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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/24/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/864,621	SNODGRASS, H. RALPH	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *12-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3, 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-11, in Paper No. 12 is acknowledged.

2. Claims 12-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

3. Applicant's preliminary amendment filed 7-31-02 has been entered. Claims 1-28 are pending and claims 1-11 are under consideration. Applicant also elected the following species for examination: (a) gene expression, (b) troglitazone and erythromycin, (c) hepatic toxins.

It should be noted that examiner for the present application has been changed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-11 read on a library of molecular profiles of chemical compositions having predetermined toxicities by contacting an isolated mammalian embryoid body with the chemical compositions, recording alterations in gene expression or protein expression in said mammalian embryoid body and compiling a library of molecular profiles for at least two chemical compositions.

The chemical compositions encompass therapeutic agents, neurotoxins, renal toxins, hepatic toxins, toxins of hematopoietic cells, myotoxins, agents that are toxic to cells of reproductive organs, teratogenic agents, carcinogens, agricultural chemicals, cosmetics, and environmental contaminants. The specification only discloses the protein expression profiles of mouse embryoid body treated with troglitazone or erythromycin compared to the control having no treatment of troglitazone or erythromycin. The chemical compositions set forth above include numerous different chemical compounds having different chemical structures, physical properties, and biological functions. They don't have common chemical structures, chemical activities, and biological functions. Common structural feature of the chemical compositions that would have a certain effect on the gene expression or protein expression pattern in a mammalian embryoid body has not been disclosed in the present invention. Further, different embryoid bodies derived from various mammal, such as humans, mice, rats, pigs, sheep, cows, whales, primates, dogs etc., would differ from each other physiologically, and their response to same chemical composition, not to mention different chemical compositions, could vary. Therefore, the alterations in gene expression or protein expression in various mammalian embryoid bodies responding to numerous different chemical compositions would not be predictable at the time of the invention. One skilled in the art at the time of the invention would

not be able to anticipate the gene expression or protein expression pattern in the mammalian embryoid body treated with various chemical compositions other than the disclosed protein expression pattern of mouse embryoid body treated with either troglitazone or erythromycin. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

The limited information disclosed in the present invention is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed libraries of molecular profiles of numerous different chemical compositions. Thus, it is concluded that the written description requirement is not satisfied for the libraries of molecular profiles of numerous different chemical compositions as claimed.

6. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the library of protein expression profile of troglitazone and erythromycin in the mouse embryoid body, does not reasonably provide enablement for libraries of molecular profiles of numerous different chemical compositions in various mammalian embryoid bodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-11 read on a library of molecular profiles of chemical compositions having predetermined toxicities by contacting an isolated mammalian embryoid body with the chemical compositions, recording alterations in gene expression or protein expression in said mammalian embryoid body and compiling a library of molecular profiles for at least two chemical

compositions. Claim 2 specifies the embryoid body is of human. Claims 6 and 7 specify the embryoid body is of non-human mammals, such as rodents. Claims 3-5 and 8-10 specify the chemical compositions are therapeutic agents, neurotoxins, renal toxins, hepatic toxins, teratogenic agents, carcinogens, agricultural chemicals, cosmetics, environmental contaminants etc.

As discussed above, the chemical compositions encompass therapeutic agents, neurotoxins, renal toxins, hepatic toxins, toxins of hematopoietic cells, myotoxins, agents that are toxic to cells of reproductive organs, teratogenic agents, carcinogens, agricultural chemicals, cosmetics, and environmental contaminants. The specification only discloses the protein expression profiles of mouse embryoid body treated with troglitazone or erythromycin compared to the control having no treatment of troglitazone or erythromycin. The chemical compositions set forth above include numerous different chemical compounds having different chemical structures, physical properties, and biological functions. Further, different embryoid bodies derived from various mammal, such as humans, mice, rats, pigs, sheep, cows, whales, primates, dogs etc., would differ from each other physiologically, and their response to same chemical composition, not to mention different chemical compositions, could vary. Therefore, the alterations in gene expression or protein expression in various mammalian embryoid bodies responding to numerous different chemical compositions would not be predictable at the time of the invention. One skilled in the art at the time of the invention would not be able to anticipate the gene expression or protein expression pattern in the mammalian embryoid body treated with various chemical compositions other than the disclosed protein expression pattern of mouse embryoid body treated with either troglitazone or erythromycin. Applicants were not in

possession of the claimed libraries of molecular profiles of numerous different chemical compositions. Thus, the present invention does not enable the use of the broadly claimed libraries of molecular profiles of numerous different chemical compositions.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spielmann et al., 1997 (In Vitro Toxicology, Vol. 10, No. 1, p. 119-127) in view of Craig et al., 1996 (Biomarkers, Vol. 1, No. 2, p. 123-135) and Wobus et al., 1999 (US Patent 6,007,993).

Claims 1-11 read on a library of molecular profiles of chemical compositions having predetermined toxicities by contacting an isolated mammalian embryoid body with the chemical compositions, recording alterations in gene expression or protein expression in said mammalian embryoid body and compiling a library of molecular profiles for at least two chemical compositions. Claim 2 specifies the embryoid body is of human. Claims 6 and 7 specify the embryoid body is of non-human mammals, such as rodents. Claims 3-5 and 8-10 specify the chemical compositions are therapeutic agents, neurotoxins, renal toxins, hepatic toxins, teratogenic agents, carcinogens, agricultural chemicals, cosmetics, environmental contaminants etc.

Spielmann teaches a method of using mouse embryonic stem cells *in vitro* for embryotoxicity testing comprising culturing the embryonic stem cells to a stage where the cells form embryoid bodies, contacting the bodies with a variety of chemical compositions, and determining the cytotoxicity of the chemical compositions by MTT cytotoxicity assay. Spielmann uses 16 test chemicals which are assigned to three classes of *in vivo* embryotoxicity and compiles libraries of the "molecular profiles" of the test chemicals and ranks the chemical compositions with respect to their relative toxicities (e.g. abstract, p. 120, 121, Figure 1, Table 1).

Spielmann does not teach creating the molecular profiles of gene expression or protein expression.

Craig teaches using embryos of the topminnow, *Fundulus heteroclitus*, for reproductive toxicity screening by exposing the embryos to teratogenic concentrations of sodium valproate (VPA) or arsenic acid (arsenate) and evaluating the frequency and types of induced malformations. Craig correlates the teratogenic outcomes to specific alterations in the expression of a panel of developmentally regulated genes and the genetic expression profiles revealed a number of genes whose expression levels were significantly altered by exposure to the test compounds (e.g. abstract). Craig also teaches generating cDNA from mRNA and using ^{32}P-labeled probes for the detection of gene expression in establishing gene expression profiles (e.g. p. 125, left column).

Wobus teaches an in vitro test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem cells or embryonic germ cells obtained from primordial germ cells of the mouse or rat. A differentiation-

dependent expression of tissue-specific genes of embryonic stem cell clones or embryonic germ cell clones is furnished in the presence of teratogenic substances. The substances act at specific times of the in vitro differentiation and subsequent differentiation. A chemically-induced activation, repression or modulation of the tissue-specific genes which influence embryonic development is detected (e.g. column 2, lines 53-67). The cell clones contain reporter gene constructs which can be specifically activated, repressed or modulated in the course of the differentiation by exogenic test substances, such as retinoic acid, and the differentiation-dependent expression during the test procedure can be carried out by embryoid body differentiation in different lines (e.g. column 3, lines 1-23). The reporter gene can be LacZ or the luciferase gene and detection can be by a simple staining reaction (e.g. column 3, lines 53-63). Promoters of the reporter gene constructs can be neuronal, cardiogenic, muscle and skeletal specific to monitor development (e.g. column 4, lines 2-14) in the presence of the exogenic test substance. Wobus teaches recording alterations in gene expression by monitoring protein expression after contacting an embryoid body with a chemical composition, and the change in expression is detected by a colorimetric label, e.g. X-Gal staining (e.g. column 4, 7).

It would have been obvious for one of ordinary skill at the time of the invention to substitute the MTT cytotoxicity assay as taught by Spielmann with detection of gene expression as taught by Craig or detection of protein expression as taught by Wobus to establish molecular profiles of different chemical compositions by treating a mammalian embryoid body with said chemical compositions because both Craig and Wobus teach testing the effect of teratogenic agents on embryoid body by determining the resulting gene expression pattern and it was known

in the art to determine the effect of a chemical compound by detecting the alteration of gene expression or alteration of protein expression.

One ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate a gene expression profile or protein expression profile of a teratogenic agent by using embryos or embryoid bodies as compared to a control having no treatment of said teratogenic agent as taught by Craig and Wobus, respectively, or to generate a library of gene expression or protein expression profiles of a test composition for typing or ranking toxicity of said test composition by using embryos or embryoid bodies according to the collective teachings of Spielmann, Craig, and Wobus with reasonable expectation of success.

9. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serbedzija et al., 2001 (US Patent 6,299,858) in view of Spielmann et al., 1997 (In Vitro Toxicology, Vol. 10, No. 1, p. 119-127).

Claims 1-11 read on a library of molecular profiles of chemical compositions having predetermined toxicities by contacting an isolated mammalian embryoid body with the chemical compositions, recording alterations in gene expression or protein expression in said mammalian embryoid body and compiling a library of molecular profiles for at least two chemical compositions. Claim 2 specifies the embryoid body is of human. Claims 6 and 7 specify the embryoid body is of non-human mammals, such as rodents. Claims 3-5 and 8-10 specify the chemical compositions are therapeutic agents, neurotoxins, renal toxins, hepatic toxins, teratogenic agents, carcinogens, agricultural chemicals, cosmetics, environmental contaminants etc.

Serbedzija teaches exposing zebrafish embryos in test compounds at different concentrations, such as aspirin and dexamethasone, to determine the toxic effect of those test compounds on zebrafish embryos (e.g. column 53, 56). A wide range of test compounds can be used for screening toxic activity, including chemical compounds, pharmaceuticals, therapeutics, environmental and agricultural agents, industrial agents, pollutants, cosmeceuticals, synthetic or natural compounds, drugs, organic compounds, lipids, glucocorticoids, peptides, antibiotics, chimeric molecules, sugars, carbohydrates etc. (e.g. column 51, lines 27-42). A response indicating toxic activity can be detected as a change in gene expression profile via subtractive library experiments using PCR-select cDNA Subtraction System. A response indicating toxic activity also can be detected as a change in a protein expression profile using two-dimensional polyacrylamide gel electrophoresis or combination of other techniques, such as in situ hybridization, antibody staining of specific proteins, colorimetry, fluorescence microscopy, light microscopy etc. (e.g. column 51, 52). Serbedzija also teaches using cDNA microarray technologyto profile combinations of gene expression in drug toxicity response and molecular activation phenomena and automation of the screening with standard instrumentation and computer software program to screen hundreds of chemical compounds (e.g. column 59).

Serbedzija does not specifically teach using embryoid body for creating library of molecular profiles of chemical compositions.

Spielmann teaches a method of using mouse embryonic stem cells *in vitro* for embryotoxicity testing comprising culturing the embryonic stem cells to a stage where the cells form embryoid bodies, contacting the bodies with a variety of chemical compositions, and determining the cytotoxicity of the chemical compositions by MTT cytotoxicity assay.

Spielmann uses 16 test chemicals which are assigned to three classes of *in vivo* embryotoxicity and compiles libraries of the "molecular profiles" of the test chemicals and ranks the chemical compositions with respect to their relative toxicities (e.g. abstract, p. 120, 121, Figure 1, Table 1).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the embryoid body as taught by Spielmann to test the cytotoxicity of the chemical composition on said embryoid body by using testing methods as described in Serbedzija to determine the alteration of gene expression or protein expression in said embryoid body because both Serbedzija and Spielmann teach method of detecting the toxic effect of chemical compositions and it would have been obvious to one of ordinary skill to substitute embryo with embryoid body for the detection of toxic effect of chemical compositions.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to screen for the chemical compositions or compounds that have toxic effect on embryos or embryoid body as taught by Serbedzija and Spielmann or to rank the toxicity of the chemical compositions as taught by Spielmann with reasonable expectation of success.

It should be noted that the claims do not specify the alterations in gene expression or protein expression in the mammalian embryoid body, therefore, although the specification only enables the disclosed protein expression pattern of embryoid body treated with troglitazone or erythromycin, the 35 U.S.C. 103(a) rejections as set forth above are considered proper.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. Due to the move of USPTO to new site in Alexandria, Virginia, examiner's telephone number will be changed to (571) 272-0726 **after January 12, 2004**. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

s/ Chen

Shin-Lin Chen, Ph.D.