

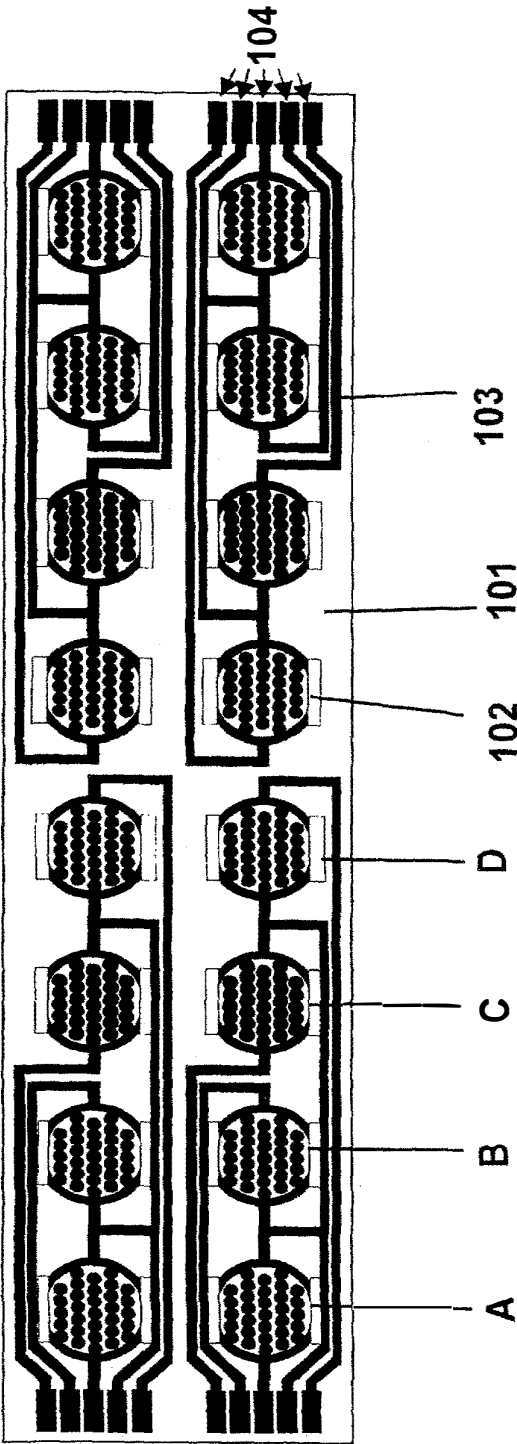


Figure 1A

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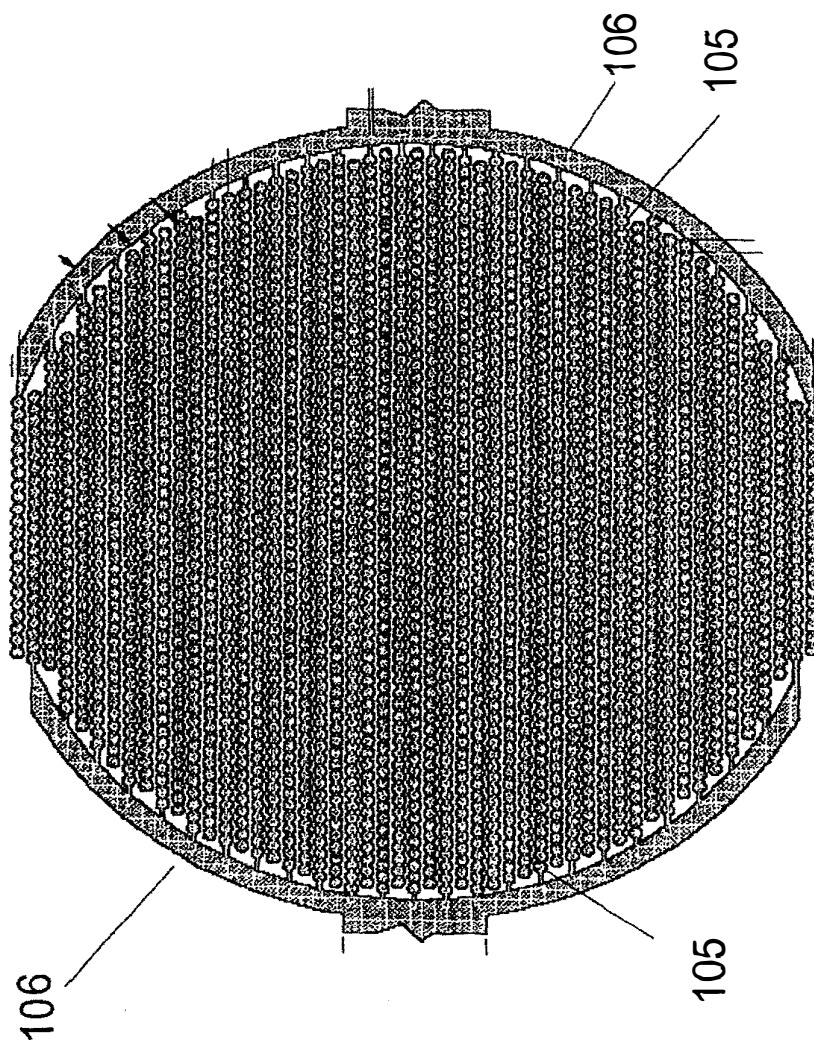


Figure 1B

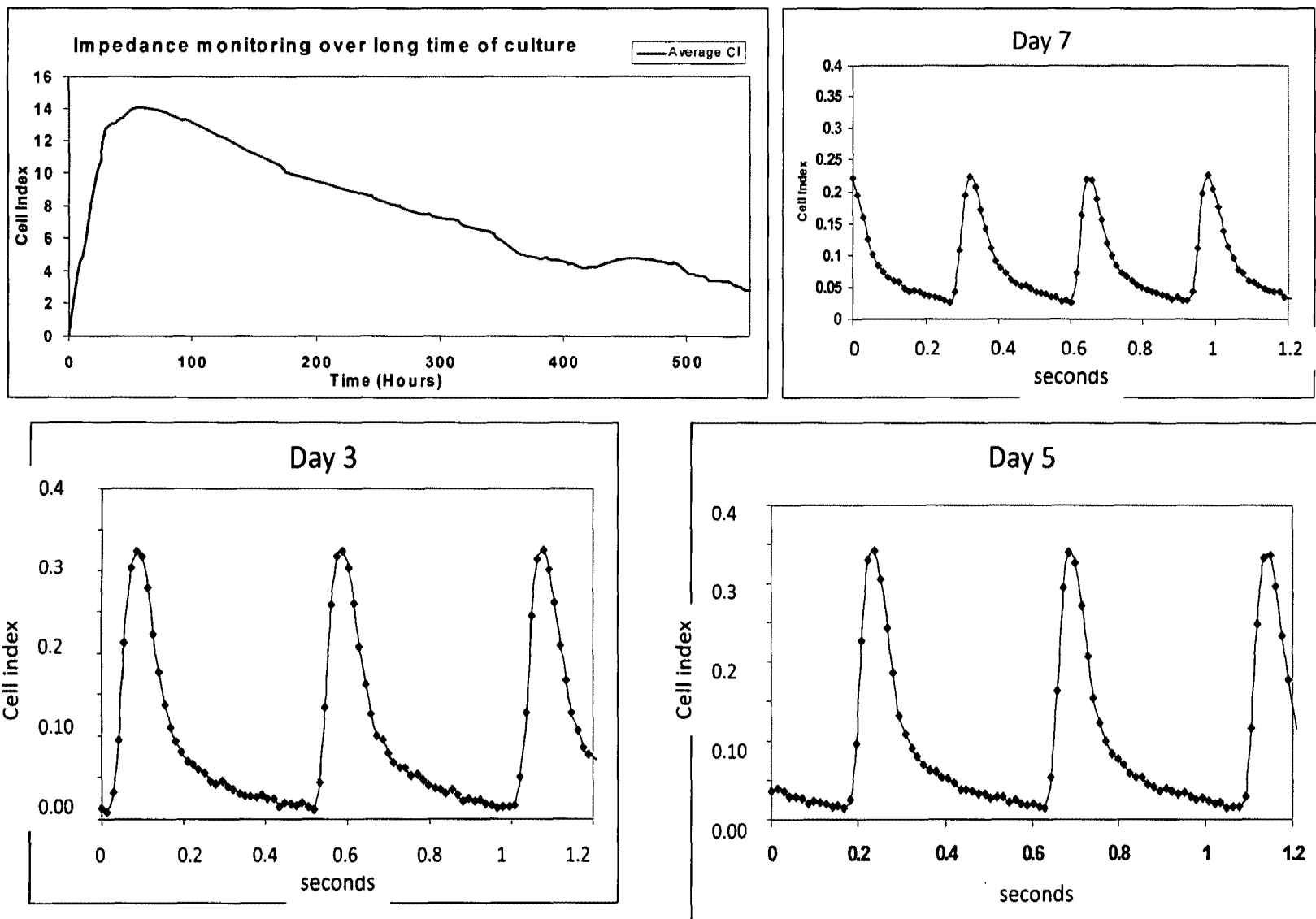


FIG. 2

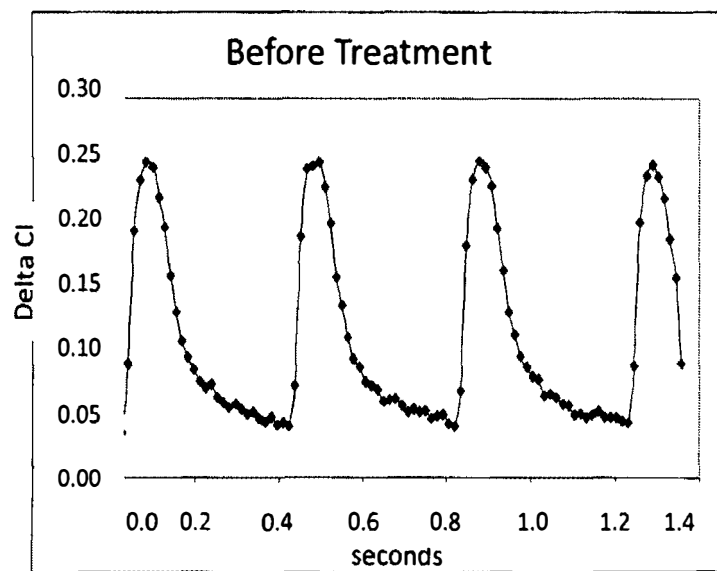
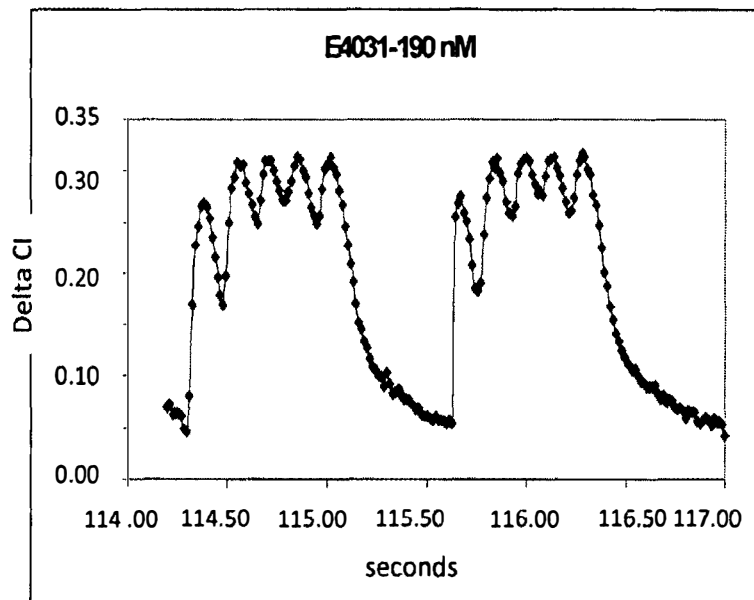
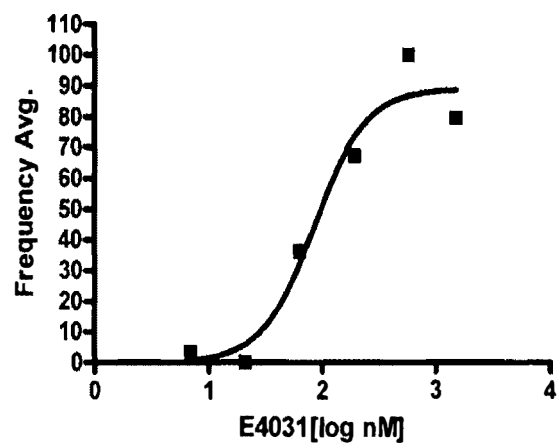


FIG. 3

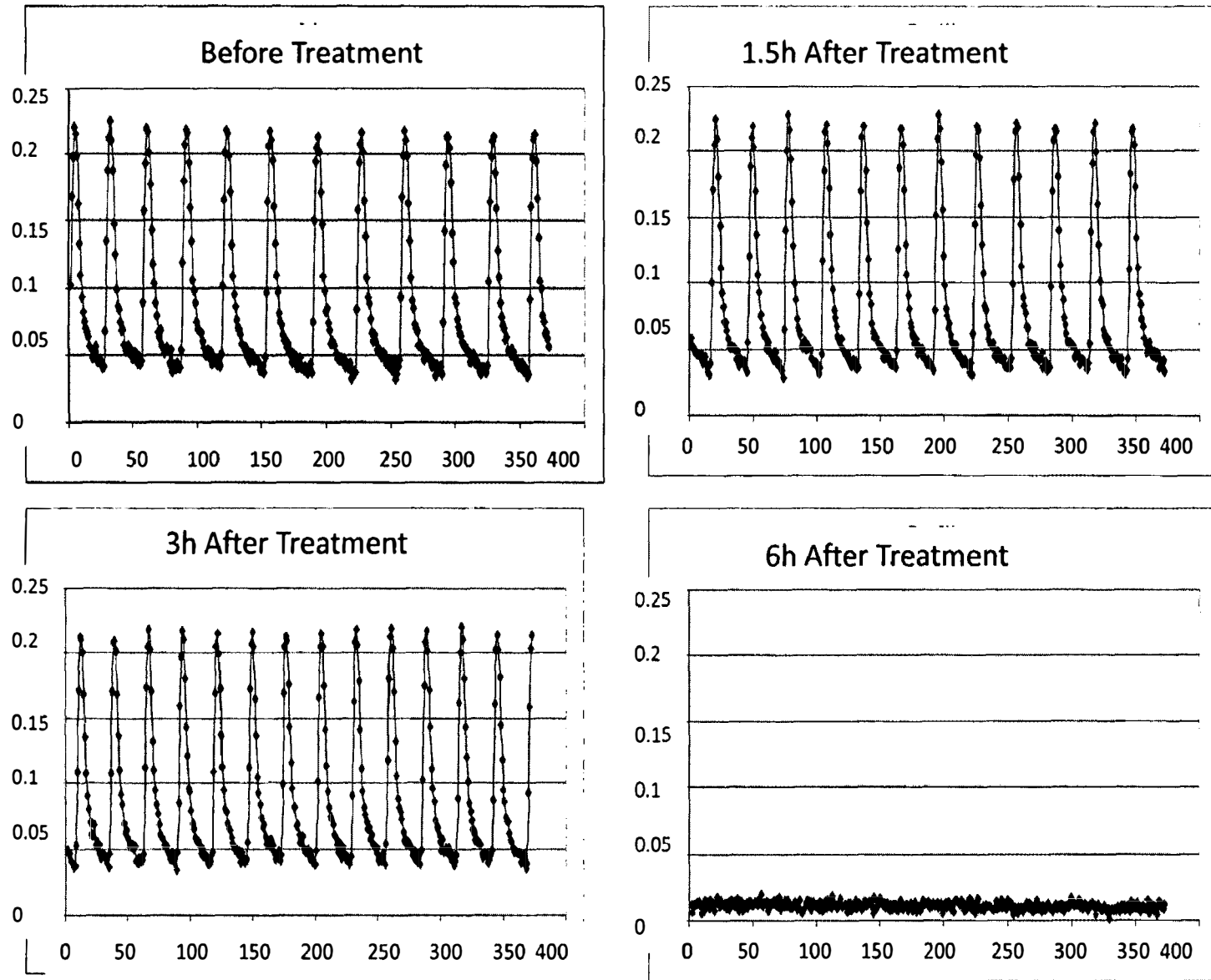


FIG. 4

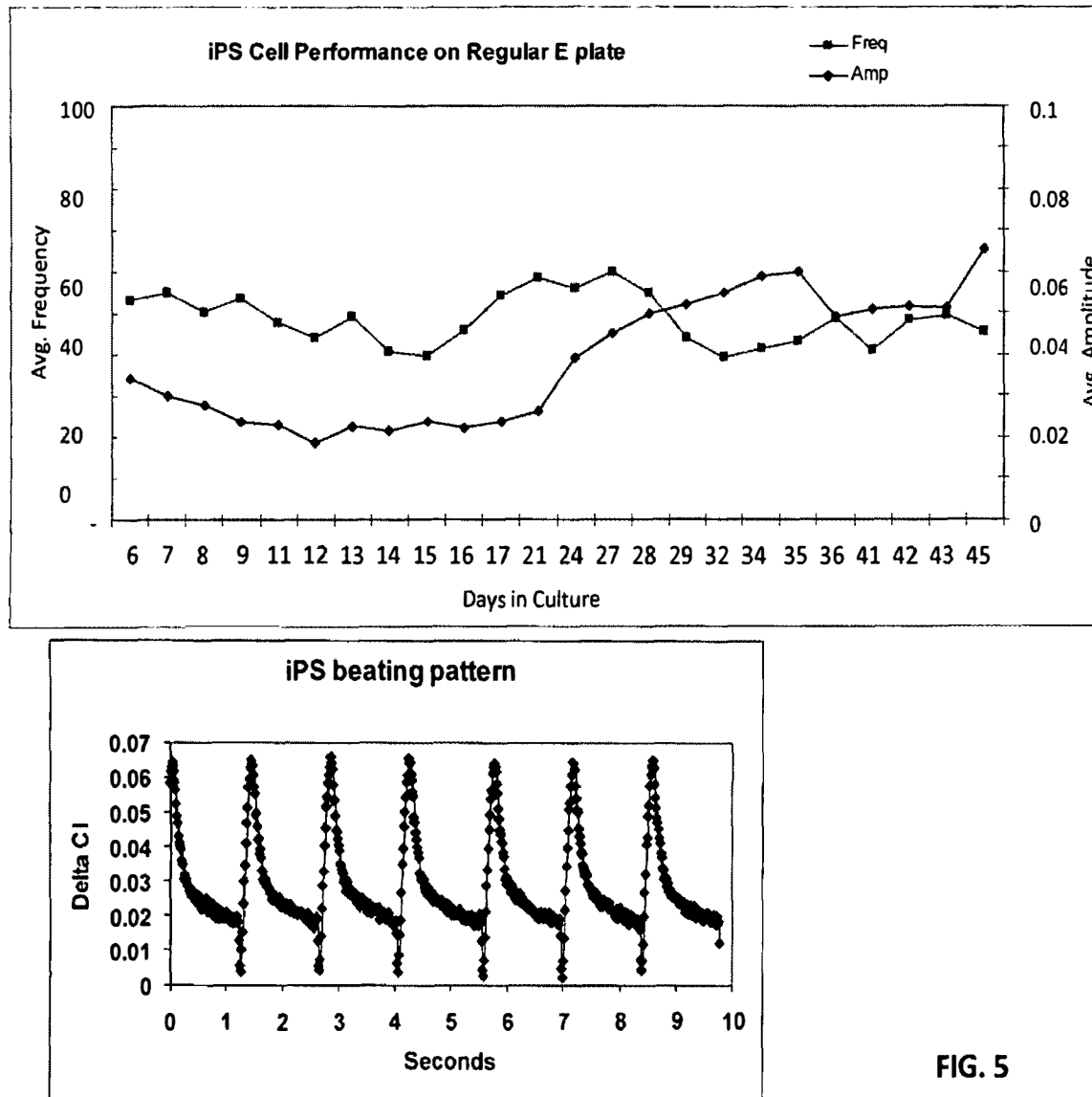


FIG. 5

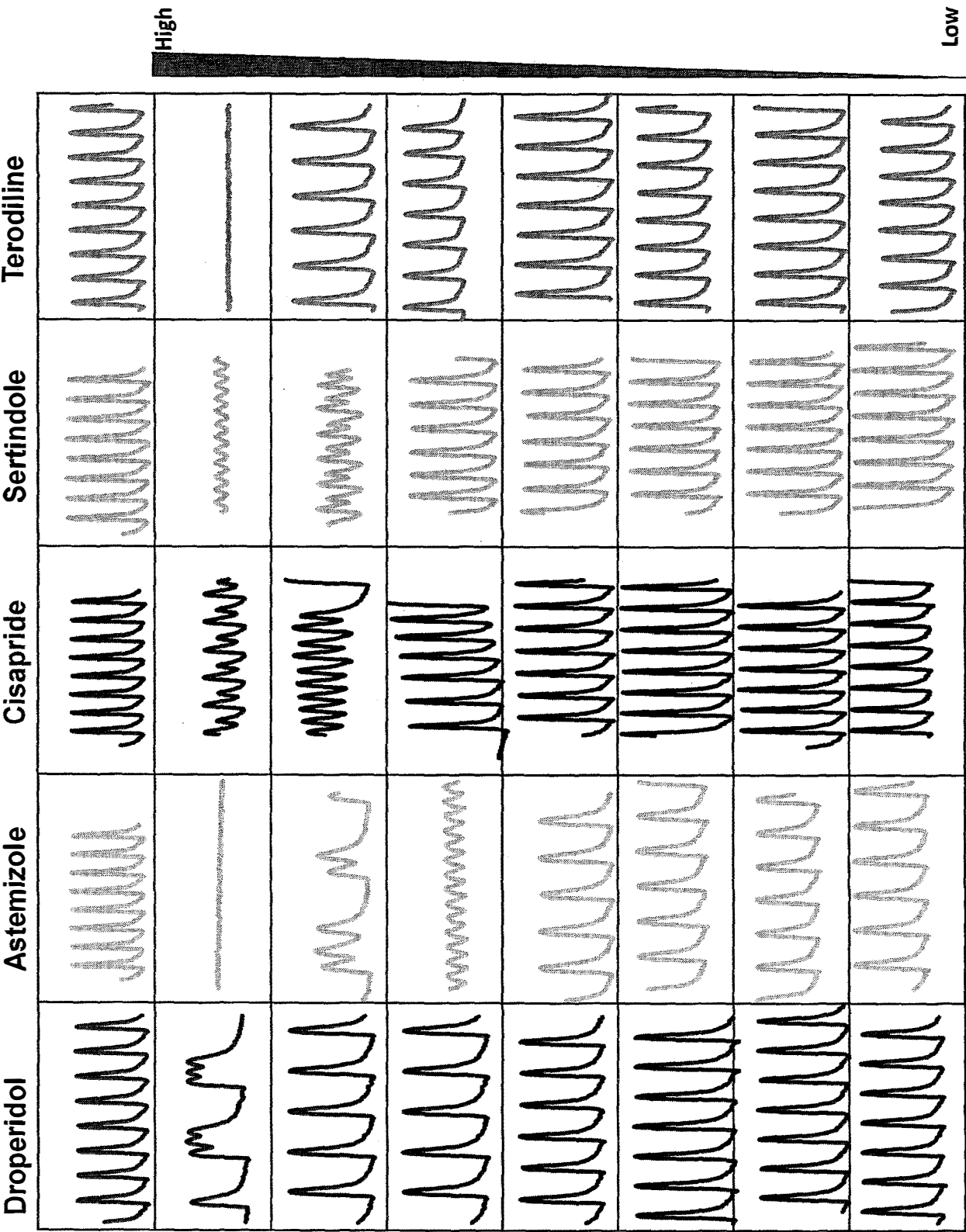


FIG.6

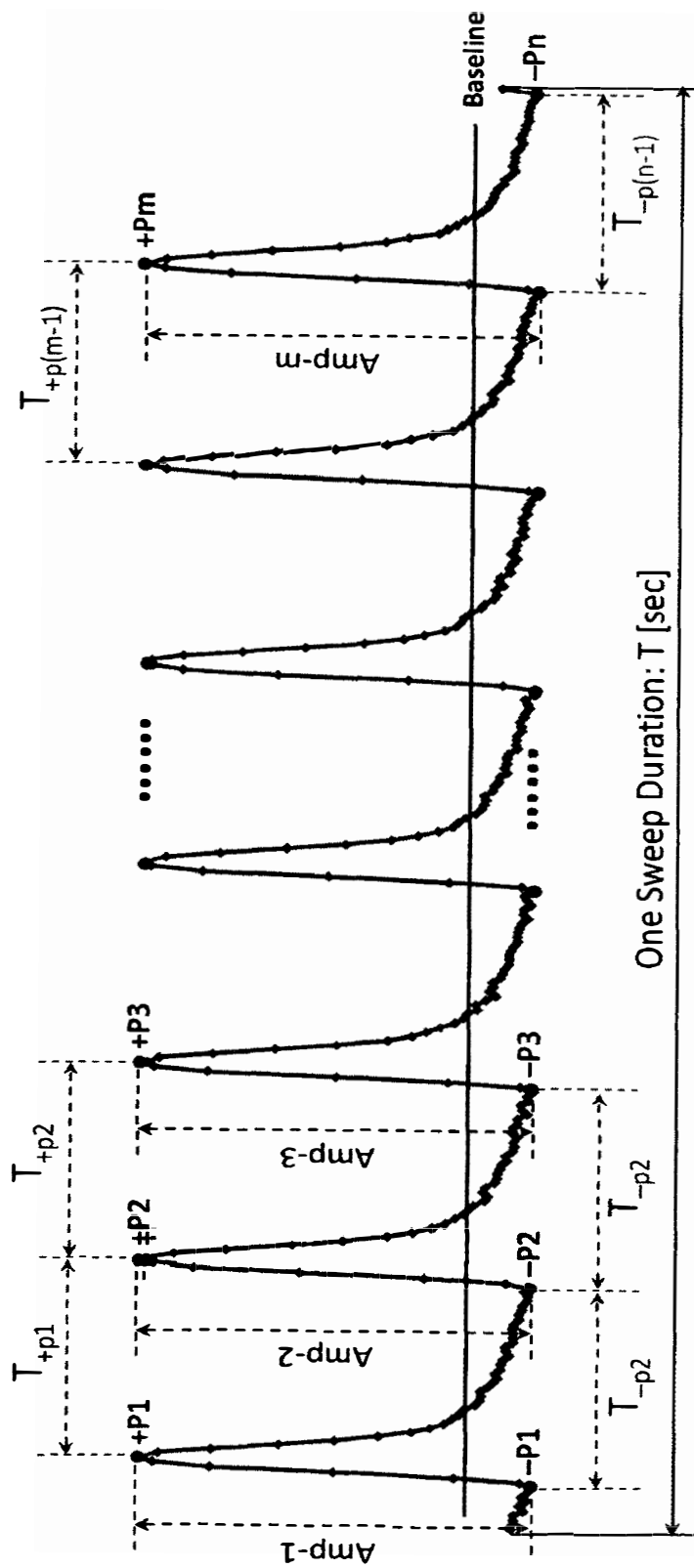


FIG. 7

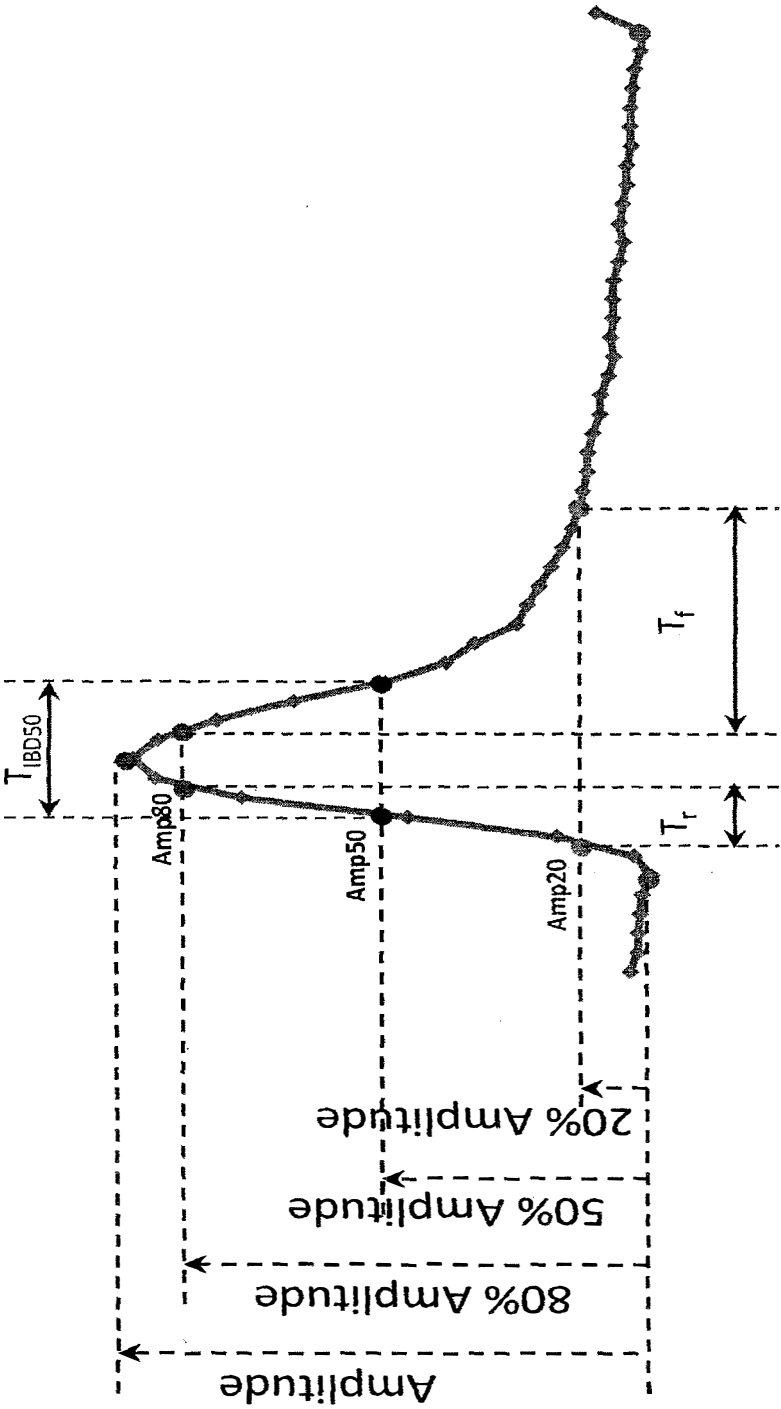
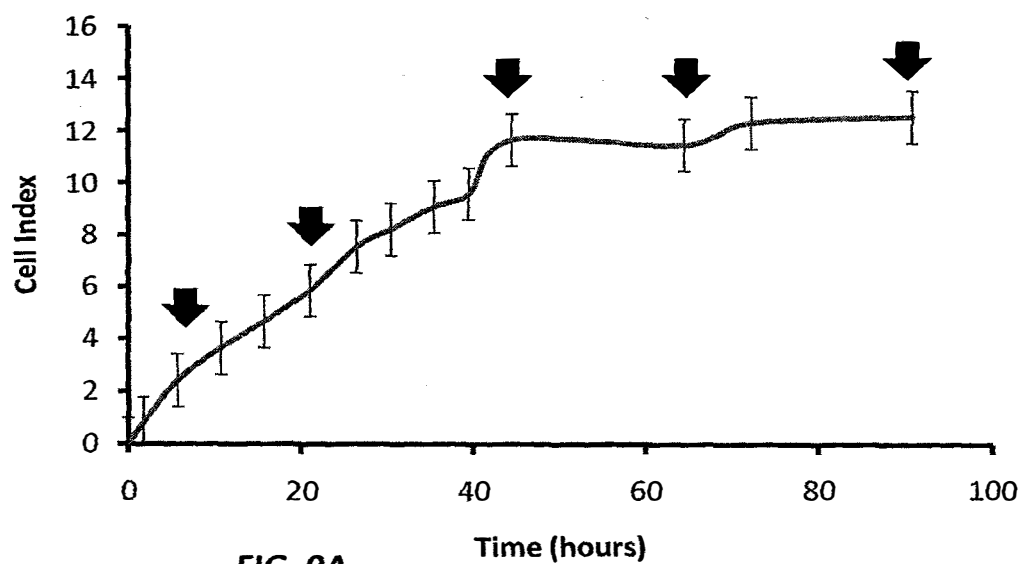


FIG. 8

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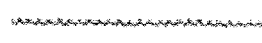
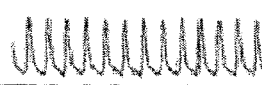
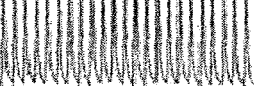
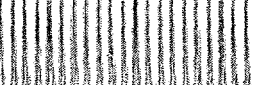
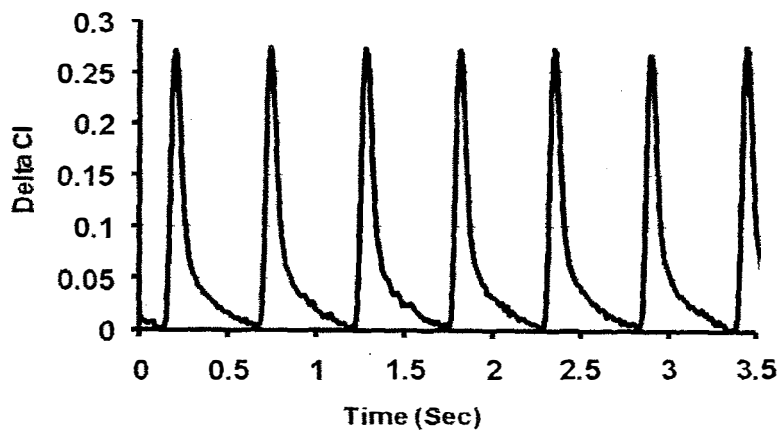
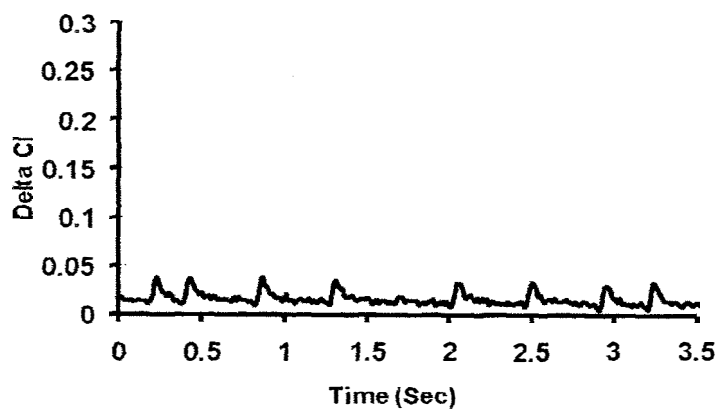
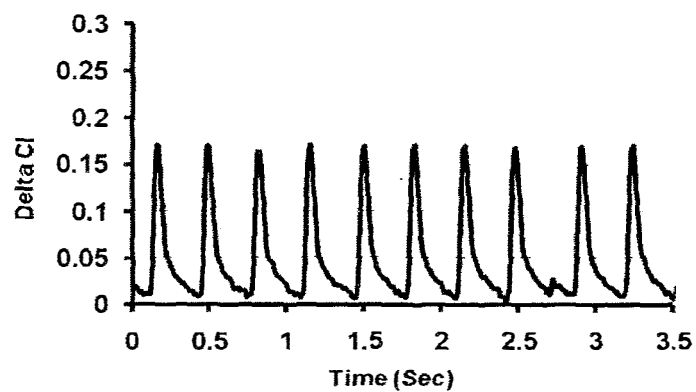
Hours Post Cultivation (hrs)	Beating Pattern	Beating Frequency (1/min $\pm$ SD) N=8	Amplitude (Δ CI) N=8	Beat Duration (ms)	Time to Max (T_r) (ms)	Decay Time (T_d) (ms)
12		NA	NA	NA	NA	NA
24		NA	NA	NA	NA	NA
48		80 ± 5.7	0.14 ± 0.003	142 ± 4.6	38 ± 1.4	124 ± 12.0
72		145 ± 2.7	0.24 ± 0.005	98 ± 3.0	29 ± 5.1	88 ± 7.2
96		127 ± 2.8	0.33 ± 0.007	105 ± 2.4	31 ± 3.3	97 ± 6.4

FIG. 9B

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Ctrl

10 μ M
Blebbistatin

Wash out

FIG. 9C

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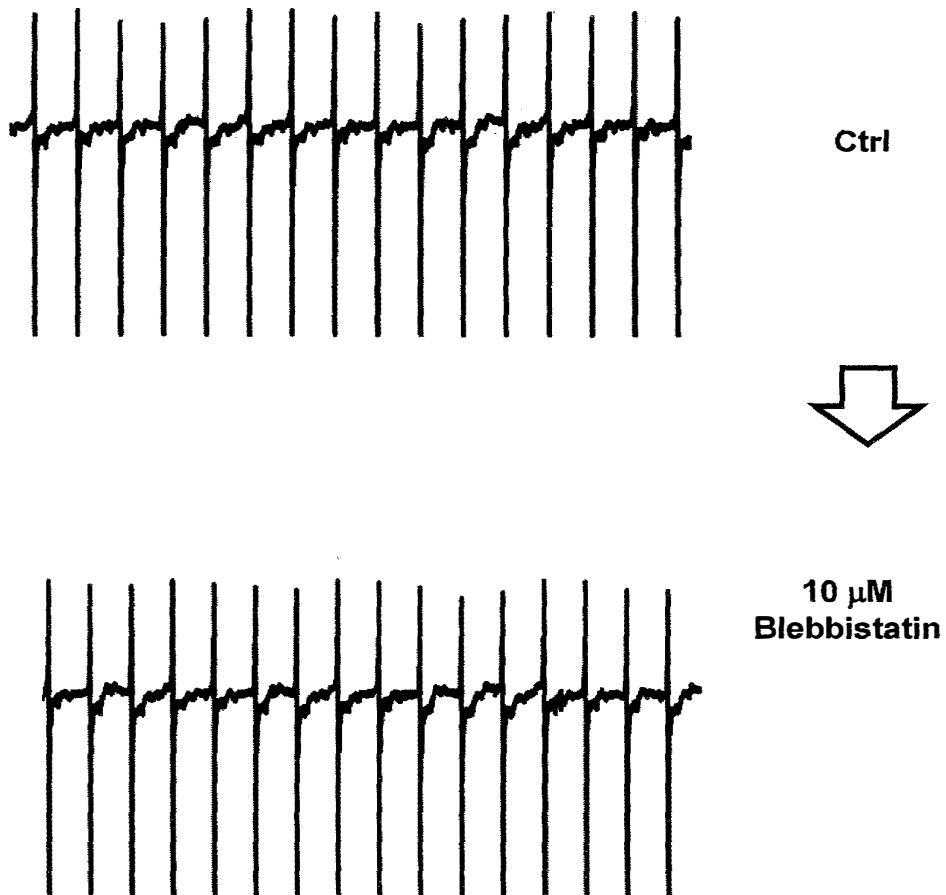
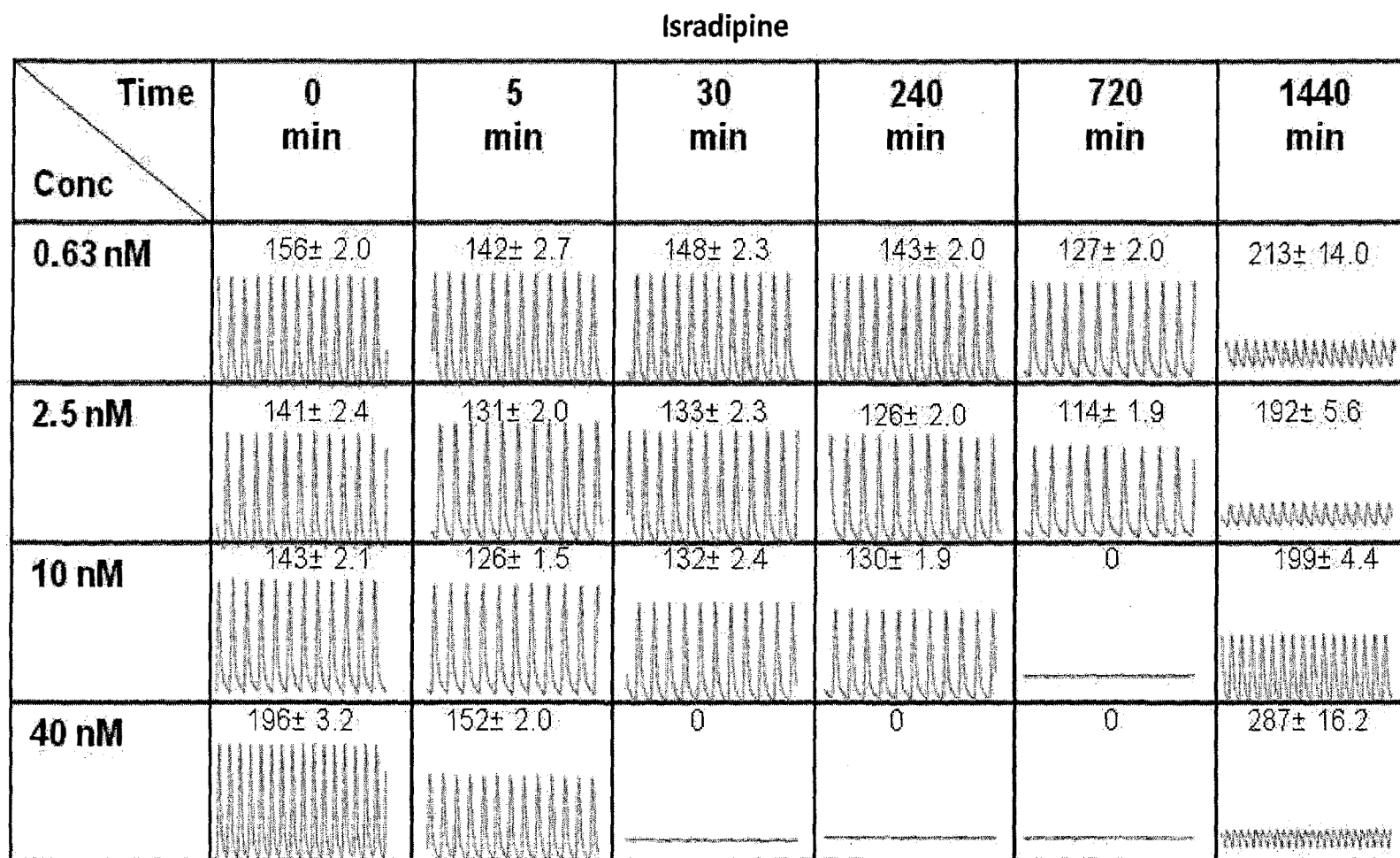
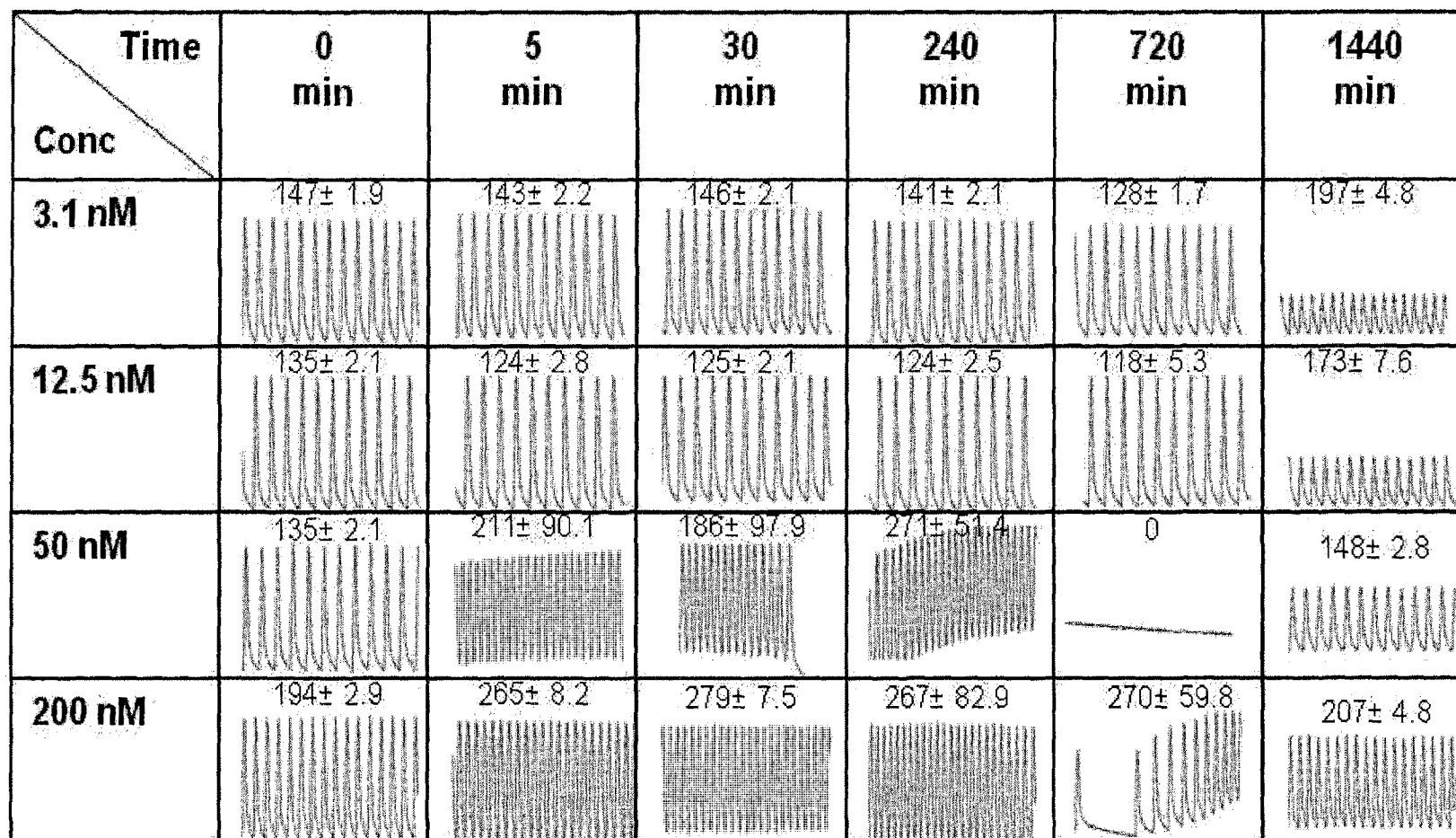


FIG. 9D

**FIG. 10A**

(S)-(-)-Bay K 8644



— 1000 ms

FIG. 10B

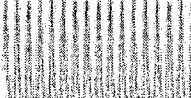
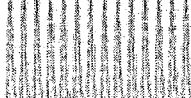
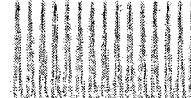
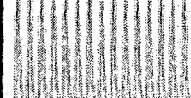
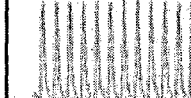
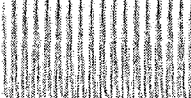
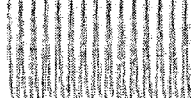
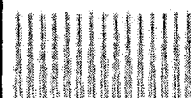
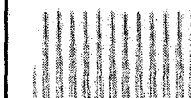
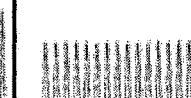
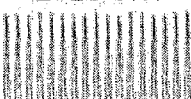
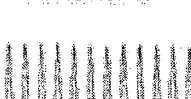
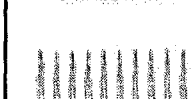
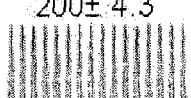
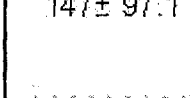
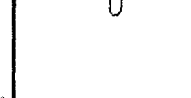
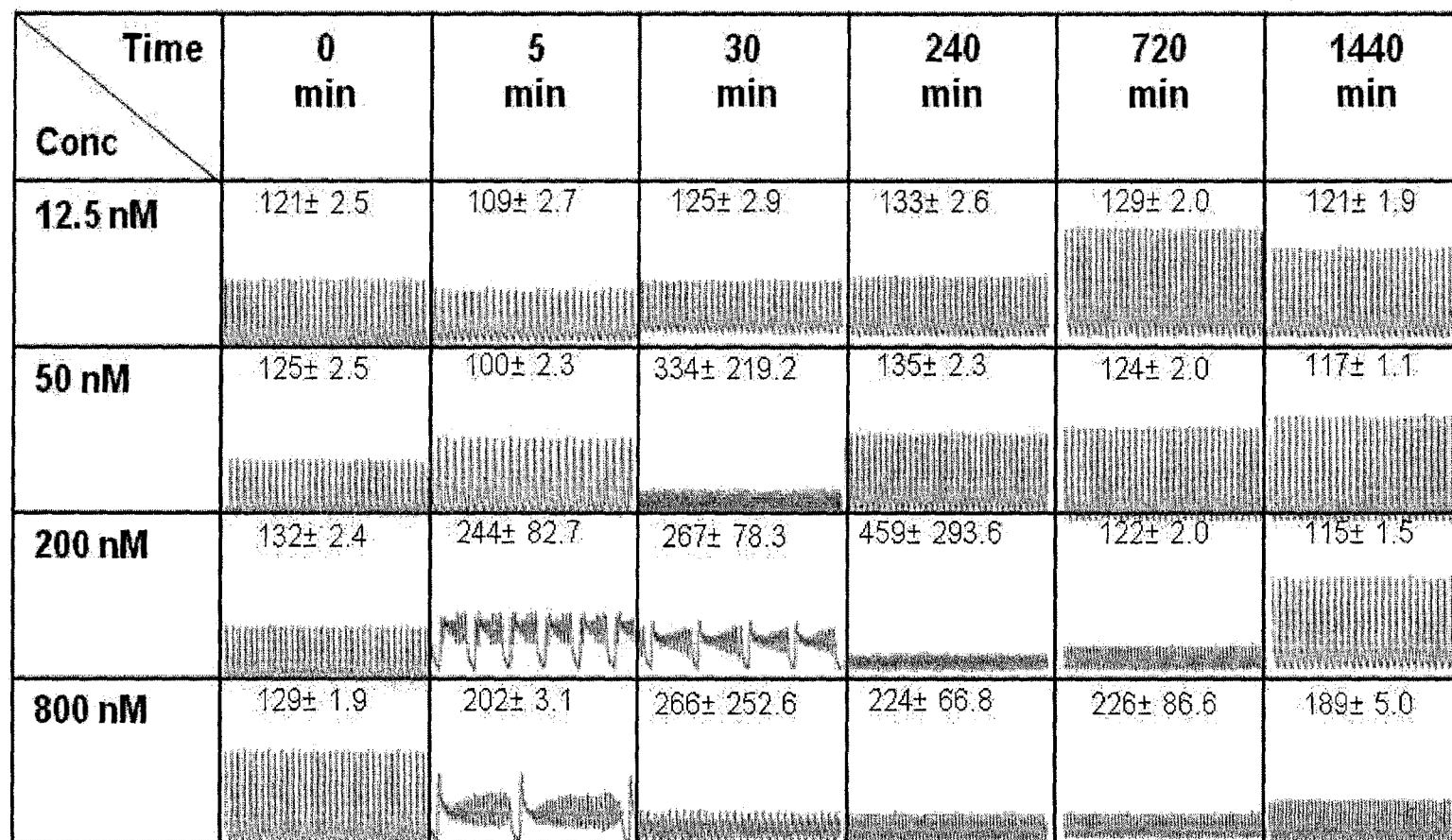
Chromanol						
Time Conc	0 min	5 min	30 min	240 min	720 min	1440 min
0.78 μ M	195 $\pm$ 2.0 	171 $\pm$ 3.1 	182 $\pm$ 3.7 	191 $\pm$ 3.9 	168 $\pm$ 2.7 	163 $\pm$ 2.7 
3.13 μ M	205 $\pm$ 4.1 	164 $\pm$ 3.3 	181 $\pm$ 2.4 	187 $\pm$ 3.0 	171 $\pm$ 3.0 	154 $\pm$ 2.5 
25 μ M	202 $\pm$ 3.7 	140 $\pm$ 2.3 	0 	161 $\pm$ 2.2 	144 $\pm$ 2.2 	147 $\pm$ 1.5 
100 μ M	200 $\pm$ 4.3 	0 	0 	0 	147 $\pm$ 97.1 	0 

FIG. 10C

E4031



1000 ms

FIG. 11A

TTX

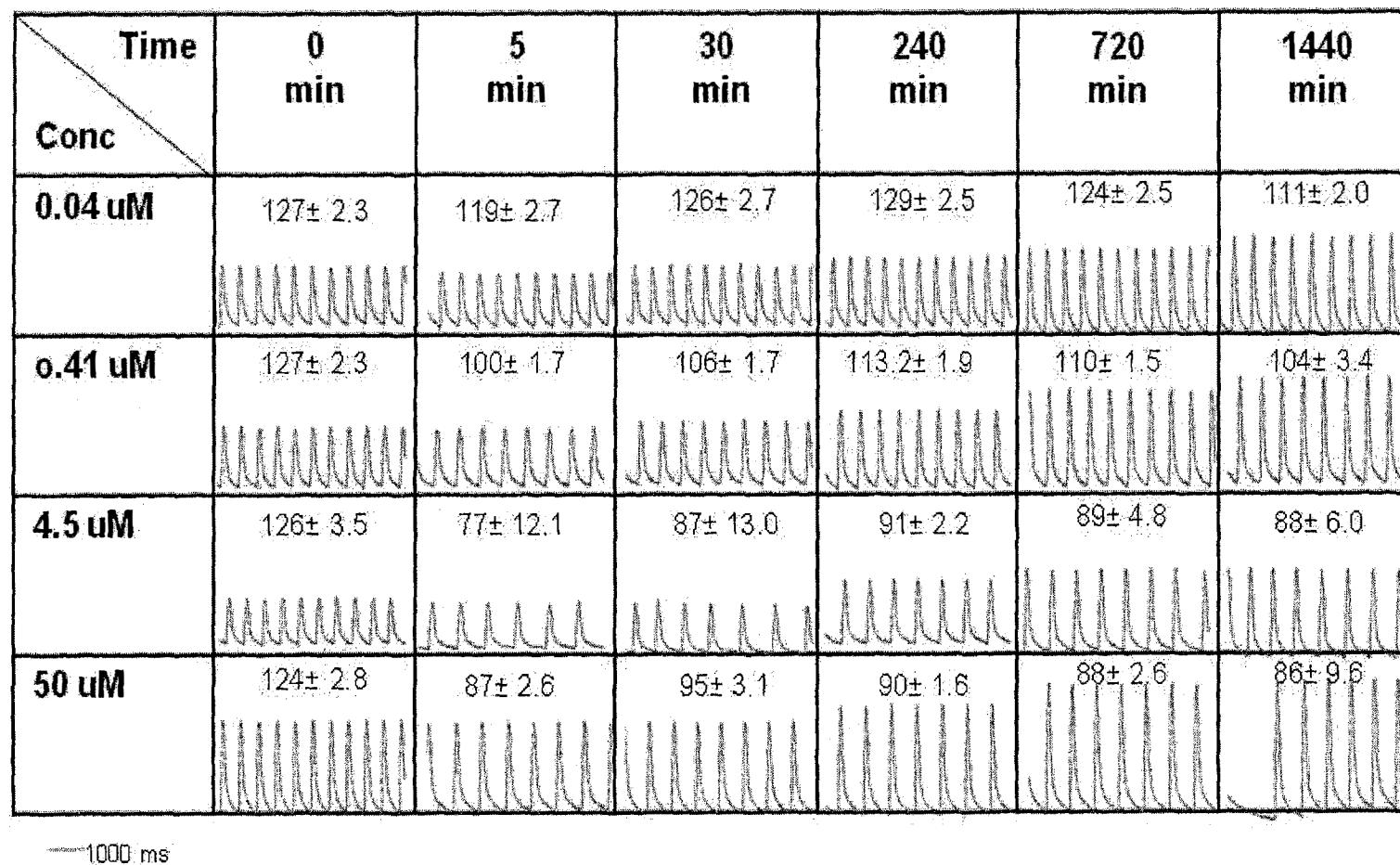
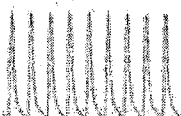
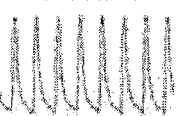
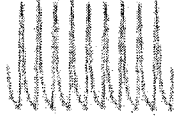
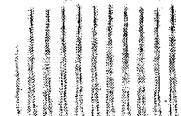
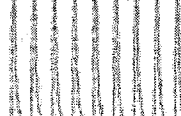
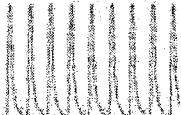
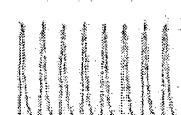
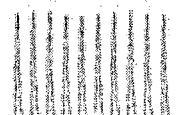
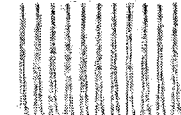
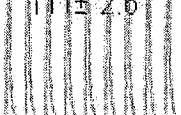
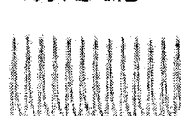
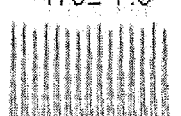
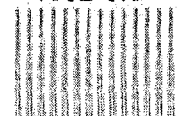
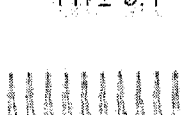
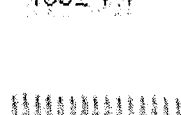
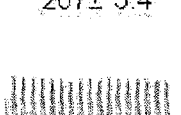
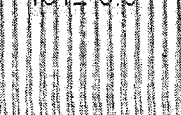


FIG. 11B

isoproterenol

Time Conc	0 min	5 min	30 min	240 min	720 min	1440 min
0.41 nM	109± 1.9 	98± 2.1 	116± 2.4 	123± 3.5 	123± 1.7 	108± 2.3 
3.7 nM	104± 2.8 	104± 2.5 	121± 2.5 	127± 3.7 	125± 3.8 	111± 2.6 
33 nM	106± 2.6 	157± 5.2 	179± 7.6 	164± 5.8 	163± 5.8 	142± 4.8 
300 nM	117± 3.1 	183± 7.7 	207± 5.4 	187± 5.6 	182± 7.9 	164± 5.8 

1000 ms

FIG. 11C

	Normalized Beating Rate (IC50; M)	Normalized Amplitude (IC50; M)	Beat Duration (IC50; M)	Beat Rate Irregularity (IC50; M)
Isradapine	$19.7 \times 10^{-9} \text{ M}$	$42.3 \times 10^{-9} \text{ M}$	N.A.	N.A.
(S)-(-)-Bay K8644	$77.3 \times 10^{-9} \text{ M}$	N.A.	N.A.	$24.2 \times 10^{-9} \text{ M}$
Chromanol 293B	$2.9 \times 10^{-5} \text{ M}$	$2.8 \times 10^{-5} \text{ M}$	N.A.	$3.0 \times 10^{-5} \text{ M}$
E4031	$26.9 \times 10^{-9} \text{ M}$	N.A.	$2.4 \times 10^{-7} \text{ M}$	$56.6 \times 10^{-9} \text{ M}$
TTX	$2.8 \times 10^{-7} \text{ M}$	$5.3 \times 10^{-8} \text{ M}$	N.A.	N.A.
Isoproterenol	$1.4 \times 10^{-8} \text{ M}$	N.A.	$7.1 \times 10^{-9} \text{ M}$	N.A.
Carbachol	$1.7 \times 10^{-7} \text{ M}$	$1.2 \times 10^{-6} \text{ M}$	N.A.	N.A.

FIG. 12

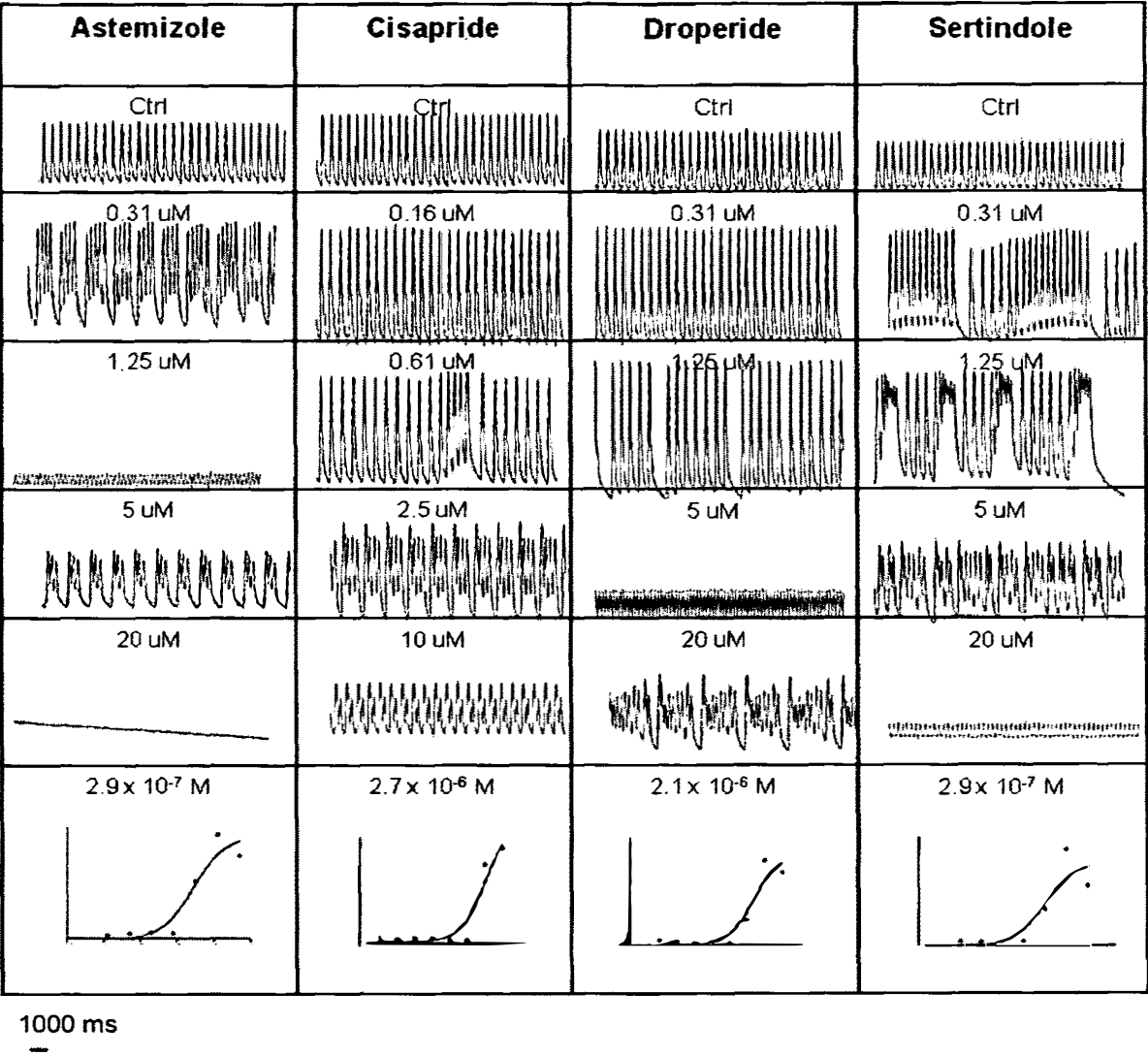
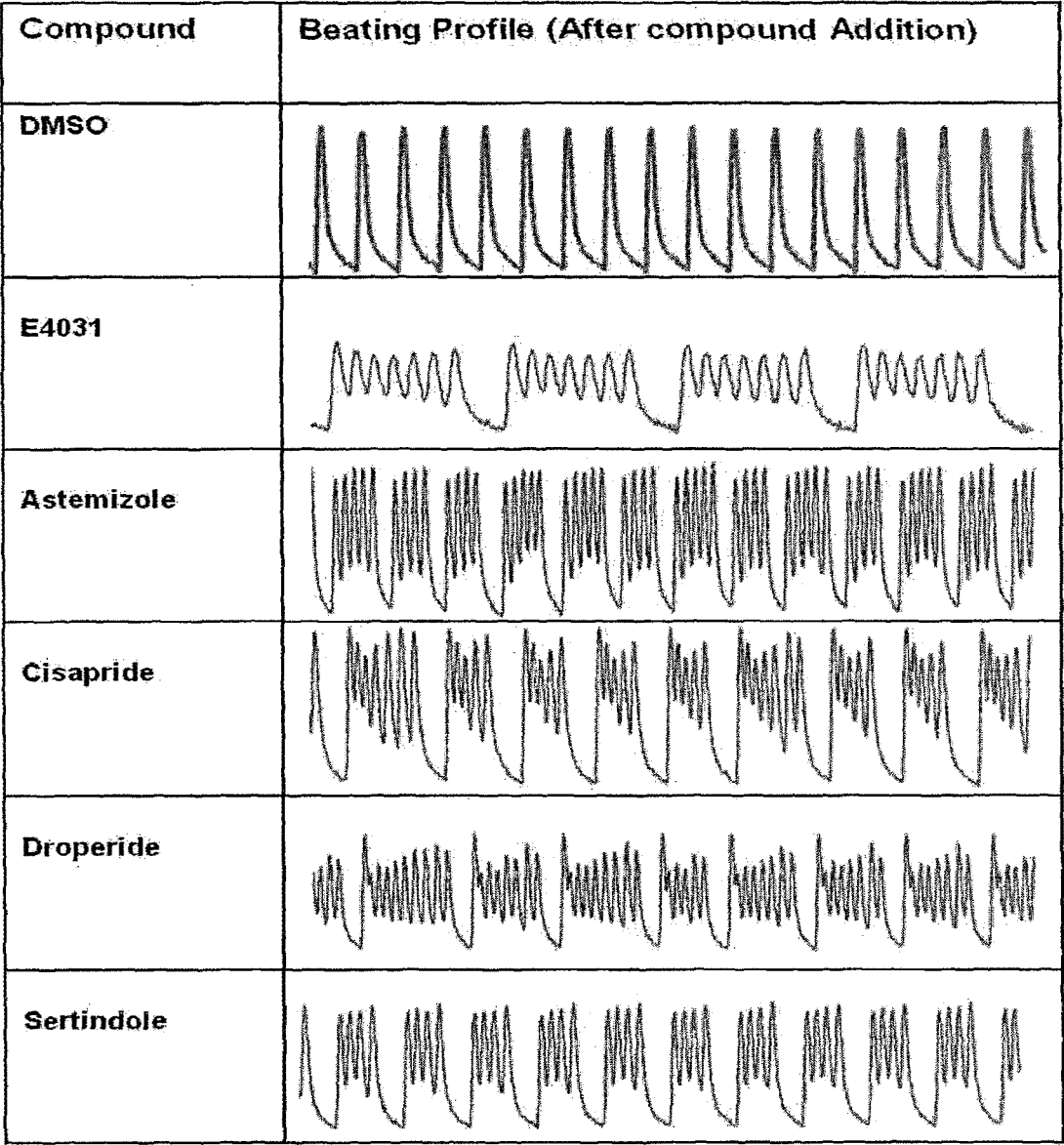


FIG. 13A



1000 ms

FIG. 13B

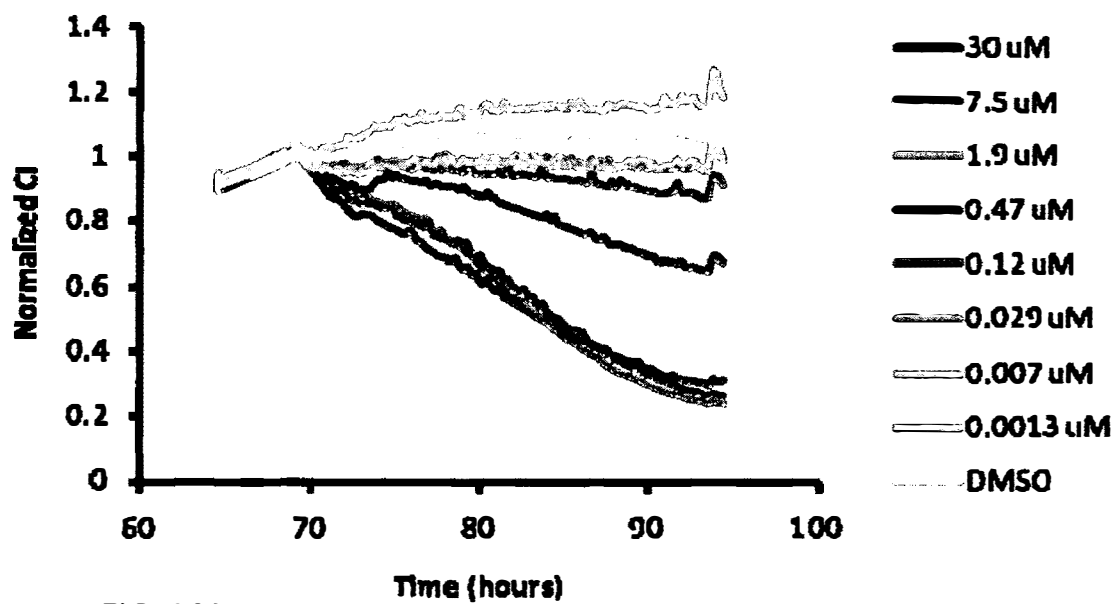
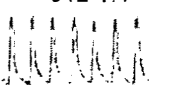
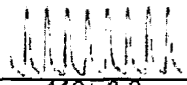
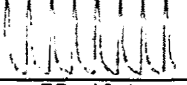
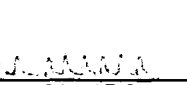
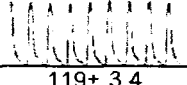
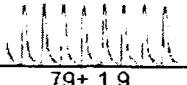
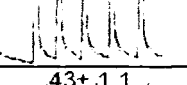
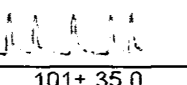
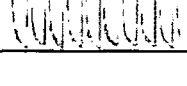
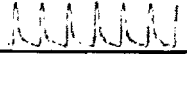
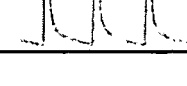
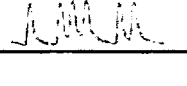


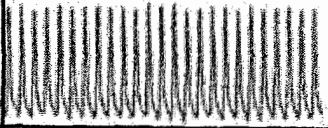
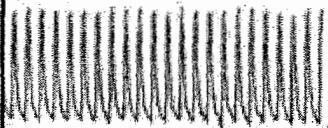
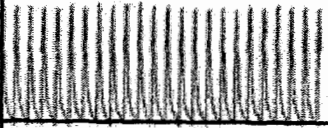
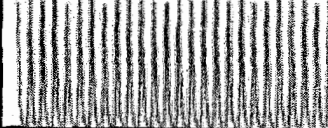
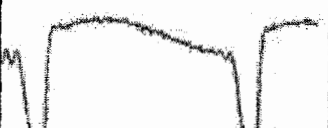
FIG. 14A

Doxorubicin				
	0 min	30 min	240 min	1440 min
0.48 uM	105± 2.9 	113± 3.1 	115± 2.9 	81± 4.4 
1.9 uM	106± 2.7 	111± 2.6 	95± 3.0 	136± 11.5 
7.5 uM	110± 3.2 	107± 2.7 	75± 18.1 	61± 15.6 
30 uM	119± 3.4 	79± 1.9 	43± 1.1 	101± 35.0 

1000 ms

FIG. 14B

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	Pentamidine Beating Profile	Norm Beating Rate	Beat Duration (Sec)
0 min		1 ± 0.03	0.37 ± 0.02
5 min		0.91 ± 0.02	0.41 ± 0.03
30 min		0.92 ± 0.02	0.41 ± 0.01
240 min		0.97 ± 0.02	0.36 ± 0.03
900 min		0.064 ± 0.01	5.8 ± 0.04
1200 min		0.04	5.3

 1000 ms

FIG. 14C

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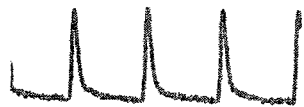
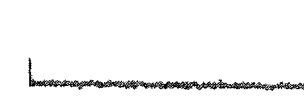
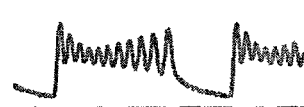
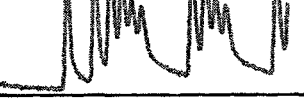
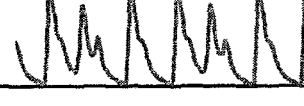
Compound	LOC	RTCA Beating Pattern
DMSO	NA	
Astemizole	0.1 uM	
Amitriptyline hydroch	10 uM	
Amiodarone	0.1 uM	
Bepridil	10 uM	
Bretylum	10 uM	
Clofilium	0.1 uM	
Chlorpheniramine	10 uM	
Cisapride	1 uM	
Chloroquine	10 uM	
Chlorpromazine	10 uM	

FIG. 15

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Compound	LOC	RTCA Beating Pattern
DMSO	NA	
Domperidone	0.1 μ M	
Droperidol	1 μ M	
Diltiazem hydrochloride	1 μ M	
4,4'-Diisothiocyanatostilbene-2,2'-disulfonic acid disodium salt	10 μ M	
Diphenhydramine hydrochloride	10 μ M	
Desipramine hydrochloride	10 μ M	
5,5-Diphenylhydantoin	10 μ M	
Disopyramide	10 μ M	
Felbamate	10 μ M	
Fluoxetine hydrochloride	10 μ M	

FIG. 15 (con't)

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Compound	LOC	RTCA Beating Pattern
DMSO	NA	
FK-506	10 uM	
Flecainide acetate	10 uM	
Fexofenadine hydrochloride	10 uM	
Haloperidol	1 uM	
Indapamide	10 uM	
Isradipine	10 nM	
Imipramine hydrochloride	100 nM	
Ketoconazole	10 uM	
Lidocaine	10 uM	
Loratadine	10 uM	

FIG. 15 (con't)

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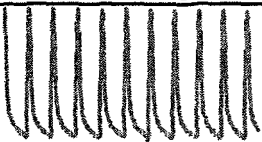
Compound	LOC	RTCA Beating Pattern
DMSO	NA	
Mefloquine hydrochloride	1 μ M	
Mexiletene hydrochloride	1 μ M	
Mesoridazine benzenesulfonate	1 μ M	
(±)-Metoprolol (+)-tartrate	10 μ M	
Mibefradil dihydrochloride	1 μ M	
Nicardipine hydrochloride	1 μ M	
(±)-Norverapamil hydrochloride	10 μ M	
F2-Terfenadine	1 μ M	
Paroxetine maleate	100 nM	
Pimozide	100 nM	

FIG. 15 (con't)

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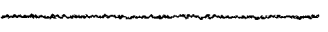
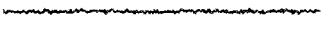
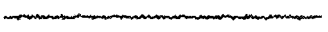
Compound	LOC	RTCA Beating Pattern
DMSO	NA	
PD-118057	10 uM	
Sodium phosphonoformate tribasic hexahydrate	10 uM	
Paroxetine hydrochloride hemihydrate (MW = 374.83)	10 uM	
Quinidine	10 uM	
(±)-Sotalol hydrochloride	1 uM	
Salmeterol xinafoate	1 uM	
Sertraline hydrochloride	1 uM	
Tamoxifen	10 uM	
Tizanidine hydrochloride	10 uM	
Thioridazine hydrochloride	10 uM	

FIG. 15 (con't)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/36877

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/02 (2011.01)

USPC - 435/29

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 435/29Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/4, 29, 325, 283.1, 287.1, 288.3, 288.4, 305.1, 305.2; 436/63
IPC(8): C12Q1/00, 3/00; C12M1/00, 1/34; G01N33/00, 33/15, 33/48 (keyword limited; terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB, USPT, EPAB, JPAB); Google
Search Terms Used: cardiomyocyte, optic\$2, waveguide, electrode, well, drug, compound, beating rate, beating amplitude, rising time, falling time, beating period, IBD10, IBD50, IBD90, rising slope, falling slope, arrhythm\$2, cardioc\$2, sens\$3, analysis, concentration

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0029506 A1 (WANG et al) 04 February 2010 (04.02.2010) fig 4, para [0009], [0016], [0072], [0130], [0132], [0144], [0148], [0153], [0168]-[169], [0178]	1-3, 5-14
Y		4, 15
Y	US 2009/0142790 A1 (FANG et al) 04 June 2009 (04.06.2009) para [0292]	4
Y	US 2003/0211500 A1 (WOOSLEY) 13 November 2003 (13.11.2003) Table 2, para [0087]	15
A	US 2007/0042347 A1 (ROSEN et al) 22 February 2007 (22.02.2007) Abstract, para [0007]-[0011], [0013]	1-15
A	US 2004/0106095 A1 (THOMSON et al) 03 June 2004 (03.06.2004) para [0013], [0016], [0018], [0022], [0031], [0033], [0040], [0052]	1-15
A	US 2007/0212423 A1 (EPSTEIN et al) 13 September 2007 (13.09.2007) para [0136]-[0141]	1-15
A	US 2009/0017465 A1 (XU) 15 January 2009 (15.01.2009) para [0032], [0142]-[0147]	1-15

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 August 2011 (29.08.2011)

Date of mailing of the international search report

02 SEP 2011

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ACE140W1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2010/033801	International filing date (day/month/year) 05 May 2010	(Earliest) Priority Date (day/month/year) 05 May 2009
Applicant ACEA BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the drawings to be published with the abstract is Figure No. 30
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2010/033801

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12M 1/34 (2010.01)

USPC - 435/287.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - C12M 1/00, 1/34, 13/00; G01N 27/00, 27/02 (2010.01)

USPC - 435/173.1, 173.4, 283.1, 287.1, 288.4; 436/149

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MicroPatent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 040 345 B1 (SUGIHARA et al) 04 October 2000 (04.10.2000) entire document	1-4, 9-14, 19, 21-22, 24, 26, 28, 30, 32, 37
Y		5-8, 15-18, 20, 23, 25, 27, 29, 31, 33-36, 38-41
Y	US 2008/0190783 A1 (HYLAND) 14 August 2008 (14.08.2008) entire document	5-8, 15-18, 23, 27
Y	US 7,459,303 B2 (WANG et al) 02 December 2008 (02.12.2008) entire document	20, 29, 31, 33, 36, 38, 41
Y	US 2006/0121446 A1 (ABASSI et al) 08 June 2006 (08.06.2006) entire document	25, 34, 35, 39, 40

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 June 2010

Date of mailing of the international search report

09 JUL 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: RAYMOND WAGENKNECHT
BIOTECH BEACH LAW GROUP PC
5677 OBERLIN DR. STE 204
SAN DIEGO, CA 92121

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

09 JUL 2010

Applicant's or agent's file reference
ACE140W1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2010/033801

International filing date (day/month/year)

05 May 2010

Priority date (day/month/year)

05 May 2009

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - C12M 1/34 (2010.01)

USPC - 435/287.1

Applicant ACEA BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion

17 June 2010

Authorized officer:

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2010/033801

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

a. (means)

- ☐ on paper
☐ in electronic form

b. (time)

- ☐ in the international application as filed
☐ together with the international application in electronic form
☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2010/033801

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement			
1. Statement				
Novelty (N)	Claims	5-8, 15-18, 20, 23, 25, 27, 29, 31, 33-36, 38-41	YES	
	Claims	1-4, 9-14, 19, 21-22, 24, 26, 28, 30, 32, 37	NO	
Inventive step (IS)	Claims	None	YES	
	Claims	1-41	NO	
Industrial applicability (IA)	Claims	1-41	YES	
	Claims	None	NO	
2. Citations and explanations:				
<p>Claims 1-4, 9-14, 19, 21-22, 24, 26, 28, 30, 32 and 37 lack novelty under PCT Article 33(2) as being anticipated by Sugihara et al.</p> <p>Referring to claim 1, Sugihara et al. disclose a device for extracellular recording of cells (para. 0001, lines 5-12), the device comprising: a. a nonconductive substrate (13) forming a base of one or more wells (para. 0010, page 2, line 54-page 3, line 4; figs. 1 & 5 & 6A-6B & 7); b. a recording electrode (11) positioned on the substrate within the well (para. 0010, page 2, line 54-page 3, line 4; figs. 3-5 & 6A-6B & 7; claim 1), wherein the recording electrode is accessible to cells when a cell sample is added to the device (para. 0011, lines 15-20; claim 1); and c. a reference electrode (10) positioned within the well in a cell-free zone (para. 0010, page 3, lines 4-9; para. 0011, lines 15-20; figs. 3-4 & 6A-6B & 7; claim 1), the cell-free zone characterized as free from contact with cells when the cell sample is added to the device (para. 0011, lines 15-20; claim 1), thereby preventing contact between cells and the reference electrode (para. 0011, lines 15-20).</p> <p>Referring to claim 12, Sugihara et al. disclose a device for parallel impedance monitoring and extracellular recording of cells (para. 0001, lines 5-12), the device comprising: a. a nonconductive substrate (13) forming a base of one or more wells (para. 0010, page 2, line 54-page 3, line 4; figs. 1 & 5 & 6A-6B & 7); b. at least two impedance electrodes capable of monitoring impedance of the cells (11; para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1), the at least two impedance electrodes positioned within a well and on the nonconductive substrate (para. 0010, page 2, line 54-page 3, line 4; figs. 3-5 & 6A-6B & 7; claim 1), wherein the at least two impedance electrodes are accessible to cells when a cell sample is added to the device (para. 0011, lines 15-20; claim 1); c. a recording electrode (11) positioned on the substrate within the well (para. 0010, page 2, line 54-page 3, line 4; figs. 3-5 & 6A-6B & 7; claim 1), wherein the recording electrode is accessible to cells when the cell sample is added to the device (para. 0011, lines 15-20; claim 1); and d. a reference electrode (10) positioned within the well in a cell-free zone (para. 0010, page 3, lines 4-9; para. 0011, lines 15-20; figs. 3-4 & 6A-6B & 7; claim 1), which is characterized as free from contact with cells when the cell sample is added to the device (para. 0011, lines 15-20; claim 1).</p> <p>Referring to claim 21, Sugihara et al. disclose a device for parallel impedance monitoring and extracellular recording of cells (para. 0001, lines 5-12), the device comprising: a. a nonconductive substrate (13) forming a base of one or more wells (para. 0010, page 2, line 54-page 3, line 4; figs. 1 & 5 & 6A-6B & 7); b. at least two impedance electrodes capable of monitoring impedance of the cells (11; para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1), the at least two impedance electrodes positioned within a well and on the nonconductive substrate (para. 0010, page 2, line 54-page 3, line 4; figs. 3-5 & 6A-6B & 7; claim 1); c. a recording electrode (11) positioned on the substrate within the well (para. 0010, page 2, line 54-page 3, line 4; figs. 3-5 & 6A-6B & 7; claim 1); and d. a reference electrode (10), wherein the recording electrode is electrically coupled to the reference electrode for performing an extracellular recording measurement at the recording electrode (para. 0018, lines 34-39).</p> <p>Referring to claims 2 and 24, Sugihara et al. disclose wherein the recording electrode has a diameter from about 10 micron to about 200 micron (para. 0034, lines 28-29).</p> <p>Referring to claim 3, Sugihara et al. disclose wherein the recording electrode comprises an electrode structure comprising a plurality of electrode elements (para. 0010, page 2, lines 54-56; claim 1).</p> <p>Referring to claims 4, 14 and 26, Sugihara et al. disclose wherein the reference electrode is positioned or deposited on the substrate in the cell-free zone (para. 0011, lines 15-20; claim 1).</p> <p>Referring to claim 9, Sugihara et al. disclose the device loaded with a cell sample, wherein cells within the cell sample contact the recording electrode but do not contact the reference electrode (para. 0011, lines 15-20; claim 1).</p> <p>Referring to claim 19, Sugihara et al. disclose the device loaded with a cell sample, wherein cells within the cell sample contact the recording electrode and the at least two impedance electrodes but do not contact the reference electrode (para. 0011, lines 15-20; claim 1).</p> <p>Referring to claim 10, Sugihara et al. disclose wherein the cell sample comprises cardiomyocytes or cardiomyocyte precursor cells (para. 0002, lines 22-26).</p> <p>Referring to claim 11, Sugihara et al. disclose the device further comprising at least two impedance monitoring electrodes (11; claim 1) positioned on the nonconductive substrate and the at least two impedance electrodes are accessible to cells (para. 0010, page 2, line 54-page 3, line 4; para. 0011, lines 15-20; figs. 3-5 & 6A-6B & 7; claim 1).</p> <p>Referring to claims 13 and 22, Sugihara et al. disclose wherein the at least two impedance electrodes (11) each have the same surface area (para. 0032, lines 4-6; para. 0034, lines 28-29) and each comprises an electrode structure comprising a plurality of electrode elements (para. 0010, page 2, lines 54-56; claim 1).</p> <p>Referring to claim 28, Sugihara et al. disclose the device loaded with a cell sample, wherein cells within the cell sample contact the at least two impedance electrodes but do not contact the reference electrode (para. 0011, lines 15-20; claim 1).</p>				
Continued in Supplemental Box				

Form PCT/ISA/237 (Box No. V) (July 2009)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2010/033801

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V

Referring to claim 30, Sugihara et al. disclose a method of extracellular recording of a cell population (para. 0001, lines 5-12), the method comprising: a. providing the device (1), operably linked to a voltage amplifier (34); b. adding a cell sample to the device (para. 0011, lines 15-20; claim 1), wherein the reference electrode remains free from contact with cells from the cell sample (para. 0011, lines 15-20; claim 1); and c. performing extracellular recording measurements by amplifying the voltage signals between the recording electrode and the reference electrode and monitoring the amplified signals (para. 0029, lines 19-29).

Referring to claim 32, Sugihara et al. disclose a method of extracellular recording of a cell population (para. 0001, lines 5-12), the method comprising: a. providing the device (1), operably linked to a voltage amplifier (34) and impedance measurement circuitry (11; para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1); b. adding a cell sample to the device (para. 0011, lines 15-20; claim 1), wherein the reference electrode remains free from contact with cells from the cell sample (para. 0011, lines 15-20; claim 1); c. performing extracellular recording measurements by amplifying the voltage signals between the recording electrode and the reference electrode and monitoring the amplified signals (para. 0029, lines 19-29); and d. performing impedance measurements by monitoring impedance between the two impedance electrodes (para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1).

Referring to claim 37, Sugihara et al. disclose a method of extracellular recording and impedance monitoring of a cell population (para. 0001, lines 5-12), the method comprising: a. providing the device (1), operably connecting the at least two impedance electrodes to an impedance measurement circuitry (11; para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1) and connecting the recording electrode and the reference electrode to a voltage amplifier (para. 0029, lines 19-29); b) adding a cell sample to the device; c. performing extracellular recording measurements by amplifying the voltage signals between the recording electrode and the reference electrode and monitoring the amplified signals (para. 0029, lines 19-29); and d. performing impedance measurements by monitoring impedance between the two impedance electrodes (para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1).

Claims 5-8, 15-18, 23 and 27 lack an inventive step under PCT Article 33(3) as being obvious over Sugihara et al. in view of Hyland.

Referring to claims 5 and 15, Sugihara et al. teach the device as shown in claims 4 and 12 above. Sugihara et al. does not teach wherein the cell-free zone is defined by a barrier, which prevents cell access to the cell-free zone. However, Hyland teaches wherein the cell-free zone is defined by a barrier (2), which prevents cell access to the cell-free zone (61 & 62). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. wherein the cell-free zone is defined by a barrier, which prevents cell access to the cell-free zone as taught by Hyland. The motivation for doing so would be to provide a better method for creating a cell-free zone.

Referring to claims 6 and 16, Sugihara et al. teach the device as shown in claims 1 and 12 above. Sugihara et al. does not teach wherein the cell-free zone is characterized as being on a different plane than the recording electrode, thereby preventing cell migration to the cell free zone. However, Hyland teaches wherein the cell-free zone (61 & 62) is characterized as being on a different plane than the recording electrode (4), thereby preventing cell migration to the cell free zone (fig. 1). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. wherein the cell-free zone is characterized as being on a different plane than the recording electrode, thereby preventing cell migration to the cell free zone as taught by Hyland. The motivation for doing so would be to provide a better method for creating a cell-free zone.

Referring to claims 7 and 17, Sugihara et al. in view of Hyland teach the device as shown in claims 6 and 16 above. Sugihara et al. does not teach wherein the cell-free zone comprises a surface vertically above the recording electrode. However, Hyland teaches wherein the cell-free zone (61 & 62) comprises a surface vertically above (fig. 1) the recording electrode (4). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. in view of Hyland wherein the cell-free zone comprises a surface vertically above the recording electrode as taught by Hyland. The motivation for doing so would be to provide a better method for creating a cell-free zone.

Referring to claims 8, 18 and 27, Sugihara et al. teach the device as shown in claims 1, 12 and 21 above. Sugihara et al. does not teach wherein the reference electrode is an external electrode free from contact with the non-conductive substrate. However, Hyland teaches wherein the reference electrode (5) is an external electrode free from contact (fig. 1) with the non-conductive substrate (1). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. wherein the reference electrode is an external electrode free from contact with the non-conductive substrate as taught by Hyland. The motivation for doing so would be to provide a better method for creating a cell-free zone.

Referring to claim 23, Sugihara et al. teach wherein the recording electrode (11; para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1) is one of the at least two impedance electrodes (11; para. 0001, lines 5-12; para. 0018, lines 34-39; para. 0026, lines 39-55; claim 1). Sugihara et al. does not teach wherein the reference electrode is an external electrode free from contact with the non-conductive substrate. However, Hyland teaches wherein the reference electrode (5) is an external electrode free from contact (fig. 1) with the non-conductive substrate (1). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. wherein the reference electrode is an external electrode free from contact with the non-conductive substrate as taught by Hyland. The motivation for doing so would be to provide a better method for creating a cell-free zone.

Continued in Next Supplemental Box

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2010/033801

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Previous Supplemental Box

Claims 20, 29, 31, 33, 36, 38 and 41 lack an inventive step under PCT Article 33(3) as being obvious over Sugihara et al. in view of Wang et al.

Referring to claims 20 and 29, Sugihara et al. teach the method operably linked to a system comprising an impedance analyzer (30) and extracellular recording amplifier (34). Sugihara et al. does not teach the device comprising switching means capable of switching measurement between the at least two impedance electrodes and the extracellular recording electrode and the reference electrode. However, Wang et al. teach the device comprising switching means capable of switching measurement between the at least two impedance electrodes and the extracellular recording electrode and the reference electrode (col. 25, lines 44-61). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Sugihara et al. to comprise switching means capable of switching measurement between the at least two impedance electrodes and the extracellular recording electrode and the reference electrode as taught by Wang et al. The motivation for doing so would be to provide a better method for recording the data.

Referring to claims 31, 33 and 38, Sugihara et al. teach the method as shown in claims 30, 32 and 37 above. Sugihara et al. does not teach wherein the cells comprise cardiomyocytes or cardiomyocyte precursor cells, the method further comprising adding a compound suspected of affecting a beating cycle of the cells. However, Wang et al. teaches wherein the cells comprise cardiomyocytes or cardiomyocyte precursor cells, the method further comprising adding a compound suspected of affecting a beating cycle of the cells (col. 30, line 64-col. 31, line 39). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Sugihara et al. wherein the cells comprise cardiomyocytes or cardiomyocyte precursor cells, the method further comprising adding a compound suspected of affecting a beating cycle of the cells as taught by Wang et al. The motivation for doing so would be to provide a better method for testing the cytotoxicity of the cells.

Referring to claims 36 and 41, Sugihara et al. teach the method as shown in claims 32 and 37 above. Sugihara et al. does not teach wherein further comprising calculating cell index from measured impedance values. However, Wang et al. teaches wherein further comprising calculating cell index from measured impedance values (col. 39, line 65-col. 40, line 30). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Sugihara et al. wherein further comprising calculating cell index from measured impedance values as taught by Wang et al. The motivation for doing so would be to provide a method for calculating the cell index.

Claims 25, 34, 35, 39 and 40 lack an inventive step under PCT Article 33(3) as being obvious over Sugihara et al. in view of Abassi et al.

Referring to claim 25, Sugihara et al. teach the device as shown in claim 21 above. Sugihara et al. does not teach wherein the reference electrode is one of the at least two impedance electrodes. However, Abassi et al. teach wherein the reference electrode (110 & 120) is one of the at least two impedance electrodes (110 & 120; fig. 1). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. wherein the reference electrode is one of the at least two impedance electrodes as taught by Abassi et al. The motivation for doing so would be to provide a better design for the electrodes.

Referring to claims 34 and 39, Sugihara et al. teach the method as shown in claims 32 and 37 above. Sugihara et al. does not teach wherein the impedance is monitored at milli-second time resolution. However, Abassi et al. teach wherein the impedance is monitored at milli-second time resolution (para. 0128). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. wherein the impedance is monitored at milli-second time resolution as taught by Abassi et al. The motivation for doing so would be to provide optimal time intervals for monitoring the impedance.

Referring to claims 35 and 40, Sugihara et al. teach the method as shown in claims 32 and 37 above. Sugihara et al. does not teach wherein the impedance is monitored at seconds or minutes time resolution. However, Abassi et al. teach wherein the impedance is monitored at seconds or minutes time resolution (para. 0254). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Sugihara et al. wherein the impedance is monitored at seconds or minutes time resolution as taught by Abassi et al. The motivation for doing so would be to provide optimal time intervals for monitoring the impedance.

Claims 1-41 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

RAYMOND WAGENKNECHT
BIOTECH BEACH LAW GROUP PC
625 Broadway
SUITE 1210
SAN DIEGO, CA 92101

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

24 JUN 2009

Applicant's or agent's file reference

ACE1344W1

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US 09/42787

International filing date
(day/month/year)

05 May 2009 (05.05.2009)

Applicant ACEA BIOSCIENCES, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ACE1344W1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 09/42787	International filing date (<i>day/month/year</i>) 05 May 2009 (05.05.2009)	(Earliest) Priority Date (<i>day/month/year</i>) 05 May 2008 (05.05.2008)
Applicant ACEA BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1A
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/42787

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - G01N 27/02; C12M 1/34 (2009.01) USPC - 435/288.4; 436/149 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8):G01N 27/02; C12M 1/34 (2009.01) USPC: 435/288.4; 436/149 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 435/283.1, 435/287.1 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWest, Google Scholar, Google Patent: monitor, cell-substrate, impedance, nanoconductive, electrode array\$2, fabricated, well\$2, surface, attach\$5, analyz\$4, millisecond, intervals, electronic circuitry, record\$2, metal, interdigitated, cardiomyocytes, beating cells, in vitro		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	2007/0172939 A1 (XU et al.) 26 Jul 2007 (26.07.2007); para [0015]-, [0016], [0074], [0098], [0109], [0114], [0120], [0183], [0240], [0274]	1-39
Y	US 2006/0161073 A1 (SINGER et al.) 20 Jul 2006 (20.07.2006); para [0002], [0003], [0018]	1-39
Y	US 2006/0057771 A1 (KOVACS et al.) 16 Mar 2006 (16.03.2006); para [0005], [0018], [0055]	8-10, 17-18
Y	US 5,800,467 A (PARK et al.) 01 Sep 1998 (01.09.1998); col 7, ln 1-15	11-14, 20-23
Y	US 5,725,563 A (KLOTZ) 10 Mar 1998 (10.03.1998); col 5, ln 30-38; col 6, ln 26-34	31-33
Y	US 7,294,334 B1 (MICHAL et al.) 13 Nov 2007 (13.11.2007); col 13, ln 4-12; col 19, ln 46-50; col 30, ln 65-col 31 ln 3	35-37
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 11 June 2009 (11.06.2009)		Date of mailing of the international search report 24 JUN 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: RAYMOND WAGENKNECHT
BIOTECH BEACH LAW GROUP PC
625 Broadway
SUITE 1210
SAN DIEGO, CA 92101

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

24 JUN 2009

Applicant's or agent's file reference
ACE1344W1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 09/42787

International filing date (day/month/year)

05 May 2009 (05.05.2009)

Priority date (day/month/year)

05 May 2008 (05.05.2008)

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - G01N 27/02; C12M 1/34 (2009.01)

USPC - 435/288.4; 436/149

Applicant ACEA BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion

11 June 2009 (11.06.2009)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 09/42787

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 09/42787

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-39	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-39	NO
Industrial applicability (IA)	Claims	1-39	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-7, 15, 16, 19, 24-30, 34, 38 and 39 inventive step under PCT Article 33(3) as being anticipated by US 2007/0172939 A1 to Xu et al. (hereinafter "Xu") in view of US 2006/0161073 A1 to Singer et al. (hereinafter "Singer").

Regarding claim 1, Xu teaches a system for monitoring impedance of excitable cells (para [0015]), comprising:

a) a device for monitoring cell-substrate impedance (para [0015]), comprising

i) a nonconductive substrate (para [0015]);

ii) one or more electrode arrays fabricated on said substrate (para [0015]);

iii) one or more wells on said substrate, wherein each of said one or more arrays is associated with one of said one or more wells; wherein each electrode array is individually addressable (para [0016]), further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array (para [0015]);

b) an impedance analyzer capable of impedance measurement at millisecond time resolution (para [0016], [0240]- can be measured at short or long intervals);

c) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer (para [0120]); and

d) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer (para [0016]). However Xu fails to teach wherein the system for monitoring impedance of excitable cells involves in vitro cells.

Singer teaches monitoring impedance (para [0003]) using electrode arrays (para [0018]) in vitro (para [0002]). In light of the fact that Singer teaches utilizing electrode arrays to measure impedance in vitro it would have been obvious to one of ordinary skill in the art to utilize the electrode array system taught by Xu on in vitro cells as taught by Singer.

Regarding claim 2, the combination of Xu and Singer teaches the system according to claim 1, and Xu further teaches wherein each of said electrode arrays comprises two electrode structures having substantially a same surface area (para [0074]).

Regarding claim 3, the combination of Xu and Singer teaches the system according to claim 2, and Xu further teaches wherein said electrode structures are each constructed from gold and chromium (para [0183]-"gold film over chromium adhesion layer").

Regarding claim 4, the combination of Xu and Singer teaches the system according to claim 2, and Xu further teaches wherein said electrode structures have a width between 20 microns and 500 microns (para [0098]).

Regarding claim 5, the combination of Xu and Singer teaches the system according to claim 2, and Xu further teaches wherein a gap between electrode structures within each electrode array is between 5 microns and 100 microns (para [0098]).

Regarding claim 6, the combination of Xu and Singer teaches the system according to claim 2, and Xu further teaches wherein each electrode array is organized in a configuration consisting of interdigitated (para [0109]).

Regarding claim 7, the combination of Xu and Singer teaches the system according to claim 2, and Xu further teaches wherein said millisecond time resolution allows for impedance measurements at more than two time points within each excitation cycle of excitable cells introduced to wells (para [0125]).

Regarding claim 15, the combination of Xu and Singer teaches the system according to claim 2, and Xu further teaches wherein said one or more wells is selected from a group of 6 wells, 8 wells, 16 wells, 32 wells, 96 wells and 384 wells (para [0114]).

Regarding claim 16, the combination of Xu and Singer teaches a method for assessing and quantifying excitable cells in vitro, comprising

a) providing the system according to Claim 1; and Xu further teaches

b) adding excitable cells to said one or more wells (para [0021]);

c) monitoring impedance of said one or more wells using millisecond time resolution (para [0016], [0240]- can be measured at short or long intervals); and

d) resolving individual cycles of said excitable cells (para [0122]).

*****Continued In Supplemental Box*****

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 09/42787

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V(2):

Regarding claim 19, the combination of Xu and Singer teaches the method according to claim 16, and Xu further teaches wherein the step of monitoring impedance comprises performing impedance measurements at millisecond time resolution (para [0016], [0240]- can be measured at short or long intervals) simultaneously across all wells (para [0274]).

Regarding claim 24, Xu further teaches a method of determining whether a compound modulates a beating cycle of an excitable cell (para [0156]-compare impedance measurements with baseline impedance), and Xu and Singer teach the method comprising:

- a) providing the system according to claim 1, wherein said system comprises at least two wells (para [0016]); Xu further teaches
- b) adding excitable cells to said at least two wells (para [0020]);
- c) monitoring impedance of said at least two wells using millisecond time resolution para [0016], [0240]- can be measured at short or long intervals);
- d) adding a compound suspected of modulation of the beating cycle to a first of said at least two wells to provide a test well, wherein a second well lacking compound is provided as a control well (para [0029]);
- e) resolving the beating cycles of both test well and control well (para [0029]); and
- d) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said compound modulates the beating cycle of the excitable cell (para [0131]). Although Xu does not specifically teach wherein the cell is a beating cell, Singer teaches wherein a testable excitable cell is a cardiomyocyte (para [0018]). It would have been obvious to one of ordinary skill in the art to conduct the method as taught by Xu on an excitable cell such as a cardiomyocyte, such as the one taught by Singer.

Regarding claim 25, the combination of Xu and Singer teaches the method according to claim 24, and Singer further teaches wherein the excitable cells are cardiomyocytes (para [0018]).

Regarding claim 26, the combination of Xu and Singer teaches the method according to claim 24, and Singer further teaches wherein said beating cycles are compared to identify changes in beating amplitude (para [0096]).

Regarding claim 27, the combination of Xu and Singer teaches the method according to claim 24, and Singer further teaches wherein said beating cycles are compared to identify changes in beating frequency (para [0078], [0096]).

Regarding claim 28, the combination of Xu and Singer teaches the method according to claim 27, and Singer further teaches wherein said changes in beating frequency are regular changes or irregular changes (para [0078], [0096]).

Regarding claim 29, the combination of Xu and Singer teaches the method according to claim 24, and Xu further teaches the method further comprising determining a cell index for each of said test well and control well, wherein the step of comparing said beating cycles comprises comparing said cell indexes between test well and control well (para [0131]).

Regarding claim 30, the combination of Xu and Singer teaches a method of characterizing rhythmic beating of a cardiomyocyte comprising:

- a) providing the system according to claim 1; and Xu further teaches
- b) adding excitable cells to said one or more wells (para [0016]);
- c) monitoring impedance of said one or more wells in millisecond time resolution (para [0016], [0240]- can be measured at short or long intervals); and Singer further teaches
- d) determining a plurality of beating cycle peaks in a time unit (para [0094]); and
- e) comparing amplitude or frequency of said peaks over said time unit (para [0094]).

Regarding claim 34, the combination of Xu and Singer teaches the method according to claim 30, and Xu further teaches the method further comprising monitoring impedance of said one or more wells over seconds, minutes or hours (para [0222]).

Regarding claim 38, Xu and Singer teaches a method for assessing and quantifying excitable cells in vitro, comprising

- a) providing the system according to claim 1; and Xu further teaches:
- b) adding excitable cells to said one or more wells (para [0016]);
- c) monitoring impedance of said one or more wells over a first time period, which is characterized as a longer time period comprising seconds, minutes or hours (para [0222]);
- d) monitoring impedance of said one or more wells over a second time period in millisecond time resolution (para [0222], [0240]);
- e) determining cell attachment (para [0228])
- f) resolving individual cycles of said excitable cells from monitoring over said second time period (para [0222]).

Regarding claim 39, the combination of Xu and Singer teaches the method according to claim 38, and Xu further teaches wherein monitoring impedance over said second time period is performed at regular or irregular time intervals within monitoring impedance over said first time period (para [0231]).

*****Continued in Supplemental Box*****

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US 09/42787

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Previous Supplemental Box:

Claims 8-10, 17 and 18 lack inventive step under PCT Article 33(3) as being obvious over Xu in view of Singer and further in view of US 2006/0057771 A1 to Kovacs et al. (hereinafter "Kovacs").

Regarding claim 8, the combination of Xu and Singer teaches the system according to claim 7. However neither Xu nor Singer teaches wherein said excitation cycle is a beating cell. Kovacs teaches an electrode array system (para [0005]) as part of a system that measures impedance (para [0055]). Kovacs further teaches wherein this system is utilized to test excitation in beating cells (para [0018]-specifically cardiomyocytes). In light of the fact that cardiomyocytes are cells which are excitable it would have been obvious to one of ordinary skill in the art to use the method taught by Xu for detecting impedance in excitable cells on cardiomyocytes as taught by Kovacs.

Regarding claim 9, the combination of Xu, Singer and Kovacs teaches the system according to claim 8. Kovacs further teaches wherein this system is utilized to test excitation in cardiomyocytes (para [0018]).

Regarding claim 10, the combination of Xu and Singer teaches the system according to claim 7. However neither Xu nor Singer teaches wherein said excitable cells are excitation-contraction coupling cells. Kovacs teaches an electrode array system (para [0005]) as part of a system that measures impedance (para [0055]). Kovacs further teaches wherein this system is utilized to test excitation in cardiomyocytes (para [0018]). In light of the fact that cardiomyocytes by definition are excitation contraction coupling cells it would have been obvious that cells that are excitation-contraction coupling cells would also be measurable by this system.

Regarding claim 17, the combination of Xu and Singer teaches the method according to claim 16. However neither Xu nor Singer teaches wherein said excitable cells are cells undergo excitation-contraction coupling. Kovacs teaches an electrode array system (para [0005]) as part of a system that measures impedance (para [0055]). Kovacs further teaches wherein this system is utilized to test excitation in cardiomyocytes (para [0018]). In light of the fact that cardiomyocytes by definition are excitation contraction coupling cells it would have been obvious that cells that are excitation-contraction coupling cells would also be measurable by this system.

Regarding claim 18, the combination of Xu, Singer and Kovacs teaches the method according to claim 17. Kovacs further teaches wherein this system is utilized to test excitation in cardiomyocytes (para [0018]).

Claims 11-14 and 20-23 lack inventive step under PCT Article 33(3) as being obvious over Xu in view of Singer and further in view of US 5,800,467 A to Park et al. (hereinafter "Park").

Regarding claims 11-14, the combination of Xu and Singer teaches the system according to claim 1. However neither Xu nor Singer further teaches wherein said impedance measurement at millisecond time resolution comprises at least two consecutive impedance measurements that are less than 100 milliseconds apart, less than 40 milliseconds apart, less than 20 milliseconds apart, or less than 10 milliseconds apart. However, Xu does teach wherein impedance is measured at varying time lengths (para [0240]). Further, Park teaches impedance measurements using an electrode (col 7, In 1-11) wherein the measurements are taken 15 milliseconds apart (col 7, In 12-15). In light of the fact that Park teaches utilizing several impedance values to generate an average and impedance slope, it would have been obvious to one of ordinary skill in the art to incorporate the multiple measurements of impedance within such a time frame in order to better measure the impedance.

Regarding claims 20-23, the combination of Xu and Singer teaches the system according to claim 1. However neither Xu nor Singer further teaches wherein said impedance measurement at millisecond time resolution comprises at least two consecutive impedance measurements that are less than 300 milliseconds apart, less than 100 milliseconds apart, less than 40 milliseconds apart, or less than 10 milliseconds apart. However, Xu does teach wherein impedance is measured at varying time lengths (para [0240]). Further, Park teaches impedance measurements using an electrode (col 7, In 1-11) wherein the measurements are taken 15 milliseconds apart (col 7, In 12-15). In light of the fact that Park teaches utilizing several impedance values to generate an average and impedance slope, it would have been obvious to one of ordinary skill in the art to incorporate the multiple measurements of impedance within such a time frame in order to better measure the impedance.

Claims 31-33 lack inventive step under PCT Article 33(3) as being obvious over Xu in view of Singer and further in view of US 5,725,563 A to Klotz.

Regarding claim 31, the combination of Xu and Singer teaches the method according to claim 30. However neither Xu nor Singer further teaches wherein the step of determining a plurality of beating cycle peaks comprises determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay. Klotz teaches measuring impedance through the use of electrodes (col 5, In 30-38) wherein the measuring comprises determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay (col 6, In 26-34). In light of the fact that measuring the various peaks and rise and decay of a cardiac cycle will detail the condition of the heart it would have been obvious to one of ordinary skill in the art to measure the peaks comprising the rise and decay of the cardiac cycle to gain a better determining of the state of the heart.

*****Continued in Supplemental Box*****

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US 09/42787

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Previous Supplemental Box:

Regarding claim 32, the combination of Xu and Singer teaches the method according to claim 30, and Xu further teaches the method further comprising determining a cell index for each of said one or more wells (para [0018]). However neither Xu nor Singer explicitly teaches wherein the step of determining a plurality of beating cycle peaks comprises for each cycle determining a rise in cell index, a decay in cell index and extrapolating each peak from each rise and decay. Klotz teaches measuring impedance through the use of electrodes (col 5, ln 30-38) wherein the measuring comprises determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay (col 6, ln 26-40). In light of the fact that measuring the various peaks and rise and decay of a cardiac cycle will detail the condition of the heart it would have been obvious to one of ordinary skill in the art to measure the peaks comprising the rise and decay of the cardiac cycle to gain a better determining of the state of the heart and to compile the data in an easy to read method such as the cell index taught by Xu.

Regarding claim 33, the combination of Xu and Singer teaches the method according to claim 30. However neither Xu nor Singer teaches wherein beating cycle peaks are determined by identifying impedance data points at which the first order derivative to time is zero or close to zero. Klotz teaches measuring impedance through the use of electrodes (col 5, ln 30-38) wherein the measuring comprises determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay at which the first order derivative to time is zero (col 6, ln 26-40). In light of the fact that measuring the various peaks and rise and decay of a cardiac cycle will detail the condition of the heart it would have been obvious to one of ordinary skill in the art to measure the peaks comprising the rise and decay of the cardiac cycle to gain a better determining of the state of the heart and to compile the data in an easy to read method such as the cell index taught by Xu.

Claims 35-37 lack inventive step under PCT Article 33(3) as being obvious over Xu in view of Singer and further in view of US 7,294,334 B1 to Michal et al. (hereinafter "Michal").

Regarding claim 35, Xu teaches a method of assessing genetic manipulation of an embryonic stem cell (para [0338]), and the combination of Xu and Singer teaches a method comprising:

a) providing the system according to claim 1, and Xu further teaches wherein said device comprises at least two wells (para [0016]).

Neither Xu nor Singer explicitly teaches:

b) mutating embryonic stem cells to comprise a genetic mutation;

However, Michal teaches testing the impedance (col 13, ln 4-12) of b) mutating embryonic stem cells to comprise a genetic mutation (col 19, ln 46). In light of the fact that Xu teaches testing cells in general it would have been obvious to one of ordinary skill in the art that various cells, such as mutating embryonic stem cells taught by Michal could be tested using the same method as ordinary cells taught by Xu.

Xu further teaches the method comprising

c) adding said mutated embryonic stem cells (cells-could be any cells, including embryonic stem cells as taught above by Michal) to a first well of said at least two wells to form a test well and control embryonic stem cells to a second of said at least two wells to form a control well (para [0020]);

c) monitoring impedance of said at least two wells in millisecond time resolution (para [0016], [0240]- can be measured at short or long intervals); and

e) resolving the beating cycles of both test well and control well, if any (para [0029]); and

d) comparing said beating cycles between said test well and control well (para [0029]). However neither Xu, Singer, nor Michal teaches wherein a difference in beating cycles indicates said genetic mutation modulates embryonic stem cell differentiation. In light of the fact that Michal utilizes mutant embryonic stem cells, it would have been obvious that a change in impedance would indicate differentiation based on alteration of the impedance due to changes in expression of genes that alter the cell impedance to one that more closely matches that of the differentiated cell type.

Regarding claim 36, the combination of Xu, Singer and Michal teaches the method according to claim 35, and Michal further teaches wherein said embryonic stem cell differentiation is differentiation into a cardiomyocyte (col 9, ln 9-21).

Regarding claim 37, the combination of Xu, Singer and Michal teaches the method according to claim 35, and Michal further teaches wherein said genetic mutation is selected from the group consisting of a genetic knock out (col 9, ln 9-21).

Claims 1-39 have industrial applicability under PCT Article 33(4) because the subject matter can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US 09/42787**Supplemental Box**

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ACE141W1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 11/36877	International filing date (<i>day/month/year</i>) 17 May 2011 (17.05.2011)	(Earliest) Priority Date (<i>day/month/year</i>) 18 May 2010 (18.05.2010)
Applicant ACEA BIOSCIENCES, INC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. 7

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/36877

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/02 (2011.01)

USPC - 435/29

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 435/29Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/4, 29, 325, 283.1, 287.1, 288.3, 288.4, 305.1, 305.2; 436/63
IPC(8): C12Q1/00, 3/00; C12M1/00, 1/34; G01N33/00, 33/15, 33/48 (keyword limited; terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB, USPT, EPAB, JPAB); Google
Search Terms Used: cardiomyocyte, optic\$2, waveguide, electrode, well, drug, compound, beating rate, beating amplitude, rising time, falling time, beating period, IBD10, IBD50, IBD90, rising slope, falling slope, arrhythm\$2, cardioc\$2, sens\$3, analysis, concentration

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0029506 A1 (WANG et al) 04 February 2010 (04.02.2010) fig 4, para [0009], [0016], [0072], [0130], [0132], [0144], [0148], [0153], [0168]-[169], [0178]	1-3, 5-14
Y		4, 15
Y	US 2009/0142790 A1 (FANG et al) 04 June 2009 (04.06.2009) para [0292]	4
Y	US 2003/0211500 A1 (WOOSLEY) 13 November 2003 (13.11.2003) Table 2, para [0087]	15
A	US 2007/0042347 A1 (ROSEN et al) 22 February 2007 (22.02.2007) Abstract, para [0007]-[0011], [0013]	1-15
A	US 2004/0106095 A1 (THOMSON et al) 03 June 2004 (03.06.2004) para [0013], [0016], [0018], [0022], [0031], [0033], [0040], [0052]	1-15
A	US 2007/0212423 A1 (EPSTEIN et al) 13 September 2007 (13.09.2007) para [0136]-[0141]	1-15
A	US 2009/0017465 A1 (XU) 15 January 2009 (15.01.2009) para [0032], [0142]-[0147]	1-15

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
29 August 2011 (29.08.2011)

Date of mailing of the international search report

02 SEP 2011

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ACE150W1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2013/072439	International filing date (day/month/year) 28 November 2013	(Earliest) Priority Date (day/month/year) 27 November 2012
Applicant ACEA BIOSCEINCES, INC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 2C
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/072439

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12Q 1/02 (2014.01) USPC - 435/29 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) - C12Q 1/00, 02; C12M 1/00, 34; G01N 27/00, 02, 28, 30, 416, 417, 419, 33/483, 487 (2014.01) USPC - 435/29, 173.4, 287.1 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC - C12Q 1/025; G01N 33/4836, 48728, 5061 (2013.01) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Orbit, Google Patents, Google Scholar		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0039294 A1 (WANG et al) 17 February 2011 (17.02.2011) entire document	1-61
Y	WO 2012/043820 A1 (YASUDA et al) 05 April 2012 (05.04.2012) see machine translation	1-61
A	US 2011/0300569 A1 (LI et al) 08 December 2011 (08.12.2011) entire document	1-61
A	US 2010/0029506 A1 (WANG et al) 04 February 2010 (04.02.2010) entire document	1-61
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 04 February 2014		Date of mailing of the international search report 19 FEB 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

Electronic Acknowledgement Receipt

EFS ID:	24297299
Application Number:	12435569
International Application Number:	
Confirmation Number:	3664
Title of Invention:	Label-Free Monitoring of Excitation-Contraction Coupling and Excitable Cells Using Impedance Based Systems with Millisecond Time Resolution
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	59538
Filer:	Raymond C. Wagenknecht/Ramona DeRyan
Filer Authorized By:	Raymond C. Wagenknecht
Attorney Docket Number:	ACEA134U1
Receipt Date:	08-DEC-2015
Filing Date:	05-MAY-2009
Time Stamp:	15:47:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	ACEA134U1_IDS3_Transmittal.pdf	125094 24ab4cc339879dd38910fc4ce5702e8078e53d7e	no	5

Warnings:

Information:

1166

2	Information Disclosure Statement (IDS) Form (SB08)	ACEA134U1_IDS-3.pdf	613040	no	6
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Information:					
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4	Foreign Reference	WO2014_085727.pdf	11003306	no	106
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Warnings:					
Information:					
5	Foreign Reference	EP2291645.pdf	1454017	no	81
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6	Foreign Reference	WO2009_137440A1.pdf	5420806	no	119
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Information:					
7	Foreign Reference	WO2010_129725.pdf	3391930	no	155
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Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
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8	Foreign Reference	WO2011_146531.pdf	5794694	no	84
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Warnings:					
Information:					
9	Non Patent Literature	Berdondini_etal.pdf	788949	no	8
			a7feb5a969c1a5c94ca93b3ebd2596765acc21d7		
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Information:					
10	Non Patent Literature	Chang.pdf 1167	456011	no	5
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Warnings:					
Information:					
11	Non Patent Literature	Yang_et al.pdf	588452	no	6
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12	Non Patent Literature	PCTUS2009033801_ISR- WO_09July2010.pdf	431480	no	7
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Warnings:					
Information:					
13	Non Patent Literature	PCTUS2009042787_ISR- WO_24June2009.pdf	557002	no	10
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Warnings:					
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14	Non Patent Literature	PCTUS2011036877_ISR_02Sept 2011.pdf	107152	no	2
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Warnings:					
Information:					
15	Non Patent Literature	PCTUS2013072439_ISR_19Feb 2014.pdf	205876	no	2
			20846ad0aecc0f8338d6483315c5f8468fcb6085		
Warnings:					
Information:					
Total Files Size (in bytes):			38206906		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Wang et al.

Serial Number: 12/435,569

Filing Date: May 5, 2009

Title: LABEL-FREE MONITORING OF
EXCITATION-CONTRACTION
COUPLING AND EXCITABLE CELLS
USING IMPEDANCE BASED SYSTEMS
WITH MILLISECOND TIME
RESOLUTION

Group Art Unit: 1653

Examiner: Shannon L. Janssen

CONFIRMATION NO: 3664

FILED ELECTRONICALLY ON:
December 8, 2015

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §1.97

Commissioner:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

- A. ☒ *37 CFR §1.97(b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.
- B. ☐ *37 CFR §1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97(e) provided concurrently herewith;
-- OR --
 - ☐ a fee of \$180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR §1.97(d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in §1.97(e);
-- AND --
 - ii. a fee of \$180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97(e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under *37 CFR §§1.97(c)*;
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under *37 CFR §§1.97(d)*;
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under *37 C.F.R. § 1.97(e)(1)* as provided for under MPEP 609.04(b) V.
- E. ☐ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart

application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

- F. ☒ 37 CFR §1.98(a)(2). The content of the Information Disclosure Statement is as follows:
- ☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.
- OR --
- ☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.
- AND/OR --
- ☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).
- AND/OR --
- ☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).
- G. ☒ 37 CFR §1.98(a)(3). The Information Disclosure Statement includes non-English patents and/or references.
- ☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.
- ☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.
- OR --
- ☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____
- ☒ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.
- H. ☐ 37 CFR §1.98(d). Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:
- ☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.
- Application in which the information was submitted: _____
- Information Disclosure Statement(s) filed on: _____
- AND
- ☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 504352.

Respectfully submitted,

WAGENKNECHT IP LAW GROUP, PC

Dated: December 8, 2015

By: /Raymond Wagenknecht/
Raymond Wagenknecht
Registration No. 50,948

5677 Oberlin Drive, Suite 204
San Diego, CA 92121
Tel. 858-587-2510

e-mail: Ray@WagenIPLaw.com

ATTORNEY FOR APPLICANT

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	12435569
	Filing Date	2009-05-05
	First Named Inventor	Xiaobo Wang
	Art Unit	1653
	Examiner Name	Shannon L. Janssen
	Attorney Docket Number	ACEA134U1

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS						Remove
Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
	2					
	3					
	4					
	5					

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

6				
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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ² i	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							
	2							
	3							
	4							
	5							
	6							

If you wish to add additional Foreign Patent Document citation information please click the Add button

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

NON-PATENT LITERATURE DOCUMENTS			Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	HORVATH et al. "Monitoring of living cell attachment and spreading using reverse symmetry waveguide sensing." Applied Physics Letters, 2005, 86, 071101	
	2	OKA et al. "A new planar multielectrode array for extracellular recording: application to hippocampal acute slice." Journal of Neuroscience Methods, 1999, 93:61-67, Elsevier Science, B.V.	
	3		
	4		
	5		
	6		
	7		

If you wish to add additional non-patent literature document citation information please click the Add button [Add](#)

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Raymond Wagenknecht/	Date (YYYY-MM-DD)	2015-12-14
Name/Print	Raymond Wagenknecht	Registration Number	50948

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	24351348
Application Number:	12435569
International Application Number:	
Confirmation Number:	3664
Title of Invention:	Label-Free Monitoring of Excitation-Contraction Coupling and Excitable Cells Using Impedance Based Systems with Millisecond Time Resolution
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	59538
Filer:	Raymond C. Wagenknecht/Ramona DeRyan
Filer Authorized By:	Raymond C. Wagenknecht
Attorney Docket Number:	ACEA134U1
Receipt Date:	14-DEC-2015
Filing Date:	05-MAY-2009
Time Stamp:	14:47:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	ACEA134U1_IDS4_Transmittal.pdf	124745 8e25f2e6ff165a80e5ef13fd944dc5f7fe3bf077	no	5

Warnings:

Information:

1180

2	Information Disclosure Statement (IDS) Form (SB08)	ACEA134U1_IDS-4.pdf	612536 e1cebf29555d169c7b30f4f31d1d8e724058935a	no	6
Warnings:					
Information:					
A U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form. You may remove the form to add the required data in order to correct the Informational Message or if you chose not to, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Non Patent Literature	Horvath_etal.pdf	463741 aa23aad7c13bd16f6f6b5d9952f7f9c9d234a1a2	no	4
Warnings:					
Information:					
4	Non Patent Literature	Oka_etal.pdf	656085 70bf31099e63d4c9220b0d8318ff4ea8d48469b1	no	7
Warnings:					
Information:					
Total Files Size (in bytes):			1857107		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Wang et al.

Serial Number: 12/435,569

Filing Date: May 5, 2009

Title: LABEL-FREE MONITORING OF
EXCITATION-CONTRACTION
COUPLING AND EXCITABLE CELLS
USING IMPEDANCE BASED SYSTEMS
WITH MILLISECOND TIME
RESOLUTION

Group Art Unit: 1653

Examiner: Shannon L. Janssen

CONFIRMATION NO: 3664

FILED ELECTRONICALLY ON:
December 14, 2015

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §1.97

Commissioner:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

- A. ☒ *37 CFR §1.97(b)*. This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;
-- OR --
 - ☐ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.
- B. ☐ *37 CFR §1.97(c)*. Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b)*, above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97(e) provided concurrently herewith;
-- OR --
 - ☐ a fee of \$180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ *37 CFR §1.97(d)*. Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in §1.97(e);
-- AND --
 - ii. a fee of \$180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ *37 CFR §1.97(e)*. Statement.
- ☐ A statement is provided herewith to satisfy the requirement under *37 CFR §§1.97(c)*;
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under *37 CFR §§1.97(d)*;
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under *37 C.F.R. § 1.97(e)(1)* as provided for under MPEP 609.04(b) V.
- E. ☐ *Statement Under 37 C.F.R. §1.704(d)*. Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart

application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ 37 CFR §1.98(a)(2). The content of the Information Disclosure Statement is as follows:

☒ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☐ 37 CFR §1.98(a)(3). The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ 37 CFR §1.98(d). Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 504352.

Respectfully submitted,

WAGENKNECHT IP LAW GROUP, PC

Dated: December 14, 2015

By: /Raymond Wagenknecht/
Raymond Wagenknecht
Registration No. 50,948

5677 Oberlin Drive, Suite 204
San Diego, CA 92121
Tel. 858-587-2510

e-mail: Ray@WagenIPLaw.com

ATTORNEY FOR APPLICANT



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/435,569	05/05/2009	Xiaobo Wang	ACEA134U1	3664

59538 7590 12/16/2015
Wagenknecht IP Law Group, PC
5677 OBERLIN DRIVE, SUITE 204
SAN DIEGO, CA 92121

EXAMINER

JANSSEN, SHANNON L

ART UNIT	PAPER NUMBER
----------	--------------

1653

MAIL DATE	DELIVERY MODE
-----------	---------------

12/16/2015

PAPER

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.

Office Action Summary	Application No. 12/435,569	Applicant(s) WANG ET AL.	
	Examiner SHANNON JANSSEN	Art Unit 1653	

-- 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) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 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 05 May 2014.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ 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

- 5) ☒ Claim(s) 16-45 is/are pending in the application.
- 5a) Of the above claim(s) 30-39 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 16-29 and 40-45 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ 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).
- 12) ☐ 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

- 13) ☐ 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.

Attachment(s)

- | | |
|--|---|
| 1) ☐ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) ☒ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/25/13</u> . | 6) ☐ Other: ____. |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 5, 2014 has been entered.

Claim Status

Claims 16-45 are currently pending. Claims 30-39 have been withdrawn and claims 16-29 and 40-45 are currently under consideration. The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Applicants elected Group III, claims 24-29 and newly added claims 40-45 with traverse in the reply filed on February 27, 2012.

Claims 1-6, 11-14 and 30-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. However, claim 16 links inventions III-VI and upon indication of allowability, the restriction requirement between the linked inventions shall be withdrawn and any claims depending from or otherwise requiring all the limitations of the allowable linking claim will be rejoined.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 25, 2013 is being considered by the examiner.

Priority

The present application claims priority based on U.S. Provisional Application Nos. 61/191,684, filed on September 11, 2008 and 61/126,533, filed on May 5, 2008.

Withdrawn Objection(s)/Rejection(s)

Any objection or rejection presented in the Office Action mailed November 4, 2013 and not reiterated below is hereby withdrawn.

Invention as Claimed

One embodiment of the present invention is drawn to a method comprising a) providing a system for monitoring impedance of excitable cells in vitro comprising: i) a device for monitoring cell-substrate impedance comprising: a) a nonconductive substrate, b) one or more electrode arrays fabricated on said substrate, c) one or more wells on said substrate, wherein each of said one or more arrays is associated with one of said one or more wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array, ii) an impedance analyzer capable of impedance measurement at millisecond time resolution, iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device

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to said impedance analyzer, and iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer; b) adding excitable cells to said one or more wells; c) monitoring cell-substrate impedance of said one or more wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate; and d) resolving individual cycles of said excitable cells.

Another embodiment of the present invention is drawn to a method of determining whether a compound modulates a beating cycle of an excitable cell, comprising: a) providing a system for monitoring impedance of excitable cells in vitro comprising: i) a device for monitoring cell-substrate impedance comprising: a) a nonconductive substrate, b) one or more electrode arrays fabricated on said substrate, c) at least two wells on said substrate, wherein each of said one or more arrays is associated with each of said at least two wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array, ii) an impedance analyzer capable of impedance measurement at millisecond time resolution, iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer; b) adding excitable cells to said at least two wells; c) monitoring cell-substrate impedance of said at least two wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate; d) adding a compound suspected of modulation of the beating cycle to a first of said at least two wells to provide a test well, wherein a second well lacking compound is provided as a

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control well; e) resolving the beating cycles of both test well and control well; and d) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said compound modulates the beating cycle of the excitable cell.

New Rejection(s)

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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 negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-29 and 40-43 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Xu et al. (U.S. Patent Application Publication No. 2005/0153425, published July 14, 2005, previously cited), Yu et al. (Real-time monitoring of morphological changes in living cells by electronic cell sensor arrays: an approach to study G protein-coupled receptors, 2006, Anal. Chem., Vol 78, pp 35-43; cited by applicants in IDS), Banach et al. (Development of electrical activity in cardiac myocyte aggregates derived from mouse embryonic stem cells, Am. J. Physiol. Heart Circ. Physiol., 2003, Vol 284, pp H2114-H2123; previously cited) as evidenced by Hescheler et al. (Determination of electrical properties of ES cell-derived cardiomyocytes using MEAs, 2004, Journal of Electrophysiology, Vol 37, pp 110-116; previously cited), and Cantor (U.S. Patent No. 6,852,525, granted February 8, 2005; previously cited).

Regarding present **claims 16 and 24**, Xu et al. teach a method for performing real-time cell-based assays investigating the effects of one or more compounds on cells comprising providing a system for monitoring cell-substrate impedance comprising a nonconducting substrate, two or more electrode arrays fabricated on the substrate, where each of the two or more electrode arrays comprises two electrode structures, and at least two connection pads, each of which is located on an edge of the substrate, at least one multiple-well device monitoring cell-substrate impedance, in which at least two of the multiple wells each comprise an electrode array at the bottom of the well which are independently addressable, an impedance analyzer, a device station capable of engaging the one or more multiple-well devices and capable of selecting and electrically connecting electrode arrays within any of the multiple wells in to the impedance

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analyzer, and a software program to control the device station and perform data acquisition and data analysis on impedance values measured by the impedance analyzer, depositing cells on at least one of the two or more arrays of the device, adding one or more compounds to the one or more wells, providing at least one control well lacking compound, and monitoring cell-substrate impedance at regular or irregular time intervals on one or more arrays of the device to ascertain if the compound modulates the cell (see [0018-0020, 0023, 0024, 0029, 0031, 0032, 0036, 0130, 0131, 0134, 0244, 0246], for example). Xu et al. further teach wherein the system monitors cell attachment, morphology, degree of adhesion (e.g.: how well the cells are attached to the electrodes), and wherein measurements can be taken in timeframes of less than a second (i.e.: milliseconds; see [0125, 0250, 0255, 0259], for example).

Regarding present **claim 29**, Xu et al. provides methods for calculating a Cell Index for quantifying and comparing cell-substrate impedance (see [0021, 0140+], for example).

In addition, **Yu et al.** teach an impedance device for cellular assays, such as measuring changes in cell morphology, capable of millisecond time resolution and collecting measurements at 50 ms/well (see entire document, particularly p 37, col 2, para 4, Figure 1). Yu et al. also teach calculating a cell index based upon impedance measurements (see Materials and Methods, Impedance and Cell Index Measurements section).

While Xu et al. teach a method for performing real-time cell-based assays investigating the effects of one or more compound on cells, Xu et al. do not teach excitable cells which undergo excitation-contraction coupling or cardiomyocytes as recited in instant **claims 16-18, 24 and 25**, resolving individual cycles or beating cycles as recited in instant **claims 16 and 24**, at least 2 consecutive impedance measurements at millisecond (ms) time resolution as recited in

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instant **claims 19-23 and 40-43**, or identifying changes in beating amplitude or beating frequency as recited in instant **claims 26-29**.

However, **Banach** et al. teach a microelectrode array for monitoring the beating cycle of cardiomyocytes and further teach monitoring electrical activity from multiple electrodes simultaneously and continuously with ms time resolution and resolving signal delays of less than 10 ms (e.g.: at least two consecutive measurements less than 10 milliseconds apart since it is continuously measured and this could be broadly and reasonably interpreted as consecutive measurements; see entire document, particularly p H2115, cols 1-2, Figs. 1, 3, and 4, for example). Banach et al. teach monitoring the interspike interval to determine the beating frequency and measuring peak amplitude (e.g.: would be regular or irregular changes; see p 2115, col 1, para 2, p H2116, col 1, para 1). Banach et al. teach measuring the effect of different compounds on beating frequency and action potential in the form of FP_{MIN} to FP_{MAX} (e.g.: amplitude; see p H2115, col 2, para 1, p H2118, col 2, para 2, p H2119, p H2120, col 1, para 1, col 2, para 4, Figs. 4, 6, and 7). Banach et al. further state:

“In the present study, we analyzed the developmental changes of spontaneous electrical activity with repeated multielectrode recordings using substrate-integrated microelectrode arrays (MEAs). This technique allows not only the long-term culture of the preparation but also the analysis of the spatial electrophysiological differences within the preparation. In the present study, we analyzed different field potential (FP) parameters to characterize the development of the spontaneous electrical activity of multicellular aggregates of ESCs and their electrophysiological properties. Furthermore, the use of an ES cell line deficient in the expression of connexin43 ($Cx43^{-/-}$), the major cardiac gap junction protein, enabled us to distinguish developmental changes of the active, voltage-dependent membrane properties from changing passive components like the intercellular resistance.” See p H2114, col 2, Para 1.

In addition, Hescheler, which cites to the microelectrode array system taught by Banach et al. (see p 113, Fig. 3) and, regarding the arrays, state:

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“It may provide a new experimental model to study the impact of cell-cell interactions and growth factors as well as of extracellular matrix proteins. In addition, the cellular system described, may be useful as an in vitro assay for pharmacological investigations of chronotropic drugs and as a cellular system for studying cardiotoxic effects during embryogenesis in vitro.” See p 115, cols 1-2, bridging para.

Further, **Cantor** teaches a method comprising a) providing a system comprising microelectrodes on a substrate, such as a glass substrate (i.e.: nonconductive), for monitoring impedance of cells and further comprising a plurality of cloning cylinders bonded to the substrate to define wells for holding the cells (see col 3, lns 29-53, col 4, lns 4-15, col 9, lns 35-37, Figs. 7 and 9, for example) and a signal monitoring and processing means such as a computer (see col 5, lns 60+, col 6, lns 1-12); b) adding excitable cells, such as neuronal cells, to said one or more wells; c) monitoring impedance of said one or more wells using millisecond time resolution (since it monitors the opening and closing of ion channels which occurs in less than a millisecond; see col 2, lns 39+; and d) resolving individual cycles (e.g.: of ion channels opening, closing, and the cell returning to a resting state) of said excitable cells (e.g.: measuring impedance peaks in millisecond time resolution; see entire document, particularly col 2, lns 39+, col 3, lns 14-27, col 4, lns 26-46, col 5, lns 1-35, col 8, lns 14-44). Cantor further states:

“For example, voltage-gated Na^+ channels (among other ion channels) help make nerve cells electrically excitable and enable them to conduct action potentials. When the membrane of a cell with many Na^+ channels is partially depolarized by a momentary stimulus, some of the channels promptly open, allowing Na^+ ions to enter the cell. The influx of positive charge depolarizes the membrane further, thereby opening more channels, which admit more Na^+ , causing still further depolarization. This process continues in a self-amplifying fashion until the membrane potential has shifted from its resting value of about -70 mV all the way to the Na^+ equilibrium potential of about +50 mV. At that point, where the net electrochemical driving force for the flow of Na^+ is zero, the cell would come to a new resting state with all its Na^+ channels permanently open, if the open channel conformation were stable. The cell is saved from such a permanent electrical tetanus by the automatic inactivation of the Na^+ channels, which now gradually close and stay closed until the membrane potential has returned to its initial negative

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resting value. The whole cycle, from initial stimulus to return to the original resting state, takes a few milliseconds or less.” See col 2, lns 46+.

“Examining the membrane potential relative to time, an action potential exhibits various characteristics or parameters, including action potential rate (if cells spontaneously depolarize), action potential amplitude, and action potential shape, among others. Action potential rate refers to the frequency with which a cell produces an action potential (rapid depolarization). Action potential amplitude refers to the height of the peak depolarization that occurs in the course of the action potential. Action potential shape refers to the time course of the depolarization and repolarization.” See col 3, lns 14-24.

“The present invention permits detection and monitoring of membrane, chemical, and electrical characteristics of a cell. As noted at the outset, these characteristics include cell impedance (cell membrane capacitance and conductance), action potential parameters, cell membrane capacitance, cell membrane conductance, neuronal action potential, cellular metabolic products (hormones, neurotransmitters, waste products, etc.), and cell/substrate seal resistance. These electrical characteristics, in turn, correlate well with the metabolic state of the cell. The present invention, thus, provides an apparatus and method for monitoring cells and for monitoring the impact that an analyte has upon the metabolism of a cell. It is to be appreciated that such analytes include pharmaceutical agents, drugs, environmental factors, toxins, chemical agents, biological agents, viruses, and cellular adhesion promoters.” See Col 4, lns 25-45.

Therefore it would have been obvious to one of skill in the art at the time of the instant invention to measure the beating cycle of excitable cells such as cardiomyocytes at millisecond time resolution, to record multiple measurements over time in millisecond time resolution, to characterize the beating cycle of the cardiomyocytes and identify changes in beating amplitude and frequency by using a cell index, extrapolating a peak, and/or identifying data points where the first order derivative to time is zero.

One would have been motivated to characterize the beating cycle and to examine various parameters of the beating cycle, such as beating frequency and amplitude, or the beating frequency and amplitude relative to the number of cells (e.g.: cell index), in order to characterize the culture of beating cardiomyocytes *in vitro* as taught by Banach et al. (e.g.: for use as a model;

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see p H2114, col 2, para 1, for example) and to utilize the culture to characterize cardiotoxic effects of drugs as taught by Hescheler et al. (see above). In light of the fact that measuring the various peaks and rise and decay of a cardiac cycle will detail the condition of the heart, or in this case, the culture representing the heart, it would have been obvious to one of ordinary skill in the art to measure the peaks comprising the rise and decay of the cardiac cycle to gain a better determining of the state of the heart. Further, due to the inherent property of signals and peaks, it is well known that for a signal that has a rise and fall (e.g.: a peak), the first derivative yields a signal that crosses zero at the maximum peak height of the original signal. One would have been motivated to utilize impedance measurements because Xu et al. and Yu et al. teach that the impedance system can be used for real-time cell-based assays in high throughput, e.g., rather than just an end-point assay which limits the time resolution and number of time points for large library screening (see Xu et al. [0014, 0016, 0024, 0025, 0031, 0032], for example, and Yu et al. Abstract, p 36, col 1, para 2, for example) and Cantor teaches the need for electrodes which can monitor cellular changes including ion channel conductance (e.g.: which are responsible for the action potentials that cause cell beating; see above and col 2, lns 31-40).

One would have had a reasonable expectation for success because Banach et al. teach successfully establishing cultures of beating cardiomyocytes and measuring electrical properties of the cultures to establish beating cycle parameters and beating frequency, including changes in the parameters after administration of drugs, Cantor teaches that electrode arrays can be used to measure cell impedance, secretion of cellular products, monitoring of ion channels and action potentials, and monitoring of compounds which affect those parameters in millisecond time resolution (see above and cols 1-2), Xu et al. teach successfully using impedance to characterize

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cellular properties (see [0428], for example), and Yu et al. teach monitoring changes in cell morphology resulting from addition of ligands to the cells and that the impedance measurements were capable of ms time resolution.

Therefore the teachings of Xu et al., Yu et al., Banach et al. as evidenced by Hescheler et al., and Cantor render the present invention *prima facie* obvious.

Response to Arguments

Applicant's arguments filed May 5, 2014 have been fully considered but they are not persuasive for the following reasons. Applicants' arguments are presented in Italics.

Applicants assert that Xu et al. do not teach millisecond time resolution and that the other references do not cure these deficiencies and do not teach measuring cell-substrate impedance and rather teach measuring membrane potential (Response, pp 15+).

In response, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

It is also noted that newly cited Yu et al. does teach millisecond time resolution and measuring changes in morphology, as discussed supra. Since the beating of cardiomyocytes results in changes in cellular morphology and Yu et al. teach millisecond time resolution, it would be expected to be capable of measuring the beating cycle of cardiomyocytes.

Further, in the instant case, it is unclear how the references do not teach measuring cell-substrate impedance. It is held that measuring the impedance using the electrodes integrated into

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the substrate would constitute measuring the cell-substrate impedance. In addition, Xu et al. teach measuring cell substrate impedance. It would have been obvious to measure the impedance in ms time resolution as taught by the other cited references in order to measure the effects of compounds on the beating cycle of cardiomyocytes (e.g.: which occurs in ms time resolution), as discussed supra, particularly in view of Yu et al. Further, Xu et al. teach wherein each measurement can take place over a narrow time frame such as "less than one second" (i.e.: less than one second would be ms; see [0125]). Given the combined teachings of all the cited references, it would have been obvious to one of skill in the art to conduct measurements in ms time resolution in order to measure the beating cycle of cardiomyocytes. Further, the instant claims recite measuring a change in morphology. It is respectfully held that measuring the beating cycle of the cardiomyocyte inherently measures a change in morphology since the morphology of the cell changes during the beating cycle. Since Yu et al. teach measuring changes in cell morphology and ms time resolution, the combination of this teaching with the cited references would result in measuring the beating cycle in cardiomyocytes by measuring changes in cellular morphology in addition to changes in membrane potential. Therefore it is respectfully held that one would have had a reasonable expectation for success at arriving at the presently claimed invention.

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Claims 16-29 and 40-45 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Xu et al. (U.S. Patent Application Publication No. 2005/0153425, published July 14, 2005, previously cited), Yu et al. (Real-time monitoring of morphological changes in living cells by electronic cell sensor arrays: an approach to study G protein-coupled receptors, 2006, Anal. Chem., Vol 78, pp 35-43; cited by applicants in IDS), Banach et al. (Development of electrical activity in cardiac myocyte aggregates derived from mouse embryonic stem cells, Am. J. Physiol. Heart Circ. Physiol., 2003, Vol 284, pp H2114-H2123; previously cited) as evidenced by Hescheler et al. (Determination of electrical properties of ES cell-derived cardiomyocytes using MEAs, 2004, Journal of Electrocardiology, Vol 37, pp 110-116; previously cited), and Cantor (U.S. Patent No. 6,852,525, granted February 8, 2005; previously cited) as applied to claims 16-29 and 40-43 above, and further in view of Schecter (U.S. Patent Application Publication No. 2005/0182447, published August 18, 2005; previously cited).

The teachings of Xu et al., Yu et al., Banach et al., and Cantor et al. are discussed supra and are herein incorporated by reference.

Regarding present **claim 45**, Xu et al. teach setting the first order derivatives to zero (see [0209], for example).

While Xu et al., Yu et al., Banach et al., and Cantor teach a method for performing real-time cell-based assays investigating the effects of one or more compound on cells and measuring beating frequency and amplitude, Xu et al., Banach et al., and Cantor do not *specifically* teach determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay as recited in instant **claim 44** or identifying impedance data points at which the first order derivative to time is zero or about zero as recited in instant **claim 45**.

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However, **Schechter** teaches a method of monitoring beating cycle of the heart using impedance measurements and further teach calculating the derivative of impedance to time at 0 and the peak and delays in time to peak incidence and changes in the impedance waveform (e.g. time to onset of positive dZ/dt , time to peak Z , time to peak dZ/dt , which can be broadly and reasonably interpreted as rise in impedance and decay in impedance and determining a peak) and/or reductions in the quantity of the integral of Z or changes in the morphology of $Z(t)dt$ (see entire document, particularly [0048, 0049, 0060, 0077, 0086-0090, 0100-0101, 0118, 0136], Figs. 5, 6, 8-10, 12). Schechter further state:

“Derivation of impedance waveforms using implanted lead systems is well known in the art and has been described in the literature. Data acquisition can be accomplished, for example, by delivering pulses of 200 uA, 30 us pulse width at a frequency of 128 Hz applied to two electrodes positioned along one vector (electrode pairs) and measuring the resulting voltage between electrodes located along the same vector. These pulses will not depolarize myocardium, cause only limited battery drain and have a frequency with an acceptable signal to noise ratio. The resultant time dependent impedance, $Z(t)$ peaks when there is maximal systolic ventricular wall thickness and minimal intracardiac blood volume.” See [0048].

“The time dependent impedance signals or waveforms derived in this fashion relate to intrinsic myocardial properties. If signals are acquired between specific electrode pairs, the regional myocardial properties can be derived. The integrity of these waveforms may be subject to significant noise (poor signal to noise ratio) and inferior signal quality may result. This is especially true if data sampling occurs in a vector where there is impairment in myocardial contractile properties. Derivation of specific characteristics of these waveforms may suffice, even though overall signal quality is poor. Measurement of peak impedance and first and second order derivatives of impedance waveforms will relate to myocardial contractility. Assessment of the time required for a waveform to reach peak impedance will relate to myocardial synchrony if comparisons can be made to waveforms derived in alternate regions (e.g. right and left ventricular vectors).” See [0049].

Therefore it would have been obvious to one of skill in the art at the time of the instant invention to characterize the beating cycle of the cardiomyocytes and identify changes in beating

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amplitude and frequency by using a cell index, extrapolating a peak, and/or identifying data points where the first order derivative to time is zero.

One would have been motivated to characterize the beating cycle and to examine various parameters of the beating cycle, such as beating frequency and amplitude, or the beating frequency and amplitude relative to the number of cells (e.g.: cell index), in order to characterize the culture of beating cardiomyocytes *in vitro* as taught by Banach et al. (e.g.: for use as a model; see p H2114, col 2, para 1, for example) and to utilize the culture to characterize cardiotoxic effects of drugs as taught by Hescheler et al. (see above). In light of the fact that measuring the various peaks and rise and decay of a cardiac cycle will detail the condition of the heart, or in this case, the culture representing the heart, it would have been obvious to one of ordinary skill in the art to measure the peaks comprising the rise and decay of the cardiac cycle to gain a better determining of the state of the heart. Further, due to the inherent property of signals and peaks, it is well known that for a signal that has a rise and fall (e.g.: a peak), the first derivative yields a signal that crosses zero at the maximum peak height of the original signal. One would have been motivated to utilize impedance measurements because Xu et al. teach that the impedance system can be used for real-time cell-based assays in high throughput, e.g., rather than just an end-point assay which limits the time resolution and number of time points for large library screening (see [0014, 0016, 0024, 0025, 0031, 0032], for example) and Cantor teaches the need for electrodes which can monitor cellular changes including ion channel conductance (e.g.: which are responsible for the action potentials that cause cell beating; see above and col 2, lns 31-40).

One would have had a reasonable expectation for success because Schecter teach that it is routine and known to derive impedance waveforms (see *supra*).

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Therefore the teachings of Xu et al., Yu et al., Banach et al. as evidenced by Hescheler et al., Cantor, and Schechter render the present invention *prima facie* obvious.

Response to Arguments

Applicant's arguments filed December 13, 2012 have been fully considered but they are not persuasive for the following reasons. Applicants' arguments are presented in Italics.

Applicants appear to assert that Schechter is not relevant to the instant invention (Response, p 18).

In response, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In the instant case, Schechter et al. was merely relied on to demonstrate that it was routine and known to derive impedance waveforms (e.g.: whether the impedance results from the beating of a heart or from the beating cycle of cardiomyocyte culture representing the heart. It is respectfully submitted that it is merely a matter of data analysis and that the result would be the same regardless of where the measurement was taken (e.g.: it is a mathematical calculation).

Future Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANNON JANSSEN whose telephone number is (571)270-1303. The examiner can normally be reached on Monday-Friday 10:00AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571) 272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Shannon L Janssen
SLJ
/SHARMILA G. LANDAU/
Supervisory Patent Examiner, Art Unit 1653

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		12435569	
	Filing Date		2009-05-05	
	First Named Inventor	Xiaobo Wang		
	Art Unit	1636		
	Examiner Name	Shannon Janssen		
	Attorney Docket Number	ACE-134-U1		

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1636
Examiner Name	Shannon Janssen
Attorney Docket Number	ACE-134-U1

/S.J./	1	European Search Report for 09743426.0 dated 11/26/13, 6 pages	☐
/S.J./	2	KLOSS et al. "Microcavity array (MCA)-based biosensor chip for functional drug screening of 3D tissue models" Biosensors and Bioelectronics 23 (2008) 1473-1480.	☐
/S.J./	3	QIU et al. "Real-Time Monitoring Primary Cardiomyocyte Adhesion Based on Electrochemical Impedance Spectroscopy and Electrical Cell-Substrate Impedance Sensing" Anal. Chem. 2008, 80, 990-996.	☐
/S.J./	4	XING et al. "Dynamic Monitoring of Cytotoxicity on Microelectronic Sensors" Chem. Res. Toxicol., 2005, 18 (2), 154-161.	☐
/S.J./	5	YU et al. "Real-Time Monitoring of Morphological Changes in Living Cells by Electronic Cell Sensor Arrays: An Approach To Study G Protein-Coupled Receptors" Anal. Chem. 2006, 78, 35-43.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Shannon Janssen/	Date Considered	11/17/2015
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¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1636
Examiner Name	Shannon Janssen
Attorney Docket Number	ACE-134-U1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

- ☐ See attached certification statement.
- ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Raymond Wagenknecht/	Date (YYYY-MM-DD)	2013-11-25
Name/Print	Raymond Wagenknecht	Registration Number	50948

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Search Notes 	Application/Control No. 12435569	Applicant(s)/Patent Under Reexamination WANG ET AL.
	Examiner SHANNON JANSSEN	Art Unit 1653

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search - PALM, EAST	12/11/15	SLJ
USPAT, USPGPUB, EPO, JPO, DERWENT- updated dearch	12/8/15	SLJ
Pubmed, Scirus - updated search	12/8/15	SLJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WANG et al.	)	Application No.: 12/435,569
	)	
Filed: 5 May 2009	)	Examiner: Shannon Janssen
	)	
Docket No.: 10101-100108 (ACEA134U1)	)	Group Art Unit: 1653
	)	
Title: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION	)	Confirmation No.: 3664
COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED	)	
SYSTEMS WITH MILLISECOND TIME RESOLUTION	)	Customer No.: 59538
	)	

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NONFINAL OFFICE ACTION

Sir:

Applicant is responding to the Office Action mailed December 16, 2015 which provides a three month period for reply. This response is filed within six months and is therefore accompanied with a request for a three month extension of time.

AMENDMENTS TO THE CLAIMS begin on page 2 of this paper.

REMARKS / ARGUMENTS begin on page 12 of this paper.

AMENDMENTS TO THE CLAIMS

Changes to the claims are provided in the below listing of claims for the convenience of the examiner.

Listing of Claims

1-15. (Cancelled)

16. (Currently Amended) A method for assessing excitable cells in vitro, comprising

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) one or more wells on said substrate, wherein each of said one or more arrays is associated with one of said one or more wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) adding excitable cells to said one or more wells;

c) monitoring cell-substrate impedance of said one or more wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart; and

d) resolving individual cycles of said excitable cells.

17. (Previously presented) The method according to claim 16, wherein said excitable cells are cells that undergo excitation-contraction coupling.

18. (Original) The method according to claim 17, wherein said excitable cells are cardiomyocytes.

19. (Original) The method according to claim 16, wherein the step of monitoring impedance comprises performing impedance measurements at millisecond time resolution simultaneously across all wells.

20-22 (Cancelled)

23. (Currently Amended) The method according to claim [[22]]_1, wherein said at least two consecutive impedance measurements are less than 10 milliseconds apart.

24. (Currently Amended) A method of determining whether a compound modulates a beating cycle of an excitable cell, comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) at least two wells on said substrate, wherein each of said one or more arrays is associated with each of said at least two wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) adding excitable cells to said at least two wells;

c) monitoring cell-substrate impedance of said at least two wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;

d) adding a compound suspected of modulation of the beating cycle to a first of said at least two wells to provide a test well, wherein a second well lacking a compound that modulates the beating cycle is provided as a control well;

e) resolving the beating cycles of both test well and control well; and

d) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said compound modulates the beating cycle of the excitable cell.

25. (Original) The method according to claim 24, wherein the excitable cells are cardiomyocytes or embryonic stem cell derived cardiomyocytes.

26. (Original) The method according to claim 24, wherein said beating cycles are compared to identify changes in beating amplitude.

27. (Original) The method according to claim 24, wherein said beating cycles are compared to identify changes in beating frequency.

28. (Original) The method according to claim 27, wherein said changes in beating frequency are regular changes or irregular changes.

29. (Original) The method according to claim 24, further comprising determining a cell index for each of said test well and control well, wherein the step of

comparing said beating cycles comprises comparing said cell indexes between test well and control well.

30. (Withdrawn-Currently Amended) A method of characterizing rhythmic beating of a cardiomyocyte comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) one or more wells on said substrate, wherein each of said one or more arrays is associated with each of said one or more wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

- b) adding excitable cells to said one or more wells;
- c) monitoring cell-substrate impedance of said one or more wells in millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;
~~and~~
- d) determining a plurality of beating cycle peaks in a time unit; and
- e) comparing amplitude or frequency of said peaks over said time unit.

31. (Withdrawn) The method according to claim 30, wherein the step of determining a plurality of beating cycle peaks comprises determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay.

32. (Withdrawn) The method according to claim 30, further comprising determining a cell index for each of said one or more wells, wherein the step of determining a plurality of beating cycle peaks comprises for each cycle determining a rise in cell index, a decay in cell index and extrapolating each peak from each rise and decay.

33. (Withdrawn) The method according to claim 30, wherein beating cycle peaks are determined by identifying impedance data points at which the first order derivative to time is zero or close to zero.

34. (Withdrawn) The method according to claim 30, further comprising monitoring impedance of said one or more wells over seconds, minutes or hours, optionally wherein said monitoring of impedance in millisecond time resolution is performed within said monitoring over seconds, minutes or hours.

35. (Withdrawn - Currently Amended) A method of assessing genetic manipulation of an embryonic stem cell, comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) at least two wells on said substrate, wherein each of said one or more arrays is associated with each of said at least two wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) mutating embryonic stem cells to comprise a genetic mutation;

c) adding said mutated embryonic stem cells to a first well of said at least two wells to form a test well and control embryonic stem cells to a second of said at least two wells to form a control well;

c) monitoring cell-substrate impedance of said at least two wells in millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart; and

e) resolving the beating cycles of both test well and control well, if any; and

d) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said genetic mutation modulates embryonic stem cell differentiation.

36. (Withdrawn) The method according to claim 35, wherein said embryonic stem cell differentiation is differentiation into a cardiomyocyte.

37. (Withdrawn) The method according to claim 35, wherein said genetic mutation is selected from the group consisting of a genetic knock out, a knock down and an inserted transgene.

38. (Withdrawn-Currently Amended) A method for assessing and quantifying excitable cells in vitro, comprising

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) one or more wells on said substrate, wherein each of said one or more arrays is associated with one of said one or more wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) adding excitable cells to said one or more wells;

c) monitoring cell-substrate impedance of said one or more wells over a first time period, which is characterized as a longer time period comprising seconds, minutes or hours;

d) monitoring cell-substrate impedance of said one or more wells over a second time period in millisecond time resolution to detect changes in cell

morphology or attachment, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart:

e) determining a characteristic selected from the group consisting of cell attachment, cell growth and cell viability from monitoring over said first time period; and

f) resolving individual cycles of said excitable cells from monitoring over said second time period.

39. (Withdrawn) The method according to claim 38, wherein monitoring impedance over said second time period is performed at regular or irregular time intervals within monitoring impedance over said first time period.

40-42 (Cancelled)

43. (Currently Amended) The method according to claim ~~[[42]]~~ 24, wherein said at least two consecutive impedance measurements are less than 10 milliseconds apart.

44. (Currently amended) The method according to claim 24, wherein the step of resolving the beating cycles comprises determining a rise in impedance and a decay in impedance, and extrapolating a ~~peak~~ peak from each rise and decay.

45. (Previously presented) The method according to claim 24, wherein the step of resolving the beating cycles comprises determining beating cycle peaks by identifying impedance data points at which the first order derivative to time is zero or about zero.

REMARKS /ARGUMENTS

Claims 16, 23, 24, 30, 35, 38, 43, and 44 are amended; and claims 20-22 and 40-42 are cancelled. Claims 16-19, 23-39, and 43-45 remain pending.

I

Support for Amendments

Claims 16, 24, 30, 35, and 38 are amended to characterize millisecond time resolution as at least two consecutive impedance measurements less than 20 milliseconds apart. Support for the amendment may be found in para. [00113],

In some instances the at least two consecutive impedance measurements are less than 20 milliseconds apart.

Claims 23 and 43 are amended to update dependency in view of the above amendment.

Claim 44 is amended to correct a typographical error.

II

Response to Rejections under 35 USC §103

In order to establish a *prima facie* case of obviousness, the Examiner must show a combination of references that teach or suggest all of the claim limitations.¹ In addition,

¹ *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). “[O]bviousness requires a suggestion of *all limitations* in a claim.” *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974) (“to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art”)); *see also* MPEP 2143.03.

there must be objective reasoning for combining the teachings in the cited references.² The mere fact that certain teachings in cited references can be combined or that modifications of the prior art were within the ability of one of ordinary skill the art does not render a claimed invention obvious.³ A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.⁴ One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.⁵ If a *prima facie* case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed.⁶

A. Claims 16-29 and 40-43 are not obvious over Xu in view of Yu, and further in view of Banach as evidenced Hescheler and Cantor

Claims 16-29 and 40-43 are rejected under 35 U.S.C. §103(a) as being obvious over US 2005/0153425 published by Xu et al. (Xu), in view of 2006, Anal Chem (78):35-43 published by Yu et al (Yu), and in further in view of Am. J. Physiol. Heart Circ. Physiol., 2003, Vol. 284, pp. H2114-23 published by Banach et al. (Banach) as evidenced by Journal of Electrocardiology, Vol. 37, pp 110-116 published by Hescheler et al. (Hescheler) and US 6,852,525 by Cantor.

Specifically, Xu is cited as teaching methods for performing real-time cell-based assays for investigating the effects of one or more compounds using an impedance-based system. Xu is also cited as teaching such a system monitors cell attachment, morphology,

² *KSR International Co. v. Teleflex Inc. et al.* 127 S. Ct. 1727, 1741 (2007) (an obvious analysis must determine “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue”) citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (“Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”).

³ MPEP 2143.01, III and IV; *see also KSR, supra* at 1740-1741; *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (BPAI 1993).

⁴ *KSR International Co. v. Teleflex, Inc.* 550 U.S. 398, 421 (2007)

⁵ *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)

⁶ *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986)

degree of adhesion and at time frames of less than a second (citing paras. [0125], [0250], [0255], and [0259]). Xu is also cited as teaching methods for calculating Cell Index.

In addition, the Examiner adds that Yu also teaches an impedance device for cellular assays that collects measurements at 50 ms/well and calculates a cell index from impedance measurements.

The Examiner acknowledges that Xu does not teach the measurement of excitable cells that undergo excitation-contraction coupling nor cardiomyocytes, resolving individual cycles or beating cycles at millisecond time resolution or identifying changes in beating amplitude or beating frequency.

Banach is cited as teaching a microelectrode array for monitoring the beating cycle of cardiomyocytes, monitoring electrical activity from multiple electrodes simultaneously and continuously with millisecond time resolution, and resolving signal delays of less than 10 milliseconds. Banach is also cited as teaching monitoring an interspike interval to determine a beating frequency, measuring peak amplitude, and measuring the effect of different compounds on beating frequency and action potential in the form of $FP_{\min}$ to $FP_{\max}$.

Hescheler is cited as a further reference suggesting that the microelectrode array of Banach may provide a new experimental model to study a cellular system for studying cardiotoxic effects during embryogenesis in vitro.

Cantor is cited as teaching a method including a microelectrode system for monitoring impedance of cells, and monitoring impedance of the opening and closing of ion channels, which occurs in less than a millisecond, and resolving individual opening and closing cycles of excitable cells.

Applicant respectfully requests reconsideration of the rejection in view of the following remarks.

Claims 16 and 24 are amended to further define the impedance resolution as at least two consecutive impedance measurements less than 20 milliseconds apart. Thus, the rejection is addressed compared to cell-substrate impedance monitoring at 20 millisecond resolution.

It is not disputed that Xu provides a cell-substrate impedance monitoring system and methods for investigating effects of one or more compounds. However, Xu indicates

that cell-substrate impedance is primarily influenced by three main parameters: the number of cells seeded on the microelectronic sensor arrays, the shape of the cell, and the strength of cell adhesion to the electrode surface. Para. [0430]. Thus, changes in cell-substrate impedance occur from differences in attachment or spreading of cells on the device. Indeed, cell-substrate impedance measures the insulating effect of cells on electrodes, which changes in response to cell attachment/detachment or spreading on electrodes.

Compared to independent claims 16 and 24, while Xu does monitor changes in cell-substrate impedance that occur over longer periods of time, such as in case of cytotoxicity (e.g. cells detaching from electrodes after cell death), Xu does not teach or suggest conducting measurements at *20 millisecond time resolution*. Further, Xu does not teach that the individual or beating cycle of excitable cells can be resolved through cell-substrate impedance monitoring. The addition of Yu, Banach, Hescheler, and Cantor does not correct the deficiency of the rejection.

Yu provides an approach to measuring changes in cell morphology as a result of ligand-dependent GPCR activation. Abstract. Yu indicates the readout could be sampled in “as little as 50 ms/well.” Pg. 37, col. 2, para. 4.

Compared to claims 16 and 24, Yu does not teach millisecond resolution, characterized by *at least two consecutive impedance measurements less than 20 milliseconds apart*. Instead, Yu indicates the readout can be *as little as 50 ms/well*. That is, Yu confirms the cell substrate measurement cannot exceed 50 millisecond resolution; whereas Applicant more than doubles this resolution.

Banach analyzed the developmental changes of spontaneous *electrical activity* of multicellular aggregates of embryonic stem cells (ESCs) by extracellular recording of *field potential* using substrate integrated microelectrode arrays (MEAs). Pg. H2114, right col., Para 1. That is, Banach analyzed changes in electrical activity of ESC aggregates by measuring the membrane potential across the membrane channels of the cells. By recording changes in field potential an interspike interval (ISI) was determined and associated with the beating frequency. Pg. H2115, right col.

Compared to claims 16 and 24, Banach’s recording of *field potential*, to determine a beating frequency through an interspike interval (ISI) does not teach or suggest that

cell-substrate impedance can be used to resolve the individual or beating cycle of excitable cells. That is, the skilled artisan would appreciate that recording field potential and monitoring cell-substrate impedance are significantly different measurements. Specifically, field potential refers to a current sink or source that fluctuates when positive charges enter or leave a group of cells through membrane channels. In other words, it measures the electric potential between the interior of a cell and the exterior of a cell. In contrast, cell-substrate impedance assesses the insulating effect of a cell on electrodes through attachment or spreading of cells over a substrate/electrode. Since field potential recording and cell-substrate impedance monitoring are significantly different measurements, the ability to determine an interspike interval (ISI) through recording of field potential would not teach or suggest that cell-substrate impedance monitoring can resolve the individual or beating cycle of an excitable cell. That is, defining a beating cycle using membrane potential does not suggest a beating cycle can be resolved using cell-substrate impedance. Cell-substrate impedance does not measure electric potential across a membrane.

In addition, whether or not extracellular recording of field potential can be accomplished in millisecond time resolution is not material as to whether one could reasonably expect to achieve cell-substrate impedance monitoring at 20 millisecond time resolution. Again, they are different measurements. In furtherance of this, Yu indicated that in cell substrate impedance the readout could be sampled in “*as little as 50 ms/well*.” Pg. 37, col. 2, para. 4. In forming the rejection, one cannot merely pick the sensitivity of one assay and apply it to an entirely different assay that measures a different cell property. This would deprecate the claimed invention as discussed in *In re Fine*.⁷

Hescheler provides an overview of the use of extracellular recording of embryonic stem cell-derived cardiomyocytes using microelectrode arrays (MEAs). Abstract. As with Banach, Hescheler confirms at page 112, right col. that the signal in the extracellular recording approach involves recording *membrane potential*:

⁷ *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)

Although the signal recording with an extracellular electrode reflects local changes of the *membrane potential*, currents generated in the electrically connected neighboring tissue influence it. (emphasis added)

Thus, like Banach the teaching of Hescheler is limited to technologies that record membrane potential. Such approaches do not teach or suggest that cell-substrate impedance can be used to resolve the individual or beating cycle of excitable cells, such as cardiomyocytes.

Cantor provides a mammalian cell culture chamber having a cover for allowing for transfer of gasses and a sensor array. Col. 3, ll.29-33. Cantor's system provides an approach for screening and assaying broad classes of materials for their impact on cellular metabolism. Col. 5, ll. 1-3. In regards to the sensor array, Cantor utilizes a small microelectrode/ large reference electrode approach where measurement occurs solely at the small microelectrode. Col. 5, ll. 4-36. Cantor suggests that the small microelectrodes can be used to monitor the impedance of the individual cell, action potential parameters of the individual cell, the cell membrane capacitance, the cell membrane conductance, and the cell/substrate seal resistance, and cell membrane potential. Col. 5, ll. 13-22. Specifically, Cantor utilizes the cell culture chamber to detect changes in *membrane potential* in response to the opening of ion channels. Col. 10, ll.22-37. The opening and closing of voltage-gated Na⁺ channels takes only a few milliseconds. Col. 2, ll. 46-67.

For completeness, the Examiner cites Cantor as measuring impedance peaks in millisecond time resolution (citing col. 2, l.39+, col. 3, ll.14-27, col. 5, ll. 1-35, col. 8, ll. 14-44.) Office Action at pg. 9. Although Cantor does indicate that the device can measure impedance and that depolarization and repolarization of Na⁺ channels takes a few milliseconds or less, Cantor clarifies at Col. 3, ll. 14-23, that examining *membrane potential* is used to assess the opening and closing of these membrane channels since action potential amplitude corresponds to the height of peak depolarization and action potential shape corresponds to the time course of depolarization and repolarization. In other words, Cantor does not teach or suggest the use of *cell-substrate impedance at 20 millisecond time resolution* to resolve the individual or beating cycle of excitable cells. Instead, like Banach and Heschler, Cantor measures cell *membrane potential* relative to

time. Col. 3, l. 14. Again, cell membrane potential is an electrical property regarding the passage of ions through channels in the cell membrane, whereas the present invention monitors cell-substrate impedance, which is an impedance measurement directed towards the physical interaction between cell and substrate/electrode. That is, they are different measurements and measure different cellular effects. Therefore obtaining peaks associated with *membrane potential* does not teach or suggest resolving the individual or beating cycle of cardiomyocytes through *cell-substrate impedance* monitoring or achieving *cell-substrate impedance* monitoring at 20 millisecond time resolution as claimed.

As to the motivation to combine the references, the Examiner argues that one would have been motivated to use impedance measurements to characterize the beating cycle to examine various parameters because Xu and Yu teach the impedance system can be used for real-time cell-based assays in high throughput and Cantor teaches the need for electrodes which can monitor changes including ion channel conductance. Office Action at pg. 11. However, there is no reasonable basis for asserting the use of cell-substrate impedance for monitoring a cell beating cycle. The entire basis of all cardiac cell measurement taught in the references involves field potential. In particular the polarization/depolarization of the cells during the beating cycle. However, cell-substrate impedance does not measure field potential. Thus, whether or not cell-substrate impedance can be measured in real time and at high throughput does not change the basis of its measurement. The art does not show cell-substrate impedance measurement of a beating cell. Further, measuring ion channel conductance (Cantor) is not a cell-substrate impedance measurement.

Still further while the Examiner argues one would have been motivated to use cell-substrate impedance monitoring of a cell beating cycle, this would involve abandoning the technical approach of each reference relied upon that actual measured a beating cell for a technology that has not been demonstrated to successfully measure a beating cell.

In addition to the above distinctions, Applicant respectfully disagrees with the analysis by the Examiner in determining a reasonable expectation of success of combining the references in the Office Action at pg. 12 for the following reasons.

In regards to Banach, the Examiner argues that Banach teaches successfully establishing cultures of beating cardiomyocytes and measuring electrical properties of the cultures to establish beating cycle parameters and beating frequency. However, the entire basis for parameter measurement operates on a different principle. Banach measures membrane potential, but membrane potential is not measured by cell substrate impedance. Cell-substrate impedance measures the insulating effect of cells on electrodes not the electric potential between the interior and the exterior of a cell. They are entirely different measurements. Thus, whether or not Banach establishes a culture of beating cardiomyocytes it does not suggest one would expect to resolve beating cycles using cell-substrate impedance.

In regards to Cantor, the Examiner argues that Cantor teaches that electrode arrays can be used to measure cell impedance, secretion of cellular products, monitoring of ion channels and action potentials, and monitoring of compounds which affect those parameters in millisecond time resolution. While Cantor suggests that different parameters can be measured, the only effect referencing a millisecond time period would be the depolarization/repolarization of Na⁺ channels. Cantor indicates this is measured by recording membrane potential.

An expectation of success in recording membrane potential would not support a reasonable expectation of success of cell-substrate impedance monitoring of a cardiomyocyte population to resolve an individual or beating cycle of a cardiomyocyte population. As discussed above, each is a significantly different measurement and thus success of one is not a predictor of success of the other.

In regards to Xu, the Examiner argues that Xu teaches successfully using impedance to characterize cellular properties (citing para. [0428]). It is agreed Xu was able to assess mast cell activation through the use of cell-substrate impedance monitoring as discussed in para. [0428], but this does not teach 20 millisecond time resolution and does not teach resolving the individual or beating cycle of an excitable cell through the use of cell-substrate impedance technology. Whether or not some morphological change could be detected by applying Xu, does not suggest a beating cycle could be resolved.

In regards to Yu, the Examiner argues that Yu teaches monitoring changes in cell morphology resulting from addition of ligands to the cells and that impedance

measurements were capable of millisecond time resolution, but the addition of ligands to a cell does not cause cell beating. Further, Yu confirms the highest resolution is 50 milliseconds, which is 2.5 times slower than that claimed.

Accordingly, Applicant respectfully requests the rejection of independent claims 16, 24 and dependent claims 17-23, 25-29, and 40-45 be withdrawn.

Response to Response to Arguments

In responding to Applicants previously submitted arguments, Applicant agrees that the test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in the art (citing *In re Keller*).

First, the Examiner argues that it would have been expected that Yu would have been capable of measuring the beating cycle of cardiomyocytes because the beating of cardiomyocytes results in changes in morphology and that Yu teaches millisecond resolution.

Whether or not there is a morphological change during beating, does not teach or suggest to one that a cell beating cycle can be resolved using cell-substrate impedance. In Yu, changes in morphology were identified in response to ligand binding. In ligand binding, the cell morphology does not cycle within milliseconds.

Nonetheless, to expedite an allowance, the independent claims are amended to characterize millisecond time resolution as at least two consecutive impedance measurements less than 20 milliseconds apart. Yu indicates the readout could be sampled in “*as little as 50 ms/well.*” Since Yu could only achieve 50 ms resolution it would not have been obvious to achieve 20 millisecond resolution.

At the paragraph bridging pgs. 12 and 13, the Examiner argues that it is held that measuring impedance using the electrodes integrated into the substrate would constitute measuring cell substrate impedance. It is presumed this is to mean that cell-substrate impedance is interpreted as being an impedance measurement taken from an electrode at the substrate since the Examiner’s proposed interpretation is not well known and thus would not be appropriate for judicial notice.

For completeness, cell-substrate impedance would not be measured whenever an electrode is positioned on the substrate. Cell-substrate impedance requires interaction between the cell and electrode. In some technologies impedance electrodes are used to monitor cell metabolism by detecting changes in the conductivity of a solution in response to the release of metabolites. In other technologies, impedance is used to confirm sealing of a cell against a pore. Both of these have electrodes on a substrate but neither are cell-substrate impedance measurements as used in the art to which the invention belongs.

As to Xu, Xu does measure cell-substrate impedance but detecting cell death from detachment or detecting morphological changes would not have suggested to one of ordinary skill in the art that a cell beating cycle could be resolved at 20 ms resolution. Further, teaching a measurement of less than 1 second does not teach or suggest 20 ms resolution.

As to the Examiner holding that measuring the beating cycle of the cardiomyocyte inherently measures a change in morphology, whether or not excitation and contraction of a beating cell changes its morphology, the only technology used to resolve cell beating prior to Applicant involves cell membrane potential measurement, which is an entirely different measurement than cell-substrate impedance.

B. Claims 16-29 and 40-43 are not obvious over Xu in view of Yu, and further in view of Banach as evidenced Hescheler and Cantor, and further in view of Schecter

Claims 16-29 and 40-43 are rejected under 35 U.S.C. §103(a) as being obvious over US 2005/0153425 published by Xu et al. (Xu), in view of 2006, Anal Chem (78):35-43 published by Yu et al (Yu), in further in view of Am. J. Physiol. Heart Circ. Physiol., 2003, Vol. 284, pp. H2114-23 published by Banach et al. (Banach) as evidenced by Journal of Electrocardiology, Vol. 37, pp 110-116 published by Hescheler et al. (Hescheler) and US 6,852,525 by Cantor, and US 2005/0182447 by Schecter.

Specifically, the Examiner incorporates the arguments as to Xu, Yu, Banach and Cantor, but acknowledges the combination of references fails to teach determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay or identifying impedance data points at which the first order derivative to time is zero or about zero.

However, Schecter is cited as teaching a method of monitoring a beating cycle of the heart using impedance measurements and calculating the derivative of impedance to time at 0, peak and delays in time to peak incidence, and changes in the impedance waveform and/or reductions in the quantity of the integral of Z or changes in the morphology of $Z(t)(Dt)$.

The object of Schecter is to utilize impedance waveforms and corresponding impedance data to direct the programming of a cardiac resynchronization therapy (CRT). Para [0046]. That is, the impedance data is from an implanted pacemaker or defibrillator. Abstract. Schecter's methods involve optimizing acquisition of impedance signals between electrodes present on implanted lead systems, automatically determining which electrodes or electrode combinations acquire impedance waveforms that have the best signal to noise ratio, and characterizing data most representative of dysynchronous electromechanical events. Abstract. Since Schecter utilizes impedance signals from a patient's implant and not from a cell-substrate impedance device as claimed Schecter would not apply to the invention set forth in claims 16 or 24.

Accordingly, Applicant respectfully requests the rejection of independent claims 16, 24 and dependent claims 17-23, 25-29, and 40-45 be withdrawn.

III

Conclusion

Applicant believes that the application as currently presented is in a condition for allowance and such favorable action is respectfully requested. If the Examiner desires, Applicant welcomes a telephone interview to expedite prosecution and is available at the telephone number below. Recognizing that Internet communications are not secure, we

also authorize the USPTO to communicate with us concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file.

The Commissioner is hereby authorized to deduct the fee, any deficiency or credit any overpayment to Deposit Account No. 504352 for entry of this response.

Respectfully submitted,

WAGENKNECHT IP LAW GROUP, PC

Dated: June 16, 2016_____

By: /Raymond Wagenknecht
Raymond Wagenknecht
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ATTORNEYS FOR APPLICANT

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 10101-100108
Application Number 12/435,569	Filed May 5, 2009	
For LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION		
Art Unit 1653	Examiner Shannon L. Janssen	

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	\$200	\$100	\$50	\$ _____
☐ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ _____
☒ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ <u>700</u>
☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____
☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____

☒ Applicant asserts small entity status. See 37 CFR 1.27.
☐ Applicant certifies micro entity status. See 37 CFR 1.29.
 Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.
☐ A check in the amount of the fee is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Director has already been authorized to charge fees in this application to a Deposit Account.
☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to
 Deposit Account Number 5 04352.
☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.
☒ attorney or agent of record. Registration number 50948.
☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Raymond Wagenknecht/

Signature

June 16, 2016

Date

Raymond Wagenknecht

Typed or printed name

858-527-2510, ext. 201

Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☒ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	12435569			
Filing Date:	05-May-2009			
Title of Invention:	Label-Free Monitoring of Excitation-Contraction Coupling and Excitable Cells Using Impedance Based Systems with Millisecond Time Resolution			
First Named Inventor/Applicant Name:	Xiaobo Wang			
Filer:	Raymond C. Wagenknecht/Lori Ford			
Attorney Docket Number:	10101-100108			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 3 months with \$0 paid	2253	1	700	700
Miscellaneous:				
Total in USD (\$)				700

Electronic Acknowledgement Receipt

EFS ID:	26087331
Application Number:	12435569
International Application Number:	
Confirmation Number:	3664
Title of Invention:	Label-Free Monitoring of Excitation-Contraction Coupling and Excitable Cells Using Impedance Based Systems with Millisecond Time Resolution
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	59538
Filer:	Raymond C. Wagenknecht/Lori Ford
Filer Authorized By:	Raymond C. Wagenknecht
Attorney Docket Number:	10101-100108
Receipt Date:	16-JUN-2016
Filing Date:	05-MAY-2009
Time Stamp:	15:05:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$ 700
RAM confirmation Number	1542
Deposit Account	504352
Authorized User	WAGENKNECHT, RAYMOND

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		10101_100108_Filed_Response.pdf	181616 <div>7a69430a2d88404e812e70ccf5071270c156adcc</div>	yes	23
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	11	
	Applicant Arguments/Remarks Made in an Amendment		12	23	
Warnings:					
Information:					
2	Extension of Time	10101_100108_EOT.pdf	163718 <div>44916c2d4acf5226e9ffe254ef550119a39acbafe</div>	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30781 <div>9e3b0c7c96b6d65435ad5c0584bc34862029b0e9</div>	no	2
Warnings:					
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



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59538 7500 04/10/2017
Wagenknecht IP Law Group, PC
12396 WORLD TRADE DRIVE
SUITE 312
SAN DIEGO, CA 92128

EXAMINER

GHAFOORIAN, REZA

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 04/10/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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12/435,569

05/05/2009

Xiaobo Wang

10101-100108

3664

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	07/10/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
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Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

59538 7590 04/10/2017
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SUITE 312
SAN DIEGO, CA 92128

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/435,569	05/05/2009	Xiaobo Wang	10101-100108	3664

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	07/10/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
GHAFOORIAN, REZA	1636	506-010000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached. ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.	2. For printing on the patent front page, list (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____ (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____ 3 _____
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted: ☐ Issue Fee ☐ Publication Fee (No small entity discount permitted) ☐ Advance Order - # of Copies _____	4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above) ☐ A check is enclosed. ☐ Payment by credit card. Form PTO-2038 is attached. ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).
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5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/435,569	05/05/2009	Xiaobo Wang	10101-100108	3664

5538 7500 04/10/2017
Wagenknecht IP Law Group, PC
12396 WORLD TRADE DRIVE
SUITE 312
SAN DIEGO, CA 92128

EXAMINER

GHAFOORIAN, REZA

ART UNIT PAPER NUMBER

1636

DATE MAILED: 04/10/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 12/435,569	Applicant(s) WANG ET AL.	
	Examiner REZA GHAFORIAN	Art Unit 1636	AIA (First Inventor to File) Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to June 16, 2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 16-19,23-39 and 43-45. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
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)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☒ Examiner's Amendment/Comment |
| 2. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other _____. |
| 4. ☒ Interview Summary (PTO-413),
Paper No./Mail Date <u>20170325</u> . | |

/REZA GHAFORIAN/
Primary Examiner, Art Unit 1636

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Mr. Wagenknecht on March 23, 2017.

Please amend the claims as follows:

16. (Currently Amended) A method for assessing excitable cells in vitro, comprising
- a) providing a system for monitoring impedance of excitable cells in vitro, comprising:
- i) a device for monitoring cell-substrate impedance, comprising:
- a) a nonconductive substrate,
- b) one or more electrode arrays fabricated on said substrate,
- c) one or more wells on said substrate, wherein ~~each of said one or more arrays is associated with one~~ each of said one or more wells comprises said one or more electrode arrays, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said

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substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) adding excitable cells to said one or more wells;

c) monitoring cell-substrate impedance of said one or more wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart; and

d) resolving individual cycles of said excitable cells.

24. (Currently Amended) A method of determining whether a compound modulates a beating cycle of an excitable cell, comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

- b) one or more electrode arrays fabricated on said substrate,
 - c) at least two wells on said substrate, wherein ~~each of said one or more arrays is associated with one~~ each of said at least two wells comprises said one or more electrode arrays, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,
- ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,
 - iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and
 - (iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;
- b) adding excitable cells to said at least two wells;
 - c) monitoring cell-substrate impedance of said at least two wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;

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d) adding a compound suspected of modulation of the beating cycle to a first of said at least two wells to provide a test well, wherein a second well lacking a compound that modulates the beating cycle is provided as a control well;

e) resolving the beating cycles of both test well and control well; and

d) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said compound modulates the beating cycle of the excitable cell.

30. (Currently Amended) A method of characterizing rhythmic beating of a cardiomyocyte comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) one or more wells on said substrate, wherein ~~each of said one or more arrays is associated with one~~ each of said one or more wells comprises said one or more electrode arrays, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

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- ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,
- iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and
- (iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;
- b) adding excitable cells to said one or more wells;
- c) monitoring cell-substrate impedance of said one or more wells in millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;
- d) determining a plurality of beating cycle peaks in a time unit; and
- e) comparing amplitude or frequency of said peaks over said time unit.

35. (Currently Amended) A method of assessing genetic manipulation of an embryonic stem cell, comprising:

- a) providing a system for monitoring impedance of excitable cells in vitro, comprising:
 - i) a device for monitoring cell-substrate impedance, comprising:
 - a) a nonconductive substrate,
 - b) one or more electrode arrays fabricated on said substrate,

- c) at least two wells on said substrate, wherein ~~each of said one or more arrays is associated with one~~ each of said one or more wells comprises said one or more electrode arrays, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,
- ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,
- iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and
- [[iv)] a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;
- b) mutating embryonic stem cells to comprise a genetic mutation;
- c) adding said mutated embryonic stem cells to a first well of said at least two wells to form a test well and control embryonic stem cells to a second of said at least two wells to form a control well;
- c) monitoring cell-substrate impedance of said at least two wells in millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart; and

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e) resolving the beating cycles of both test well and control well, if any; and
d) comparing said beating cycles between said test well and control well,
wherein a difference in beating cycles indicates said genetic mutation modulates
embryonic stem cell differentiation.

38. (Currently Amended) A method for assessing and quantifying excitable
cells in vitro, comprising

a) providing a system for monitoring impedance of excitable cells in vitro,
comprising:

b) one or more electrode arrays fabricated on said substrate,
c) one or more wells on said substrate, wherein ~~each of said one or more~~
~~arrays is associated with one~~ each of said one or more wells comprises said one or
more electrode arrays, wherein each electrode array is individually addressable, further
wherein said substrate has a surface suitable for cell attachment, wherein said cell
attachment on said substrate can result in a detectable change in impedance between
electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond
time resolution,

iii) electronic circuitry that can engage said device and selectively connect said
two or more electrode arrays of said device to said impedance analyzer, and

[[()iv) a software program that controls said electronic circuitry and records and
analyzes data obtained from said impedance analyzer;

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- b) adding excitable cells to said one or more wells;
- c) monitoring cell-substrate impedance of said one or more wells over a first time period, which is characterized as a longer time period comprising seconds, minutes or hours;
- d) monitoring cell-substrate impedance of said one or more wells over a second time period in millisecond time resolution to detect changes in cell morphology or attachment wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;
- e) determining a characteristic selected from the group consisting of cell attachment, cell growth and cell viability from monitoring over said first time period; and
- f) resolving individual cycles of said excitable cells from monitoring over said second time period.

Rejoinder

Claims 30-39 have been rejoined and examined on merits.

Allowable Subject Matter

Claims 16-19, 23-39 and 43-45 are allowed.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006);

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see also *KSR*, 550 U.S. at 418, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval).

Applicants' arguments are persuasive with respect to the teaching of the prior art. Xu does not teach millisecond time resolution but conducts measurements over a long period of time and does not teach identifying changes in beating amplitude or beating frequency. Banach is directed to a different measuring convention and teaches a method of measuring membrane potential across membrane channels of cells, i.e., measuring field potential not cell-substrate impedance. Yu teaches measurements "as little as" 50 millisecond resolution." Arguably, Yu teaches away from measuring impedance at lower resolution because it requires "as little as" 50 ms resolution. Hecheler discloses membrane potential recording which constitute a different measurement convention than impedance measurement. Cantor teaches measuring membrane potential using small electrodes and that small electrodes may be used to measure impedance. But Cantor does not teach or is enabling for cell-substrate impedance at 20 ms time resolution to resolve the individual or beating cycle of excitable cells.

Accordingly, a *prima facie* case of obviousness is not established by combining the instant references because in light of the foregoing, the prior art references do not uniformly represent analogous art and there is no reasonable expectation that the combination of the teachings of the references would yield a method for measuring impedance using 20 ms resolution to resolve the individual or beating cycle of excitable cells.

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It can be argued that given the teaching of Xu, it would be obvious to optimize the time resolution to 20 ms resolution. However, the optimization concept does not apply because 20 millisecond resolution is considered a results-effective variable. (See, MPEP 2144.05 and *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977), the CCPA held that a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation, because “obvious to try” is not a valid rationale for an obviousness finding. The argument of whether the claim limitations are obvious because optimization of ranges (here, optimization of millisecond resolution) are obvious to a skilled artisan also does not apply because a *prima facie* case is not established by combining the references and in light of the following.

With respect to an optimization argument, the limitation of at least two consecutive and less than 20 millisecond resolution to detect changes in cell morphology or cell attachment is results-effective variable because “significant reconfiguration of a traditional impedance-based system is required to obtain millisecond time resolution,” “advances in multiple steps are required to achieve millisecond time resolution, including the impedance measurement circuitry together with electronic switching circuitry,” “[t]echnological advances are further required when performing millisecond time resolution over multiple wells,” “comparing two impedance analyzers, one for impedance measurement of 96 wells with millisecond resolution and another for impedance measurement of a single well with millisecond time resolution,

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the one for 96 well measurement is effectively 96-times faster than one for a single well measurement since it is required to have a capability for performing impedance measurement for all 96 wells with millisecond time resolution” and with millisecond time resolution for impedance measurement “[i]t becomes possible to resolve individual beating cycles of cardiomyocytes cultured on electrodes.” See, specification, [00114]-[00116].

The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. In *re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). Upon consideration of the entire record and taking into account applicant’s arguments, it is the decision of the Examiner that the instant claims are patentable because the evidence provided by Applicants are more convincing than the evidence which is offered in opposition to it.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Any inquiry concerning this communication or earlier communications from the examiner should be directed to REZA GHAFORIAN whose telephone number is (571)270-1624. The examiner can normally be reached on Monday-Friday 6 AM-3 PM EST.

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Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Gussow can be reached on (571)272-6047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REZA GHAFORIAN/
Primary Examiner, Art Unit 1636

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2012. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	12435569
	Filing Date	2009-05-05
	First Named Inventor	Xiaobo Wang
	Art Unit	1653
	Examiner Name	Shannon L. Janssen
	Attorney Docket Number	ACEA134U1

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Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1	20140203818		2014-06-24	Wang et al.	
	2	20060161073		2006-07-20	Singer et al.	
	3	20090142790		2009-06-04	Fang et al.	
	4	20030211500		2003-11-13	Woosley et al.	
	5	20070042347		2007-02-22	Rosen et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

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First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

6	20040106095	2004-06-03	Thomson et al.
7	20070212423	2007-09-13	Epstein et al.
8	20090017465	2009-01-15	Xu et al.

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2012/043820	WO		2012-04-05	Natl Univ Corp Tokyo Med & Dent Univ		×
	2	2014/085727	WO		2014-06-05	ACEA Biosciences, Inc.		☐
	3	2291645	EP		2015-09-09	ACEA Biosciences, Inc.		☐
	4	2009/137440	WO		2009-11-12	ACEA Biosciences, Inc.		☐
	5	2010/129725	WO		2009-11-11	ACEA Biosciences, Inc.		☐
	6	2011/146531	WO		2011-11-24	ACEA Biosciences, Inc.		☐

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	BERDONDINI et al. "High-density electrode array for imaging in vitro electrophysiological activity." Biosensors and Bioelectronics, 2005, 21:167-174	
	2	CHANG et al. "Impedimetric monitoring of cell attachment on interdigitated microelectrodes." Sensors and Actuators, 2005, B 105:159-163	
	3	YANG et al. "A novel microfluidic impedance assay for monitoring endothelin-induced cardiomyocyte hypertrophy." Biosensors and Bioelectronics, 2007, 22:1688-1693	
	4	PCT/US2009/033801 International Search Report and Written Opinion mailed 09 July 2010	
	5	PCT/US2009/042787 International Search Report and Written Opinion mailed 24 June 2009	
	6	PCT/US2011/036877 International Search Report mailed 02 September 2011	
	7	PCT/US2013/072439 International Search Report mailed 19 February 2014	

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EXAMINER SIGNATURE

Examiner Signature	/REZA GHAFORIAN/	Date Considered	03/25/2017
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
Art Unit	1653
Examiner Name	Shannon L. Janssen
Attorney Docket Number	ACEA134U1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Raymond Wagenknecht/	Date (YYYY-MM-DD)	2015-12-08
Name/Print	Raymond Wagenknecht	Registration Number	50948

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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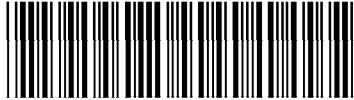
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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

<i>Index of Claims</i> 	Application/Control No. 12435569	Applicant(s)/Patent Under Reexamination WANG ET AL.
	Examiner REZA GHAFORIAN	Art Unit 1636

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant			☐ CPA			☒ T.D.			☐ R.1.47		
CLAIM		DATE									
Final	Original	03/24/2017									
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<p align="center"><i>Index of Claims</i></p> 	Application/Control No. 12435569	Applicant(s)/Patent Under Reexamination WANG ET AL.
	Examiner REZA GHAFORIAN	Art Unit 1636

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CLAIM		DATE								
Final	Original	03/24/2017								
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	42	-								
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	44	=								
	45	=								

Search Notes 	Application/Control No. 12435569	Applicant(s)/Patent Under Reexamination WANG ET AL.
	Examiner Reza Ghafoorian	Art Unit 1636

CPC- SEARCHED		
Symbol	Date	Examiner
G01N 33/4836	3/25/2017	/rg/

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
A classification search was not conducted.			

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search - PALM, EAST	12/11/15	SLJ
USPAT, USPGPUB, EPO, JPO, DERWENT- updated search	12/8/15	SLJ
Pubmed, Scirus - updated search	12/8/15	SLJ
Prior art search was conducted in EAST (including a text limited search of class/subclass 506/10) and PALM. Search results are attached.	3/25/2017	/rg/
Inventor search was conducted in EAST and PALM. Search results are attached.	3/25/2017	/rg/

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
506	10	3/25/2017	/rg/

	/REZA GHAFORIAN/ Primary Examiner.Art Unit 1636
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INTERFERENCE SEARCH

US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
USPAT and USPGPUB text search.	See, EAST search results.	3/25/2017	/rg/

/REZA GHAFORIAN/
Primary Examiner.Art Unit 1636

PALM Resource Center

Inventor Information for 12/435569

Inventor Name	City	State/Country
WANG, XIAOBO	SAN DIEGO	CALIFORNIA
ABASSI, YAMAA A.	SAN DIEGO	CALIFORNIA
LI, BIAO	SAN DIEGO	CALIFORNIA
ZHANG, WEN FU	SAN DIEGO	CALIFORNIA
XU, XIAO	SAN DIEGO	CALIFORNIA

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	167	((("WANG") near3 ("Xiaobo"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/03/25 09:51
L2	37	((("ABASSI") near3 ("Yama"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/03/25 09:51
L3	17	((("XI") near3 ("Biao"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/03/25 09:51
L4	364	((("ZHANG") near3 ("Wen"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/03/25 09:51
L5	248	((("XU") near3 ("Xiao"))).INV.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/03/25 09:51
L13	57	506/10.ccls. and impedance	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2017/03/25 09:52
L14	5	506/10.ccls. and impedance and excitable cells	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2017/03/25 09:52
L15	471	impedance and excitable cells	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2017/03/25 09:52
L17	186	impedance and excitable cells and millisecond	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2017/03/25 09:52
L18	33	impedance.clm. and excitable cells and millisecond	US-PGPUB; USPAT; EPO; JPO; DERWENT	ADJ	ON	2017/03/25 09:53

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L6	37	((("ABASSI") near3 ("Yama"))).INV.	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:51
L7	17	((("XI") near3 ("Biao"))).INV.	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:51
L8	364	((("ZHANG") near3 ("Wen"))).INV.	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:51
L9	248	((("XU") near3 ("Xiao"))).INV.	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:51
L10	167	((("WANG") near3 ("Xiaobo"))).INV.	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:51
L11	1206	506/10.ccls.	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:51
L12	50	506/10.ccls. and impedance	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:51
L16	465	impedance and excitable cells	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:52
L19	33	impedance.clm. and excitable cells and millisecond	US-PGPUB; USPAT	ADJ	ON	2017/03/25 09:53

C:\Users\rghafoorian\Documents\EAST\Workspaces\12435569.wsp

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2012. OMB 0651-0031

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	12435569
	Filing Date	2009-05-05
	First Named Inventor	Xiaobo Wang
	Art Unit	1653
	Examiner Name	Shannon L. Janssen
	Attorney Docket Number	ACEA134U1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

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Attorney Docket Number	ACEA134U1

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Art Unit	1653
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NON-PATENT LITERATURE DOCUMENTS

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	HORVATH et al. "Monitoring of living cell attachment and spreading using reverse symmetry waveguide sensing." Applied Physics Letters, 2005, 86, 071101	
	2	OKA et al. "A new planar multielectrode array for extracellular recording: application to hippocampal acute slice." Journal of Neuroscience Methods, 1999, 93:61-67, Elsevier Science, B.V.	
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EXAMINER SIGNATURE

Examiner Signature	/REZA GHAFORIAN/	Date Considered	03/25/2017
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
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Application Number	12435569
Filing Date	2009-05-05
First Named Inventor	Xiaobo Wang
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See attached certification statement.

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Signature	/Raymond Wagenknecht/	Date (YYYY-MM-DD)	2015-12-14
Name/Print	Raymond Wagenknecht	Registration Number	50948

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AMENDMENTS TO THE CLAIMS

Changes to the claims are provided in the below listing of claims for the convenience of the examiner.

Listing of Claims

1-15. (Cancelled)

16. (Currently Amended) A method for assessing excitable cells in vitro, comprising

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) one or more wells on said substrate, wherein each of said one or more arrays is associated with one of said one or more wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) adding excitable cells to said one or more wells;

c) monitoring cell-substrate impedance of said one or more wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart; and

d) resolving individual cycles of said excitable cells.

17. (Previously presented) The method according to claim 16, wherein said excitable cells are cells that undergo excitation-contraction coupling.

18. (Original) The method according to claim 17, wherein said excitable cells are cardiomyocytes.

19. (Original) The method according to claim 16, wherein the step of monitoring impedance comprises performing impedance measurements at millisecond time resolution simultaneously across all wells.

20-22 (Cancelled)

23. (Currently Amended) The method according to claim ~~[[22]]~~1, wherein said at least two consecutive impedance measurements are less than 10 milliseconds apart.

24. (Currently Amended) A method of determining whether a compound modulates a beating cycle of an excitable cell, comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) at least two wells on said substrate, wherein each of said one or more arrays is associated with each of said at least two wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) adding excitable cells to said at least two wells;

c) monitoring cell-substrate impedance of said at least two wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;

d) adding a compound suspected of modulation of the beating cycle to a first of said at least two wells to provide a test well, wherein a second well lacking a compound that modulates the beating cycle is provided as a control well;

e) resolving the beating cycles of both test well and control well; and

d) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said compound modulates the beating cycle of the excitable cell.

25. (Original) The method according to claim 24, wherein the excitable cells are cardiomyocytes or embryonic stem cell derived cardiomyocytes.

26. (Original) The method according to claim 24, wherein said beating cycles are compared to identify changes in beating amplitude.

27. (Original) The method according to claim 24, wherein said beating cycles are compared to identify changes in beating frequency.

28. (Original) The method according to claim 27, wherein said changes in beating frequency are regular changes or irregular changes.

29. (Original) The method according to claim 24, further comprising determining a cell index for each of said test well and control well, wherein the step of

comparing said beating cycles comprises comparing said cell indexes between test well and control well.

30. (Withdrawn-Currently Amended) A method of characterizing rhythmic beating of a cardiomyocyte comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) one or more wells on said substrate, wherein each of said one or more arrays is associated with each of said one or more wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

- b) adding excitable cells to said one or more wells;
- c) monitoring cell-substrate impedance of said one or more wells in millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;
~~and~~
- d) determining a plurality of beating cycle peaks in a time unit; and
- e) comparing amplitude or frequency of said peaks over said time unit.

31. (Withdrawn) The method according to claim 30, wherein the step of determining a plurality of beating cycle peaks comprises determining a rise in impedance and a decay in impedance and extrapolating a peak from each rise and decay.

32. (Withdrawn) The method according to claim 30, further comprising determining a cell index for each of said one or more wells, wherein the step of determining a plurality of beating cycle peaks comprises for each cycle determining a rise in cell index, a decay in cell index and extrapolating each peak from each rise and decay.

33. (Withdrawn) The method according to claim 30, wherein beating cycle peaks are determined by identifying impedance data points at which the first order derivative to time is zero or close to zero.

34. (Withdrawn) The method according to claim 30, further comprising monitoring impedance of said one or more wells over seconds, minutes or hours, optionally wherein said monitoring of impedance in millisecond time resolution is performed within said monitoring over seconds, minutes or hours.

35. (Withdrawn - Currently Amended) A method of assessing genetic manipulation of an embryonic stem cell, comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) at least two wells on said substrate, wherein each of said one or more arrays is associated with each of said at least two wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) mutating embryonic stem cells to comprise a genetic mutation;

c) adding said mutated embryonic stem cells to a first well of said at least two wells to form a test well and control embryonic stem cells to a second of said at least two wells to form a control well;

c) monitoring cell-substrate impedance of said at least two wells in millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart; and

e) resolving the beating cycles of both test well and control well, if any; and

d) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said genetic mutation modulates embryonic stem cell differentiation.

36. (Withdrawn) The method according to claim 35, wherein said embryonic stem cell differentiation is differentiation into a cardiomyocyte.

37. (Withdrawn) The method according to claim 35, wherein said genetic mutation is selected from the group consisting of a genetic knock out, a knock down and an inserted transgene.

38. (Withdrawn-Currently Amended) A method for assessing and quantifying excitable cells in vitro, comprising

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

- a) a nonconductive substrate,
- b) one or more electrode arrays fabricated on said substrate,
- c) one or more wells on said substrate, wherein each of said one or more arrays is associated with one of said one or more wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

(iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;

b) adding excitable cells to said one or more wells;

c) monitoring cell-substrate impedance of said one or more wells over a first time period, which is characterized as a longer time period comprising seconds, minutes or hours;

d) monitoring cell-substrate impedance of said one or more wells over a second time period in millisecond time resolution to detect changes in cell

morphology or attachment, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart:

e) determining a characteristic selected from the group consisting of cell attachment, cell growth and cell viability from monitoring over said first time period; and

f) resolving individual cycles of said excitable cells from monitoring over said second time period.

39. (Withdrawn) The method according to claim 38, wherein monitoring impedance over said second time period is performed at regular or irregular time intervals within monitoring impedance over said first time period.

40-42 (Cancelled)

43. (Currently Amended) The method according to claim ~~[[42]]~~ 24, wherein said at least two consecutive impedance measurements are less than 10 milliseconds apart.

44. (Currently amended) The method according to claim 24, wherein the step of resolving the beating cycles comprises determining a rise in impedance and a decay in impedance, and extrapolating a ~~peak~~ peak from each rise and decay.

45. (Previously presented) The method according to claim 24, wherein the step of resolving the beating cycles comprises determining beating cycle peaks by identifying impedance data points at which the first order derivative to time is zero or about zero.



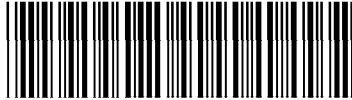
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BIB DATA SHEET

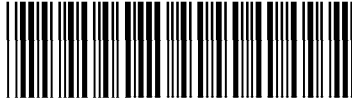
CONFIRMATION NO. 3664

SERIAL NUMBER 12/435,569	FILING or 371(c) DATE 05/05/2009 RULE	CLASS 506	GROUP ART UNIT 1636	ATTORNEY DOCKET NO. 10101-100108	
APPLICANTS INVENTORS Xiaobo Wang, San Diego, CA; Yama A. Abassi, San Diego, CA; Biao Xi, San Diego, CA; Wen Fu Zhang, San Diego, CA; Xiao Xu, San Diego, CA; ** CONTINUING DATA ***** This appln claims benefit of 61/191,684 09/11/2008 and claims benefit of 61/126,533 05/05/2008 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 05/14/2009					
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and /REZA GHAFORIAN/ Acknowledged Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 42	TOTAL CLAIMS 39	INDEPENDENT CLAIMS 1
ADDRESS Wagenknecht IP Law Group, PC 12396 WORLD TRADE DRIVE SUITE 312 SAN DIEGO, CA 92128 UNITED STATES					
TITLE Label-Free Monitoring of Excitation-Contraction Coupling and Excitable Cells Using Impedance Based Systems with Millisecond Time Resolution					
FILING FEE RECEIVED 1301	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		

<i>Index of Claims</i> 	Application/Control No. 12435569	Applicant(s)/Patent Under Reexamination WANG ET AL.
	Examiner REZA GHAFORIAN	Art Unit 1636

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant				☐ CPA		☒ T.D.		☐ R.1.47	
CLAIM		DATE							
Final	Original	03/24/2017	05/09/2017						
	1	-	-						
	2	-	-						
	3	-	-						
	4	-	-						
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	31	=	=						
	32	=	=						
	33	=	=						
	34	=	=						
	35	=	=						
	36	=	=						

<i>Index of Claims</i> 	Application/Control No. 12435569	Applicant(s)/Patent Under Reexamination WANG ET AL.
	Examiner REZA GHAFORIAN	Art Unit 1636

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant				☐ CPA				☒ T.D.				☐ R.1.47			
CLAIM		DATE													
Final	Original	03/24/2017	05/09/2017												
	37	=	=												
	38	=	=												
	39	=	=												
	40	-	-												
	41	-	-												
	42	-	-												
	43	=	=												
	44	=	=												
	45	=	=												

Issue Classification 	Application/Control No. 12435569	Applicant(s)/Patent Under Reexamination WANG ET AL.
	Examiner REZA GHAFORIAN	Art Unit 1636

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION									
CLASS		SUBCLASS				CLAIMED					NON-CLAIMED				
435		4				C	4	0	B	30 / 06 (2006.01.01)					
CROSS REFERENCE(S)						G	0	1	N	7 / 00 (2006.01.01)					
						C	1	2	Q	1 / 00 (2006.01.01)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)														
506	10														
422	83														

NONE		Total Claims Allowed:	
		24	
(Assistant Examiner)	(Date)		
/REZA GHAFORIAN/ Primary Examiner.Art Unit 1636	05/09/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	16	1



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/435,569	05/05/2009	Xiaobo Wang	10101-100108	3664

59538 7590 05/15/2017
Wagenknecht IP Law Group, PC
12396 WORLD TRADE DRIVE
SUITE 312
SAN DIEGO, CA 92128

EXAMINER

GHAFOORIAN, REZA

ART UNIT	PAPER NUMBER
----------	--------------

1636

NOTIFICATION DATE	DELIVERY MODE
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05/15/2017

ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

office@wageniplaw.com
docketing@wageniplaw.com

**Corrected
Notice of Allowability**

Application No.
12/435,569

Applicant(s)
WANG ET AL.

Examiner
REZA GHAFORIAN

Art Unit
1636

**AIA (First Inventor to File)
Status**
No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to internal communication dated April 21, 2017.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 16-19, 23-39 and 43-45. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
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)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material
4. ☒ Interview Summary (PTO-413),
Paper No./Mail Date 20170509.
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/REZA GHAFORIAN/
Primary Examiner, Art Unit 1636

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephonic interview with Raymond Wagenknecht on May 9, 2017.

The application has been amended as follows:

Claim 23. (Currently Amended) The method according to claim ~~[[1]]~~ 16, wherein said at least two consecutive impedance measurements are less than 10 milliseconds apart.

Claim 24. (Currently Amended) A method of determining whether a compound modulates a beating cycle of an excitable cell, comprising:

- a) providing a system for monitoring impedance of excitable cells in vitro, comprising:
 - i) a device for monitoring cell-substrate impedance, comprising:
 - a) a nonconductive substrate,
 - b) one or more electrode arrays fabricated on said substrate,

- c) at least two wells on said substrate, wherein each of said one or more arrays is associated with each of said at least two wells, wherein each electrode array is individually addressable, further wherein said substrate has a surface suitable for cell attachment, wherein said cell attachment on said substrate can result in a detectable change in impedance between electrodes within each electrode array,
- ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,
- iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and
- [[()] iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;
- b) adding excitable cells to said at least two wells;
- c) monitoring cell-substrate impedance of said at least two wells using millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart;
- d) adding a compound suspected of modulation of the beating cycle to a first of said at least two wells to provide a test well, wherein a second well lacking a compound that modulates the beating cycle is provided as a control well;
- e) resolving the beating cycles of both test well and control well; and

Art Unit: 1636

[[d]] f) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said compound modulates the beating cycle of the excitable cell.

Claim 35. (Currently Amended) A method of assessing genetic manipulation of an embryonic stem cell, comprising:

a) providing a system for monitoring impedance of excitable cells in vitro, comprising:

i) a device for monitoring cell-substrate impedance, comprising:

a) a nonconductive substrate,

b) one or more electrode arrays fabricated on said substrate,

c) at least two wells on said substrate, wherein each of said one

or more arrays is associated with each of said at least two wells, wherein

each electrode array is individually addressable, further wherein said

substrate has a surface suitable for cell attachment, wherein said cell

attachment on said substrate can result in a detectable change in

impedance between electrodes within each electrode array,

ii) an impedance analyzer capable of impedance measurement at millisecond time resolution,

iii) electronic circuitry that can engage said device and selectively connect said two or more electrode arrays of said device to said impedance analyzer, and

Art Unit: 1636

- [[c]]iv) a software program that controls said electronic circuitry and records and analyzes data obtained from said impedance analyzer;
- b) mutating embryonic stem cells to comprise a genetic mutation;
- c) adding said mutated embryonic stem cells to a first well of said at least two wells to form a test well and control embryonic stem cells to a second of said at least two wells to form a control well;
- [[c]] d) monitoring cell-substrate impedance of said at least two wells in millisecond time resolution to detect changes in cell morphology or cell attachment to said substrate, wherein the millisecond time resolution comprises at least two consecutive impedance measurements less than 20 milliseconds apart; and
- e) resolving the beating cycles of both test well and control well, if any; and
- [[d]] f) comparing said beating cycles between said test well and control well, wherein a difference in beating cycles indicates said genetic mutation modulates embryonic stem cell differentiation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to REZA GHAFORIAN whose telephone number is (571)270-1624. The examiner can normally be reached on Monday-Friday 6 AM-3 PM EST.

Art Unit: 1636

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Gussow can be reached on (571)272-6047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REZA GHAFORIAN/
Primary Examiner, Art Unit 1636

<i>Examiner-Initiated Interview Summary</i>	Application No. 12/435,569	Applicant(s) WANG ET AL.	
	Examiner REZA GHAFORIAN	Art Unit 1636	

All participants (applicant, applicant's representative, PTO personnel):

(1) REZA GHAFORIAN. (3) ____.

(2) Raymond Wagenknecht. (4) ____.

Date of Interview: 09 May 2017.

Type: ☒ Telephonic ☐ Video Conference
 ☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
 If Yes, brief description: ____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
 (For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 23.

Identification of prior art discussed: ____.

Substance of Interview
 (For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner obtained authorizaion for amending claim 23 to depend from claim 16. Mr. Wagenknecht further requested and authorized to amend claims 24 and 35 to correct numbering of claim elements.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/REZA GHAFORIAN/ Primary Examiner, Art Unit 1636	
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PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

59538 7590 04/10/2017
Wagenknecht IP Law Group, PC
12396 WORLD TRADE DRIVE
SUITE 312
SAN DIEGO, CA 92128

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/435,569	05/05/2009	Xiaobo Wang	10101-100108	3664

TITLE OF INVENTION: LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	07/10/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
GHAFOORIAN, REZA	1636	506-010000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Wagenknecht IP Law Group PC
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE
ACEA Biosciences, Inc.
(B) RESIDENCE: (CITY and STATE OR COUNTRY)
San Diego, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 504352 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Raymond Wagenknecht/

Date June 15, 2017

Typed or printed name Raymond Wagenknecht

Registration No. 50,948

Electronic Patent Application Fee Transmittal

Application Number:	12435569			
Filing Date:	05-May-2009			
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION			
First Named Inventor/Applicant Name:	Xiaobo Wang			
Filer:	Raymond C. Wagenknecht/Allen Isabelo			
Attorney Docket Number:	10101-100108			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				480

Electronic Acknowledgement Receipt

EFS ID:	29513406
Application Number:	12435569
International Application Number:	
Confirmation Number:	3664
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	59538
Filer:	Raymond C. Wagenknecht/Allen Isabelo
Filer Authorized By:	Raymond C. Wagenknecht
Attorney Docket Number:	10101-100108
Receipt Date:	15-JUN-2017
Filing Date:	05-MAY-2009
Time Stamp:	17:25:01
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 480
RAM confirmation Number	061617INTEFSW17262700
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Authorized User	Allen Isabelo

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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	10101-100108_Issue_Fee_Transmittal.pdf	151737	no	1
			4668ea553965ab748104b8c5a7ccc8c7f8d373df		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30842	no	2
			c4240c4f115d2cd45c00cb4906f4aa236f83393f2		
Warnings:					
Information:					
Total Files Size (in bytes):			182579		
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Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2012. OMB 0651-0031

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	12435569
	Filing Date	2009-05-05
	First Named Inventor	Xiaobo Wang
	Art Unit	1653
	Examiner Name	Shannon L. Janssen
	Attorney Docket Number	ACEA134U1

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8206903		2012-06-26	Abassi et al.	
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

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Examiner Initial*	Cite No	Publication Number	Kind Code ¹	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
Change(s) applied to document, /J.G./ 5/18/2017	1	20140203818		07-2014 2014-06-24	Wang et al.	
	2	20060161073		2006-07-20	Singer et al.	
	3	20090142790		2009-06-04	Fang et al.	
	4	20030211500		2003-11-13	Woosley et al.	
	5	20070042347		2007-02-22	Rosen et al.	



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/435,569	07/18/2017	9709548	10101-100108	3664

59538 759 6/28/2017

Wagenknecht IP Law Group, PC
12396 WORLD TRADE DRIVE
SUITE 312
SAN DIEGO, CA 92128

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 881 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Xiaobo Wang, San Diego, CA;
Yama A. Abassi, San Diego, CA;
Biao Xi, San Diego, CA;
Wen Fu Zhang, San Diego, CA;
Xiao Xu, San Diego, CA;

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
12/435,569	05/05/2009	Xiaobo Wang	10101-100108	121947

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 09/28/2020 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

☒ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Raymond Wagenknecht/
Name:	Raymond Wagenknecht
Registration Number:	50948

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**CHANGE OF
CORRESPONDENCE ADDRESS**
*Patent*Address to:
Mail Stop Post Issue
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Patent Number	9,709,548
Issue Date	July 18, 2017
Application Number	12/435,569
Filing Date	May 5, 2009
First Named Inventor	Xiaobo Wang
Attorney Docket Number	10101-100108

Please change the Correspondence Address for the above-identified patent to:



The address associated with Customer Number:

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Patentee.



If the Patentee was not the applicant for patent (37 CFR 1.42), then a Statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is enclosed or was filed on _____. See 37 CFR 3.71.

Attorney or agent of record. Registration Number 50,948.Patent practitioner acting in a representative capacity whose correspondence address is the correspondence address of record. Notice has been given to the patentee or owner. Registration Number 50,948.

Signature /Raymond Wagenknecht/

Typed or
Printed Name Raymond Wagenknecht

Date 2/26/2021

Telephone 858-592-4141

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

*Total of 1 forms are submitted.This collection of information is required by 37 CFR 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Post Issue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	42050698
Application Number:	12435569
International Application Number:	
Confirmation Number:	3664
Title of Invention:	LABEL-FREE MONITORING OF EXCITATION-CONTRACTION COUPLING AND EXCITABLE CELLS USING IMPEDANCE BASED SYSTEMS WITH MILLISECOND TIME RESOLUTION
First Named Inventor/Applicant Name:	Xiaobo Wang
Customer Number:	59538
Filer:	Raymond C. Wagenknecht/Antonia Gordon
Filer Authorized By:	Raymond C. Wagenknecht
Attorney Docket Number:	10101-100108
Receipt Date:	01-MAR-2021
Filing Date:	05-MAY-2009
Time Stamp:	13:31:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Change of Address	10101-100108_Change_of_Correspondence_Address.pdf	251733	no	2
			040be12139c6f8042229d2a839d65528533ae1de		

Warnings:

1315

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Total Files Size (in bytes):	251733
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