combine them. For example where the disclosed features seem at first sight to have an inherent incompatibility or where one document has a tendency to lead from the mosaic, this would be a pointer towards the combinations being inventive.*

b. *Whether the documents come from the same technical field or from neighbouring or remote technical fields.*

c. *The presence of references in one document to another.*

d. *The amount of selection required to isolate the separate disclosures from the surrounding documentary material.*

e. *Whether the contents of one document are so well known that the skilled person would always have them in mind in reading other documents.*

f. *The age of the documents.*

---

[10] *Pfizer Ltd's Patent [2001] FSR 16*

[11] *Dow Chemical Company (Mildner's Patent) [1973] RPC 804*

73 Looking at D1-D6, they are from the same technical field (PSC research), and there is no incompatibility between them as they all relate to pluripotency markers. This field of research is relatively new and therefore the age of the documents is not of concern. Whilst none of D2-D6 cross-reference D1 (or *vice versa*), in a field as well-known as PSC research, this is not surprising given the large number of documents available discussing the role of the miRNAs in pluripotency. Notably, D2 and D5 are review articles available before the priority date of the application that discuss the specificity of expression of the miR-302 cluster in PSCs. I note that D2, in particular, discusses recent studies where introducing miRNAs into cells (and particularly the miR-302 cluster) is a more efficient way to reprogramme cells than the more traditional factors such as Oct 3/4, Sox2, Nanog and Lin28; whereas D3, D4 and D6 are all research articles confirming the importance of the miR-302 cluster in pluripotency. Each of D2-D6 confirm that the miR-302 cluster is highly expressed during early development, declines prior to differentiation, and is not found in differentiated cells. It is clear that these are merely examples of documents demonstrating the role of the miR-302 cluster in pluripotency and therefore the contents of these documents would be in the forefront of the skilled person's mind when investigating PSCs and their differentiation. I am therefore happy that I have given due consideration to factors (a)-(c), (e) and (f) above.

74 This leaves me to consider the amount of selection required to isolate these disclosures from the surrounding material. I have no doubt that there are a number of factors that are known to influence and/ or induce pluripotency of cells, these include the more traditional reprogramming / pluripotency factors, such as Oct 3/4, Sox2, Nanog and Lin28, as well as a number of miRNAs. In fact, D1 also compares mRNA levels from the other pluripotency factors Oct3/4, Klf4, c-Myc, Sox2, Nanog and Rex1, with Lin28 detection being the most sensitive. This would therefore suggest to the reader to immediately disregard Oct3/4, Klf4, c-Myc, Sox2, Nanog and Rex1 as potential candidates for *increasing* sensitivity of the assay, thereby narrowing the field of prior art from which to select. It is also clear from the prior art that the miR-302 cluster has a well-established role in pluripotency, and D2-D6 are examples of documents that demonstrate their importance. There may be other factors or miRNAs that could also be investigated, but the miR-302 cluster would, in my opinion, be considered as suitable candidates. As such, I think that given the importance of the miR-302 cluster in maintaining pluripotency, and the large amount of documentary evidence supporting this, the skilled person would particularly be drawn to D2-D6 (amongst others discussing miR-302 and pluripotency), when looking to identify alternatives to Lin28 as a marker in the assay of D1.

75 Now that I have established that the skilled person would consider combining the teachings surrounding miR-302 of D2-D6 in their search for alternative markers to identify residual undifferentiated cells in the assay of D1, I need to consider whether they would, in fact, have chosen these markers and done so with a reasonable expectation of success.

76 I can take some guidance here from Dillon LJ in *Genentech*[12] where (referencing the judgement of Whitford J in *Philips*[13]) he stated that *"to render an invention obvious it*

[12] *Genentech Inc's Patent [1989] RPC 147*

[13] *Philips (Bosgra's) Application [1974] 5 R.P.C. 241*

was not necessary that the materials in question should have been the first choice of the notional research worker; it was enough that the materials were "lying in the road" and there for the research worker to use". In the present case, the miR-302 cluster was 'lying in the road'- it was a well-known marker for pluripotency and had been shown to induce pluripotency in adult cells. In fact, even if it hadn't been the first choice, given how important a role this cluster has in pluripotency, it would have been pretty close.

77 I am also of the opinion that in choosing the miR-302 cluster, the skilled person would have a reasonable expectation that they would find a successful alternative to Lin28 in the detection of residual undifferentiated PSCs. I acknowledge that they may not know whether it would be more sensitive than the method disclosed in D1, but this uncertainty would not preclude them from trying. As pointed out by Kitchin LJ in Novartis[14], (see parapgraph 55), what is a reasonable expectation of success will depend on the facts of the individual case:

> *"In deciding whether the invention was obvious to the skilled but unimaginative addressee at the priority date the court will have regard to all the circumstances of the case including, where appropriate, whether it was obvious to try a particular route with a reasonable or fair expectation of success. What is a reasonable or fair expectation of success will again depend upon all the circumstances and will vary from case to case……..simply including something in a research project in the hope that something might turn up is unlikely to be enough. But I reject the submission that the court can only make a finding of obviousness where it is manifest that a test ought to work. That would be to impose a straight-jacket upon the assessment of obviousness which is not warranted by the statutory test and would, for example, preclude a finding of obviousness in a case where the results of an entirely routine test are unpredictable".*

78 In the present case, I do not think that the skilled team combining the teachings of D1 with D2-D6 would be embarking on a research project merely in the hope that something would turn up; they would have more certainty than that. They would know that the method of D1 can detect the mRNA of pluripotency markers, and that it is sensitive enough to detect undifferentiated PSCs in a spiked RPE culture using qRT-PCR specific for the mRNA transcripts of either Lin28, Nanog and Oct3/4, and this is due to the expression of these in PSCs but not in the differentiated RPE cells. They would also know from D2-D6 that the miR-302 cluster was highly expressed in PSCs but is not expressed in differentiated cells, two of the key advantages of Lin28 in D1. Therefore, they would have some degree of certainty that the use of one of the miR-302 cluster in the method of D1 would enable detection of residual undifferentiated PSCs in amongst a sample of differentiated cells.

79 Consequently, I am of the opinion that the skilled person seeking to improve on the assay of D1 would, in light of the disclosure of any one of D2-D6 (or indeed any similar documents disclosing the role of the miR-320 cluster in pluripotency), be motivated to substitute Lin28 with a member of the miR-320 cluster, namely hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p. In doing so, and following the

---

[14] *Novartis AG v Generics (UK) Ltd [2012] EWCA Civ 1623*

method of D1, they would assay a sample of the PSC-derived population by measuring the levels of the miRNAs: hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p; using qRT-PCR. I will now consider whether the claims themselves are obvious in light of this conclusion.

Claims 1, 17 and 19

80 As I established above, claim 1 defines a method suitable for determining the presence of PSC contaminants in a PSC-derived cell population by assaying for one or more of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p, using a method selected from qRT-PCR, dPCR or ddPCR, said method inherently determining whether there are ten or fewer PSC contaminant cells per one million cells of the sample.

81 As I am of the view that the skilled person would be motivated to substitute Lin28 from D1 with hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p and that by doing so and, following the method of D1, they would arrive at an assay using qRT-PCR to detect the presence of any of these miRNAs in a PSC-derived population, the presence of any these miRNAs will indicate the presence of PSC contaminants. Thus, there are no features in the method of claim 1 that would distinguish it from the method disclosed in D1 when Lin28 is substituted by one of the miR-302 cluster, and therefore by following this method, the skilled person would inherently detect ten or fewer PSC contaminants per one million cells of the sample.

82 As such, in the absence of any evidence to dispute this, I am of the opinion that claim 1 lacks an inventive step in light of D1, when read in combination with the teachings of any one of D2-D6. I note that claim 1 also defines alternative commercially available assays to qRT-PCR for the measurement of the miRNAs, yet these assays were well within the purview of the CGK of the skilled person (which was not disputed by the applicants). Therefore, even if the claims were limited to dPCR and ddPCR, my decision would be the same.

83 The same applies to claim 17, which defines a method *suitable for* detection of ten or fewer PSC contaminants in a PSC-derived population. Substitution of Lin28 with one of the miR-302 cluster in the method of D1 would result in such a method, and therefore claim 17 is also obvious.

84 Claim 19 has the additional step of producing a PSC-derived cell population and then detecting the presence of residual undifferentiated cells therein. D1 discloses this step and therefore this claim also lacks an inventive step.

Claim 15

85 Claim 15 defines the use of miRNA expression profiles from a member of the miR-302 cluster to determine whether the level of contamination by PSC contaminants meets the criterion of ten or fewer PSC contaminant cells per one million cells of a PSC-derived population. This claim specifically requires that the skilled person would be working the method with the intent of reaching this specificity of detection of cell contamination. The consideration here is different to that of claims 1 and 17, where the wording was such that this specificity was a desired result and, in the absence of any distinguishing technical features, it can be assumed that the choice of one of the

miR-302 cluster, from amongst the other potential markers available to the skilled person, would inherently result in a method that could detect ten residual undifferentiated PSC cells per million.

86 Whilst I have decided that the skilled person would modify the method of D1 by substituting Lin28 with one or more of hsa-miR-302a-3p, hsa-miR-302b-3p, hsa-miR-302c-3p or hsa-miR-302d-3p, I need to consider the choice of a member of this miR-302 cluster over the other alternatives; and use it in a method to detect ten residual undifferentiated PSCs in a sample of one million cells is obvious.

87 Taking D1 at face value, whilst it discusses that it is desirable to develop a highly sensitive assay for the detection of residual PSCs, there is nothing that would suggest a target LLOD of ten residual undifferentiated PSCs per million. D1 does refer to prior research that demonstrates that 245 undifferentiated hESCs spiked into a million feeder fibroblasts produced a teratoma, thereby suggesting an upper limit, but there is nothing to suggest a lower limit. Whilst I think that it would be a known goal for the researcher to have as low a level of detection as possible, and anyone with the aim of improving the method of D1 would look at a target LLOD of fewer than twenty PSCs per million cells in a sample, there is nothing that would direct towards this target being ten cells or fewer per million cells.

88 However, similar to D1, there is nothing in the present application that would indicate what a target LLOD should be. The method of the invention detects ten residual PSCs per million, but there is nothing in the specification that suggests that this is anything other than a consequence of the use of the sensitive PCR assays and the targeting of the miR-302 cluster. In other words, there is nothing to indicate that the presence of ten residual undifferentiated PSCs is the upper limit in terms of safety, it merely appears that this is the limit of the detection methods used. I therefore cannot dismiss that this is merely an arbitrary lower limit of detection and therefore am not convinced that this alone is sufficient to impart an inventive step to the claim. I see nothing in the evidence before me that indicates that this lower limit has a surprising impact upon the safety of the differentiated cell sample, beyond the ability to detect fewer residual undifferentiated PSCs, and I have already concluded that improving the target LLOD of the method of D1 would be a known goal for the skilled person.

89 In the absence of any indication that the target LLOD of ten residual PSCs per million imparted by the method of the present application has any technical significance beyond being a consequence of the use of one of qRT-PCR, dPCR or ddPCR to detect one or more of the miR-302 cluster, and, in line with my conclusions regarding claims 1, 17 and 19 above, I find that claim 15 does not involve an inventive step.

Conclusion

90 In conclusion, I find that independent claims 1, 17 and 19 lack an inventive step under section 1(1)(b) of the Act in light of D1 when read in combination with any one of D2-D6 and in view of the CGK of the skilled person[15].

91 Claim 15 lacks an inventive step in light of the disclosure of D1 when read in combination with any one of D2-D6, as the detection limit of ten or fewer residual

[15] For specific details of D1-D6 see paragraph 24 above.

undifferentiated PSCs per million sample cells appears to be no more than an arbitrary limit resulting from the modification of the method of D1 to detect one or more of the miR-302 cluster.

92 Given my conclusion above in relation to the lack of an inventive step for claims 1, 15, 17 and 19, it is not necessary for me to remit the application for the outstanding issues identified to be dealt with in relation to claims 16 and 18 and the optional administration step referred to in claim 19.

93 As regards the dependent claims, in the absence of any evidence before me suggesting any surprising effect of the selection of a specific member of the miR-302 cluster, claim 2 would also appear to be obvious. Similarly, there does not appear to be any surprising effect of the choice of ddPCR beyond what is known about the sensitivity of this assay when used according to the manufacturer's instructions (as is the case in the present application), and therefore claim 3 also lacks an inventive step. The same arguments apply *mutatis mutandis* to the remaining dependent claims 4-14.

94 Thus, I refuse patent application GB1900893.7 under section 18(3) of the Act.

Appeal

95 Any appeal must be lodged within 28 days after the date of this decision.

Dr L Cullen

Deputy Director, acting for the ComptrollerDeputy Director, acting for the Comptroller