<table>
<thead>
<tr>
<th>APPLICATION NO.</th>
<th>FILING DATE</th>
<th>FIRST NAMED INVENTOR</th>
<th>ATTORNEY DOCKET NO.</th>
<th>CONFIRMATION NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/433,707</td>
<td>04/30/2009</td>
<td>Robert Benezra</td>
<td>MSK.P-088</td>
<td>9624</td>
</tr>
</tbody>
</table>

Larson & Anderson, LLC  
re: MSK  
P. O. BOX 4928  
DILLON, CO 80435-4928

Please find below and/or attached an Office communication concerning this application or proceeding. The time period for reply, if any, is set in the attached communication.
DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims directed to methods of identifying and isolating cells. The Examiner rejects the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

---

1 According to Appellants, the real party in interest is Sloan-Kettering Institute for Cancer Research. (App. Br. 1.)
STATEMENT OF THE CASE

Claims 1–26 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claims 1 and 7 are representative of the claims on appeal, and read as follows:

1. A method for identifying cells as potential stem cells comprising the step of screening the cells for expression of Inhibitor of DNA Binding-1 (Id1), wherein expression of Id1 is indicative that the cells are adult stem cells.

7. A method for isolating stem cells from a sample, comprising the steps of:
   combining a mixture of cells from which stem cells are to be isolated with a molecule that binds specifically to Inhibitor of DNA Binding-1 (Id1), and
   separating cells that bind to the molecule from cells that do not.

Appellants request review of the Examiner’s rejection of claims 1–26 under 35 U.S.C. § 103(a) as unpatentable over Jankovic3 in view of Jurga,4 Wagner,5 and Namba.6 (App. Br. 2.)

---

2 The Appeal Brief does not contain page numbers, any reference to the Appeal Brief in this opinion numbers the pages consecutively starting with the cover page as page one.
5 Wagner et al., *Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood*, 33 Exp. Hematology 1402–1416 (2005) (“Wagner”).
Obviousness over Jankovic, Jurga, Wagner, and Namba

The issue is: Does the preponderance of evidence of record support the Examiner’s conclusion that the combination of references renders the use of Idl as a marker for adult stem cells obvious?

Findings of Fact

We adopt the Examiner’s findings of fact and reasoning regarding the scope and content of the prior art as set out in the Examiner’s Answer and Final Action\(^7\). For emphasis only we highlight the following:

FF1. According to the Specification, “‘stem cell’ refers to a cell that retains the ability to divide throughout life and give rise to both new stem cells and to more differentiated/specialized cells” (Spec. 6). Further according to the Specification, stem cells contribute to the body’s ability to renew and repair its tissues, because unlike mature (differentiated) cells, they are not permanently committed to their fate. Stem cells are recognized as being “multipotent” or “pluripotent”, i.e. as having the ability to differentiate into more than one type of specialized mature cell. (Spec. 1).

FF2. “[A]dult stem cell’ refers to stem cells derived from (either directly or as a source of a cell line) from a non-embryonic source” (Spec. 6). “[T]erms for ‘adult stem cells’ include tissue stem cells, somatic stem cells and post-natal stem cells” (Spec. 1).

FF3. Jankovic teaches detection of “Idl mRNA and protein expression in the immature (Lin-) fraction but not in the differentiated (Lin+) fraction of murine bone marrow cells” (Jankovic 1260; see Ans. 6).

\(^7\) Office Action dated Mar. 23, 2013 (“Final Act.”)
Idl is responsible for “maintaining the self-renewal capacity of hematopoietic stem cells[,] Idl plays a regulatory role in myeloerythroid lineage choice during HSC [(hematopoietic stem cell)] differentiation” (Jankovic 1264). “Id[1] protein is required for the proper self-renewal of adult tissue stem cells and is a key transcriptional regulator of HSC lineage commitment” and is required to maintain immaturity (Jankovic 1264; Final Act. 8; Ans. 5).

FF4. Jankovic teaches the use of fluorescence-activated cell sorting (FACS) to separate cells from a mixture. Specifically, Jankovic teaches that “FACS-purified subsets of immature bone marrow hematopoietic cells [from mice] were purified by multiparameter flow-cytometric sorting and [further] analyzed for Id1 RNA expression by qPCR” (Jankovic 1261; see Ans. 6).

FF5. Jurga recognizes that ID1 not only plays a role in hematopoietic stem cell proliferation but that ID1 is “specifically required for proliferation of neuroepithelial cells and for timing of neuronal differentiation in the embryonic stage, at least in mice” (Jurga 993). “ID1 expression caused inhibition of differentiation of mouse embryonic stem (ES) cells toward the neural pathway independently of BMP4 activation, the main negative signal of cell differentiation in mice” (Jurga 993–994).

FF6. Jurga teaches “the direct effect of ID1 overexpression on human stem/progenitors differentiation was evaluated in gain-of-function experiments after transfection of HUCB-NSC [(human umbilical cord blood-derived neuronal stem-like cells)]” (Jurga 994). The fact that “ID1 expression [was correlated] with undifferentiated HUCB-NSC
phenotype was further confirmed by RT-PCR analysis” (Jurga 997; see Final Act 10; Ans. 6–7).

FF7. Jurga teaches that HUCB-NSCs grown in continuous lab culture “remained round and formed floating spheres/aggregates. Most cells were immunopositive for antinestin and human antiglial fibrillary acidic protein (GFAP) antibodies, suggesting their undifferentiated, NSC-like character” (Jurga 994; Ans. 7)

FF8. Wagner teaches that “microarray analysis might provide a better tool for the characterization of MSC” (mesenchymal stem cells) (Wagner, Abstract; see Ans. 7).

FF9. Namba teaches that “it has been demonstrated that proliferation of neural precursors [in the adult] occurs in the subgranular zone . . . , and the precursor cells expressing GFAP give rise to neurons” (Namba 1711; see Ans. 7).

FF10. Namba teaches PSA-NCAM and NeuN as neuronal markers (Namba 1704.)

Principles of Law

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”


If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

Id. at 417.
We have reviewed Appellants’ contentions that the Examiner erred in rejecting claims 1–26 as obvious over the cited art. (App. Br. 5-9; Reply Br. 1–3.) We disagree with Appellants’ contentions and adopt the findings and conclusions concerning the scope and content of the prior art set forth in the Examiner’s Answer and Final Action. For emphasis, we highlight and address the following:

Appellants contend that the Examiner relied on hindsight in formulating the present rejection (App. Br. 5–6). Although Appellants acknowledge that Jankovic teaches Id1 protein expression in the (Lin-) fraction of murine bone marrow cells and “concluded that this suggested a regulatory role for Id1 in early hematopoiesis,” Appellants contend that the reference does not suggest a role for Id1 in identification and separation (App. Br. 7). Appellants contend that “Jankovic discloses cell sorting based on LKS, CMP, GMP and MEP markers, not Id1” (App. Br. 6).

While we are fully aware that hindsight bias often plagues determinations of obviousness, *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966), we are also mindful that the Supreme Court has clearly stated that the “combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416. The *KSR* reasoning is applicable here, where Jankovic teaches that cells expressing Id1 are immature hematopoietic cells that are associated with the ability to self-renew and are thereby considered stem cells (FF3), and Jurga teaches that Id1 is also associated with immature human neuronal cells (FF5 & FF6). In addition, Jankovic teaches the use of FACS to sort bone marrow cells using markers that are expressed only in
immature hematopoietic stem cells and these same cells are also shown to express Id1 (FF4, see FF3, FF5–FF9; see Ans. 11–13). Accordingly, we are not persuaded by Appellants contention that the Examiner relied on hindsight to formulate the rejections because the Examiner is basing the rejection only on information taught in the art.

Claim 1

Claim 1 only requires the identification of cells expressing Id1, there is no further requirement in claim 1 to sort the cells based on the actual expression of Id1.

The Examiner found that Jankovic teaches the use of ID1 to identify cells that have self-renewal capacity and maintain “HSC lineage commitment” (Final Act. 8; Ans. 5; FF3). The Examiner identified Jurga as teaching that ID1 protein is a negative regulator of human derived neuronal stem cells (Final Act. 9; Ans. 6; FF6). We agree with the Examiner’s conclusion that the combination of Jankovic and Jurga provides the requisite teaching to identify adult stem cells based on the expression of ID1 (see also Final Act. 9 (“identify potential stem cells by screening and detecting the expression of Id1 using an anti-Id1 antibody . . . or by qPCR”).

Based on the disclosure of Jankovic, we find that one of ordinary skill in the art would have drawn the reasonable inference that Id1 is a marker to identify adult tissue hematopoietic stem cells. After all, the question of obviousness cannot be approached on the basis that an artisan having ordinary skill would have known only what was read in the references, because such artisan must be presumed to know something about the art apart from what the references disclose. See In re Jacoby, 309 F.2d 513, 516 (CCPA 1962). Moreover, the law presumes skill on the part of the artisan
rather than the converse. See In re Sovish, 769 F.2d 738, 742-43 (Fed. Cir. 1985). We find that based on the teaching of Jankovic there is a reasonable inference that the expression of Id1 can function to identify adult tissue hematopoietic stem cells because these cells are more immature than the Lin+ cells that are already identified as being more differentiated and that do not express Id1 (FF3; see Ans. 11).

Jankovic concluded that Id1 is responsible for maintaining the immaturity of the hematopoietic stem cell and is required for the self-renewal of these adult tissue stem cells (FF3). Here, the use of either Id1 reactive antibodies or qPCR would predictably allow for the identification of cells that express the ID1 protein. Indeed, Jankovic did just that when they identified cell fractions that expressed ID1 (FF4), that these cells happen to also be adult stem cells predictably flows from the practice of the method disclosed in the Jankovic.

Even though the Examiner acknowledges that Jankovic does not “explicitly teach identifying potential stem cells by screening the cells for expression of Id1, Jankovic . . . teach[es] that the expression of Id1 protein is required for proper self[re]newal of adult stem cells and [that] the loss of Id1 results in induction of myeloid differentiation in LKS HSCs” (Final Act. 8). In other words, the Examiner recognizes that Jankovic does not use ID1 to sort cells, but that this marker could be used for that purpose can reasonably be inferred from the teaching of the reference. Here, Jankovic detects Id1 in cells, albeit previously sorted cells, and identifies that same cell population as capable of self-renewal (FF3), a required characteristic of adult stem cells (FF1 and FF2; see Ans. 11). This observation is buttressed by Jurga, which teaches that “ID1 protein is a potent negative regulator of
neural stem cell differentiation because . . . overexpression of exogenous Id1 protein inhibits neuronal differentiation” (Final Act. 9). In other words, the combined references show that cells that express Id1 are not differentiated cells.

We find that the preponderance of the evidence of record supports the Examiner’s conclusion that the combination of Jankovic, Jurga, Wagner, and Namba renders obvious the method of identifying cells of claim 1. We thus affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as being obvious. As claims 2–5 fall with that claim, we affirm the rejection as to those claims as well. 37 C.F.R. § 41.37(c)(1)(iv).

Claim 7

Claim 7 does not require the identification of stem cells, but instead uses Id1 for the isolation of cells that express the Id1 molecule from a population of cells that includes cells not expressing the molecule.

Appellants acknowledge that Jankovic sorted cells into adult stem cells and differentiated cells using FACS sorting based on other markers (see App. Br. 6; FF4).

Appellants recognize that

Id1 is reasonably predicted to be present in at least some stem cells, but [contend that this] does not provide the second part of teaching that would be necessary for a suggestion of us[ing] a marker for identification or separation, namely that it is differentially expressed compared to other cell types in the same natural environment. (App. Br. 7).

We recognize, but are not persuaded by Appellants contention, that there is no teaching in the references to use Id1 as a marker for cell sorting. It is proper to “take account of the inferences and creative steps that a person
of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418. *See also id.* at 421 (“A person of ordinary skill is also a person of ordinary creativity, not an automaton.”). One of ordinary skill in the art would understand that a marker that is present in one type of cell but not in another type of cell would allow that marker to be used to sort between those two cell populations. The ordinary artisan would know that cell sorting can be achieved via FACS, and detection can be achieved either via FACS and or qPCR (*see* Ans. 5). Although Jankovic did not sort cells by FACS using an Id1 marker, the cells populations sorted by Jankovic’s method were tested for the expression of Id1 protein, and it was found that Id1 is preferentially expressed only in the Lin- cells which are the immature cells (FF3).

Appellants contend that in the cited art, the “expression in differentiated cells is only assessed in cells that have been subjected to induced differentiation in vitro. The undifferentiated cells are already isolated, so the statement that there is Id1 expression is not made relative to any cells present in a natural environment” (Reply Br. 2).

We are also not persuaded by this argument, as there is no requirement in the claims to apply the method on cells without any pretreatment steps. Claim 7 contain the transitional term “comprising” which allows for additional steps not recited in the claims. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) (“The transition ‘comprising’ in a method claim indicates that the claim is open-ended and allows for additional steps.”). Here, the claims are broad enough to encompass additional steps, such as including induced differentiation as a pretreatment step, before separating the cell population into immature and differentiated populations.
Furthermore, it is well established that limitations not appearing in the claims cannot be relied upon for patentability. *In re Self*, 671 F.2d 1344, 1348 (CCPA 1982). Thus, we are not persuaded by Appellants contentions about separating cells in “a natural environment” as this limitation is not part of the claims (Reply Br. 2).

We conclude that the preponderance of the evidence of record supports the Examiner’s conclusion that the combination of Jankovic, Jurga, Wagner, and Namba renders obvious the method of sorting cells that express Id1 as required by claim 7. We thus affirm the rejection of claim 7 under 35 U.S.C. § 103(a) as being obvious. As claims 8–13 and 16–22 fall with that claim, we affirm the rejection as to those claims as well.

*Claims 6, 14, and 23*

Appellants contend that “[c]laims 6, 14 and 23 recite an additional screening step, in which cells are further selected for expression of glial fibrillary acidic protein (GFAP) in addition to Id1” and the Examiner is relying on hindsight in making the rejection (App. Br. 8–9).

We have reviewed, but are not persuaded by, Appellants contentions that the Examiner erred in rejecting claims 6, 14, and 23 as obvious over the combination of references. We adopt the Examiner’s finding concerning the scope and content of the art and agree with the reason set forth in the Answer and Final Act. While we are fully aware that hindsight bias often plagues determinations of obviousness the “combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416. The *KSR* rationale is applicable here, where Jurga teaches that not only Id1 but also GFAP is associated with the undifferentiated state of NSC-like cells (FF5–
FF7). This teaching is buttressed by Namba indicating that precursor cells that give rise to neurons express GFAP (FF9). Based on the combined teachings of the cited references, we find no error with the Examiner’s rationale that it would have been obvious to include “additional steps of detecting and separating cells” (Final Act. 11).

Claims 15 and 24–26

Appellants contend that “Namba does not say anything about the expression or nonexpression of [polysialylated neural cell adhesion molecule (PSA-NCAM) and NeuN] . . . in stem cells, unless one were to interpret the immature neuronal cell as a stem cell” and contend that the examiner is relying on hindsight in making the rejection (App. Br. 9).

We have reviewed, but are not persuaded by, Appellants’ contentions that the Examiner erred in rejecting claims 15 and 24–26 as obvious over the combination of references. The Specification explains that stem cells retain their ability to divide throughout life and are not mature or differentiated (see FF1 and FF2). Namba teaches that PSA-NCAM and NeuN are neuronal markers (FF10), i.e., markers for a differentiated cell. Accordingly, we find that it would be obvious in a method for isolating stem cells to enrich the stem cells in the sample by first removing cells expressing these markers.
SUMMARY
We affirm the rejection of all claims under consideration.

TIME PERIOD FOR RESPONSE
No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED