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October 24, 2015

The Honorable Michelle K. Lee
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
United States Patent and Trademark Office
600 Dulany Street
Alexandria, VA 22314

Via email: 2014_interim_guidance@uspto.gov

Re: Request for Comments on July 2015 Update on Subject Matter Eligibility, 80 Fed. Reg. 45429 (July 30, 2015)

Dear Under Secretary Lee:

Thank you for the opportunity to comment on the July 2015 Update on Subject Matter Eligibility (July 2015 IEG)[1] by the U.S. Patent and Trademark Office (USPTO).

I am a registered patent attorney with over 15 years of experience drafting and prosecuting patent applications covering inventions in the life sciences technology sector. In my practice, I also opine for clients on the scope and validity of the patent claims of others. I have a technical degree in biochemistry and molecular biology, and prior to entering the legal field, I was a cytogeneticist on one of the major genome projects. I was an adjunct professor at Franklin Pierce Law Center where I taught Advanced Biotech Patent Preparation and Prosecution. Currently, I am a partner with Canady + Lortz LLP, an IP law boutique, the Chair of the Biotechnology Committee of the American Intellectual Property Law Association (AIPLA), and a member of the American Society of Gene & Cell Therapy (ASGCT). I am also a member of a few informal groups of patent practitioners who meet and discuss case law and USPTO practice and procedure that may impact patent protection of inventions in the life sciences.

Although the comments herein are based on my experience above, the opinions expressed herein are mine and should not be attributed to the organizations to which I belong and any other person or client of Canady + Lortz LLP. Additionally, the focus on "combination biomarker" and "weighted biomarker" assay claims should not be interpreted to mean that diagnostic assays involving one biomarker are patent ineligible.

These comments relate to the (improper) application of abstract ideas and/or natural laws and products as the judicial exceptions in the 101 subject matter eligibility determination of diagnostic biomarker assay claims.

[1] 80 Fed. Reg. 45429 (July 30, 2015)

Well-Understood, Routine, and Conventional

As set forth in the 2014 Interim Guidance on Subject Matter Eligibility (2014 IEG)[2] and the July 2015 IEG, the use of unconventional process steps or objects may result in significantly more than the judicial exception recited in a method claim and therefore confer subject matter eligibility, whereas "well-understood, routine, and conventional" steps and objects do not. Nowhere, however, does the USPTO set forth any guidance on what is considered "well-understood, routine, and conventional". Based on my interactions with several examiners in different art units and discussions with other practitioners, the USPTO's position appears to be that if a process or object has been used for any reason in any technological field, the process or object is "well-understood, routine, and conventional" even if the use is a single use that is completely unrelated to the technological field of the claimed invention.

I respectfully submit that this position is incorrect. Specifically, when discussing whether pre- or post-solution activity is "well-understood, routine, and conventional" in *Mayo v. Prometheus*[3], it is clear that the Supreme Court evaluated the activity in the context of the particular field of art at issue by its use of "the field" (emphasis added) rather than "a" field or "any" field throughout the decision. And, as a specific example, when discussing the "determining" step, the Supreme Court noted that "scientists routinely measured metabolites as part of their investigations into the relationships between metabolite levels and efficacy and toxicity of thiopurine compounds … [and] this step tells doctors to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field" (emphasis added). Not all doctors administer thiopurine compounds to their patients. Hence, not all doctors measure metabolite levels of thiopurine compounds. Thus, "the field" in the discussion of "well-understood, routine, and conventional" must be understood to be the treatment of subjects with thiopurine drugs, and not any field such as radiological imaging. At the time of the invention, measuring metabolites of thiopurine compounds may have been well-understood, routine, and conventional in the treatment of subjects with thiopurine drugs, and yet unconventional in the radiological imaging field.

Additionally, some examiners have asserted that in the "significantly more" analysis of Step 2B, consideration of the steps and elements "individually, and in ordered combination" means that the steps and elements are to be considered independently from or in the absence of the so-called judicial exception. Perhaps, this is the result of the USPTO's interpretation of the following statement in *Mayo*:

> In particular, the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field.

(emphasis added). See Slip, page 8.

I respectfully submit that when considering whether a claim recites steps or elements that result in something significantly more than the judicial exception itself, it is improper to exclude

[2] 79 Fed. Reg. 74618 (December 16, 2014)
[3] *Mayo Collaborative Svcs. v. Prometheus Labs.*, 566 U.S. __, 132 S. Ct. 1289 (2012)

consideration of the steps or elements in combination with the judicial exception. In fact, in *Diamond v. Diehr*[4], the Supreme Court considered the judicial exception, i.e., Arrhenius' equation, as incorporated and applied to the combination of steps for molding and curing rubber. Arrhenius' equation is a general equation with variables that are specifically tailored to the particular chemical reaction at issue. In the claims at issue in *Diehr*, the variables in the equation are defined and specifically tailored to molding and curing rubber as, for example, the activation energy constant (C) is unique to each batch of said compound being molded, and constant (x) is dependent upon the geometry of the particular mold of the press.

Additionally, the Supreme Court stated "[i]t is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis". See id., 450 U.S. 175, 188. Thus, not only should the steps and elements of a claim be considered in combination with the judicial exception, but the combination of any well-understood, routine, and conventional steps (in addition to any unconventional steps and elements) should be considered in combination with the judicial exception and as applied to the technological field of the claimed invention.

In other words, the "as a whole" inquiry required by *Diehr*, and even the "in ordered combination" of *Mayo*, requires consideration of the combination of all the elements of a claim, old and new, in conjunction with the asserted judicial exception to determine if what is claimed is significantly more than the judicial exception itself.

If one were to consider the steps and elements of the claims in *Diehr* independently from or in the absence of the so-called judicial exception, one would be left with nothing more than "a method of operating a rubber-molding press for precision molded compounds with the aid of a digital computer" because everything after the transitional phrase "comprising" involves or is based on Arrhenius' equation. Unfortunately, this is the analysis by some examiners many practitioners, including myself, are experiencing.

Thus, I recommend that in the next iteration of the Interim Guidance, the USPTO makes clear that the consideration of whether something is "well-understood, routine, and conventional" is to be as applied to the technological field of the claimed invention. I also recommend that the next iteration clarifies that the "ordered combination" analysis requires the inclusion of old elements and steps, as well as, the asserted judicial exception such that the claimed invention, "as a whole", is considered.

The Science of Diagnostic Biomarker Assay Claims

The term "biomarker" has various meanings in the art of clinical research and can include "everything from pulse and blood pressure through basic chemistries to more complex laboratory tests of blood and other tissues" that has relevance and validity for a given clinical endpoint or indication. See Strimbu & Tavel (2010) "What are Biomarkers?" Curr Opin HIV AIDS 5(6): 463-466. Thus, for example, in the case of a biomolecule such as protein as a biomarker, the presence, absence, or amount thereof must have a statistically significant correlation to the given

[4] *Diamond v. Diehr*, 450 U.S. 175, 209 U.S.P.Q. 1 (1981)

condition in the given population pool. The validity of a biomolecule as a biomarker depends on a variety of different internal and external factors such as the presence of the biomolecule in subjects not having the given condition, the association of the biomolecule with other markers or variables, and the extent to which subjects having the biomolecule have or will develop the condition. See Schulte & Mazzuckelli (1991) "Validation of Biological Markers for Quantitative Risk Assessment" Environ Health Perspectives 90:239-246.

This means, for example, the presence of a biomolecule, e.g., interleukin 2 (IL-2), that is commonly found in all subjects, healthy and afflicted with an indication, has no clinical relevance and no validity as a biomarker for the presence (or absence) of the indication. When, however, IL-2 is considered in combination with one or more additional biomarkers, the presence, absence, or amount of IL-2 might have statistical significance.

Whether IL-2 has statistical significance when in combination with one or more additional biomarkers depends on the particular biomarkers. For example, the presence of the combination of IL-2, IL-4, VEGF, PKC, and RANTES may have relevance and validity for diagnosing one as likely to have Disease D. On the other hand, the presence of the combination of IL-2, MIP-1a, Eotaxin, SLK, and TARC may have no statistically significant correlation to Disease D. Additionally, while the presence of the combination of IL-2, IL-4, VEGF, PKC, and RANTES has a statistically significant correlation to Disease D, the same combination might not have any relevance or validity for a different disease. Further, there may be other combinations that have a statistically significant correlation to Disease D, e.g., IL-2, IL-10, TNF, and MIP-1a.

Finally, the particular combinations of biomarkers that have relevance and validity might not have the same statistical significance when considered in combination with all the biomolecules present in a subject as would be in nature. One of the many scientific reasons for this is that the biological mechanisms in an organism that regulate the levels of various biomolecules are complex arrays of various feedback loops and regulatory pathways. A simplified schematic of some of the many biomolecules involved in cancer is set forth in Exhibit A. See also http://www.genome.jp/kegg-bin/show_pathway?map=hsa05200&show_description=show. As shown in Exhibit A, many biomolecules play different roles.

For many diagnostic assays that involve the combination of a set of biomarkers, the inventors first arbitrarily select a pool of biomolecules to evaluate in given population pools, and then from that arbitrary pool biomolecules, the inventors select a subset of biomolecules and conduct exhaustive experiments, measurements, and statistical analysis to make the subset of biomolecules informative as a "combination biomarker". As explained above, such subsets of biomolecules do not have the same relevance and validity as they would in nature, i.e., when considered with the entire universe of biomolecules in a given subject. A human makes a combination biomarker; nature does not.

Thus, the correlation of a given combination of biomolecules in a sample from a subject is not a law of nature, and the use of the given combination of biomolecules to diagnose a subject as having or likely having a specific indication is a human-made method based on an inventor's selection of a set of biomolecules to be used in combination. Consequently, these "combination biomarker" assays should be recognized as patent eligible subject matter.

An example of a "combination biomarker" assay claim is:

1. A method of diagnosing a subject as having Disease D, which comprises
   measuring in a sample from the subject the amounts of at least 3 biomarkers selected from the group consisting of A, B, C, D, and E, and
   diagnosing the subject as having Disease D where the at least 3 biomarkers are present in the sample.

Similar to "combination biomarker" assays, "weighted biomarker" assays involve an inventor's selection of a set of biomolecules to be used in combination, which set of biomolecules, might not have any statistical significance to the presence or absence of a given indication. Weighted biomarker assays, however, additionally require the use of an algorithm, e.g., a logistic regression algorithm, that is specifically tailored by the hand of a human to the given indication, the given population pool, and the particular set of biomolecules. In particular, the variables and constants used in the algorithm are based on the prevalence or level of each biomolecules when considered in combination of the other biomolecules selected to be part of the set of biomolecules in samples from subjects known to have the given indication and subjects known to not have the given indication. The relevance (i.e., weights) of each biomolecule when considered as a combination of selected biomolecules are different from the relevance they would have when considered along with all of the biomolecules present in the subject. One of the reasons for this is that the downstream effect or impact of an amount of a biomolecule in the combination may be compensated for by a biomolecule that is not part of the combination considered.

Examples of "weighted biomarker" assay claims are:

2. A method of diagnosing a subject as having a Disease which comprises
   measuring the amounts of at least 3 biomarkers selected from the group consisting of A, B, C, D, and E,
   assigning a weighted value to each measured amount of each biomarker, multiplying the amounts measured as follows Ax0.5, Bx0.4, Cx0.8, Dx0.2, and Ex0.9,
   summing the total of the weighted values, and
   diagnosing the subject as having the disease when the total of the weighted values is above 25.7.

3. A method of diagnosing the likelihood of a subject as having Disease D which comprises
   measuring the amounts of at least 3 biomarkers selected from the group consisting of A, B, C, D, and E,
   using Algorithm A, $$P_Z = \frac{e^{\alpha+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_P X_P}}{1+e^{\alpha+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_P X_P}}$$, where each β is the amount of the given biomarker and each X is the regression coefficient for the given biomarker, and
   diagnosing the subject as having N% likelihood of having the Disease where the predicted probability is n and $0<n<1$ and $N = n \times 100$.

Since the relevance and validity of combinations of biomolecules in combination and weighted biomarker assays is different from their relevance and validity when considered in nature along

with all the other biomolecules that may be present, it cannot be said that the correlation of the combination or weighted combination is a law of nature. Nature does not create the correlation of a combination of biomolecules; humans do by their selection of biomolecules to be used in the combination. In other words, with combination and weighted biomarker assays, the particular biomolecules that are selected to be considered as set is by the hand of a human and the relevance and validity of the set of biomolecules as a combination biomarker is provided by the hand of a human, not nature.

Additionally, "weighted biomarker" assay claims are not claims to the abstract idea, i.e., algorithm itself. Instead, "weighted biomarker" assay claims are analogous to the specifically tailored Arrhenius' equation and its integral application to the molding and curing of rubber at issue in *Diehr*.

In the first paragraph of Section III of the July 2015 IEG, the USPTO explains that the 2014 Interim Guidance on Subject Matter Eligibility (2014 IEG)[5] instructs examiners to refer to case law precedent to identify abstract ideas by way of comparison in order to "ensure that a claimed concept is not identified as an abstract idea unless it is similar to at least one concept the courts have identified as an abstract idea" (emphasis added). To date, however, there are no Supreme Court or Federal Circuit decisions holding "combination biomarker" and "weighted biomarker" assay claims are directed to nothing more than an abstract idea or law of nature. Additionally, no court decision, not even *Ariosa v. Sequenom*[6], holds that the use of a natural product is patent ineligible.

Thus, in the next iteration of the Interim Guidance, examiners should be instructed that "combination biomarker" and "weighted biomarker" assay claims are not directed to abstract ideas, laws of nature, or products of nature and therefore such assay claims should be found patent eligible.

Further Recommendations

For over three years since the *Mayo* decision in 2012, stakeholders and patent practitioners in the biotechnological arts have been anxiously awaiting examination guidance on the patent eligibility of diagnostic biomarker assay claims. Many hoped that the USPTO would provide informative guidance on the eligibility of diagnostic biomarker assay claims after the *Myriad*[7] decision in 2013, and then after *UURF v. Ambry*[8] in 2014. Many were told by the USPTO that the USPTO would publish guidance on the examination of diagnostic assay claims shortly after *Ariosa*.

It is now the end of 2015 and the USPTO has yet to provide any guidance on diagnostic biomarker assay claims and applicants are receiving seemingly inconsistent eligibility examinations of their diagnostic biomarker assay claims from examiners. Some examiners assert

[5] 79 Fed. Reg. 74618 (December 16, 2014)
[6] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015)
[7] *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. __, 133 S. Ct. 2107 (2013)
[8] *Univ. of Utah Research Found. v Ambry Genetics Corp.*, 774 F.3d 755 (Fed. Cir. 2014)

a law of nature is involved, others assert an abstract idea is involved, and yet others assert that such claims are directed to no more than a natural product as the methods and reagents involved are allegedly well-understood, routine, or conventional.

These inconsistent examinations suggest that (1) the USPTO and examiners do not know how to determine the eligibility of diagnostic biomarker assays, or (2) the USPTO has an idea or position on how diagnostic biomarker assays should be examined for eligibility, but does not want to disclose such to stakeholders. For whatever reason, the lack of examination guidance on diagnostic biomarker assay claims is detrimental to further innovation and development of personalized medicine as we are beginning to see investors pull their monetary support from further R&D and efforts to bring such diagnostics to the American public. Additionally, the extra prosecution costs resulting from inconsistent eligibility rejections are often cost prohibitive especially for non-profit research institutions who funnel royalties from licensed patented technologies back into further R&D.

Therefore, I recommend that the USPTO suspends examination of certain types of claims, such as diagnostic biomarker assay claims, until the USPTO formulates and publishes its official position. I recommend that the USPTO seeks comments and input from the public to formulate a proposed position, and then seeks comment and input again from the public on the proposed position of the USPTO before making it final.

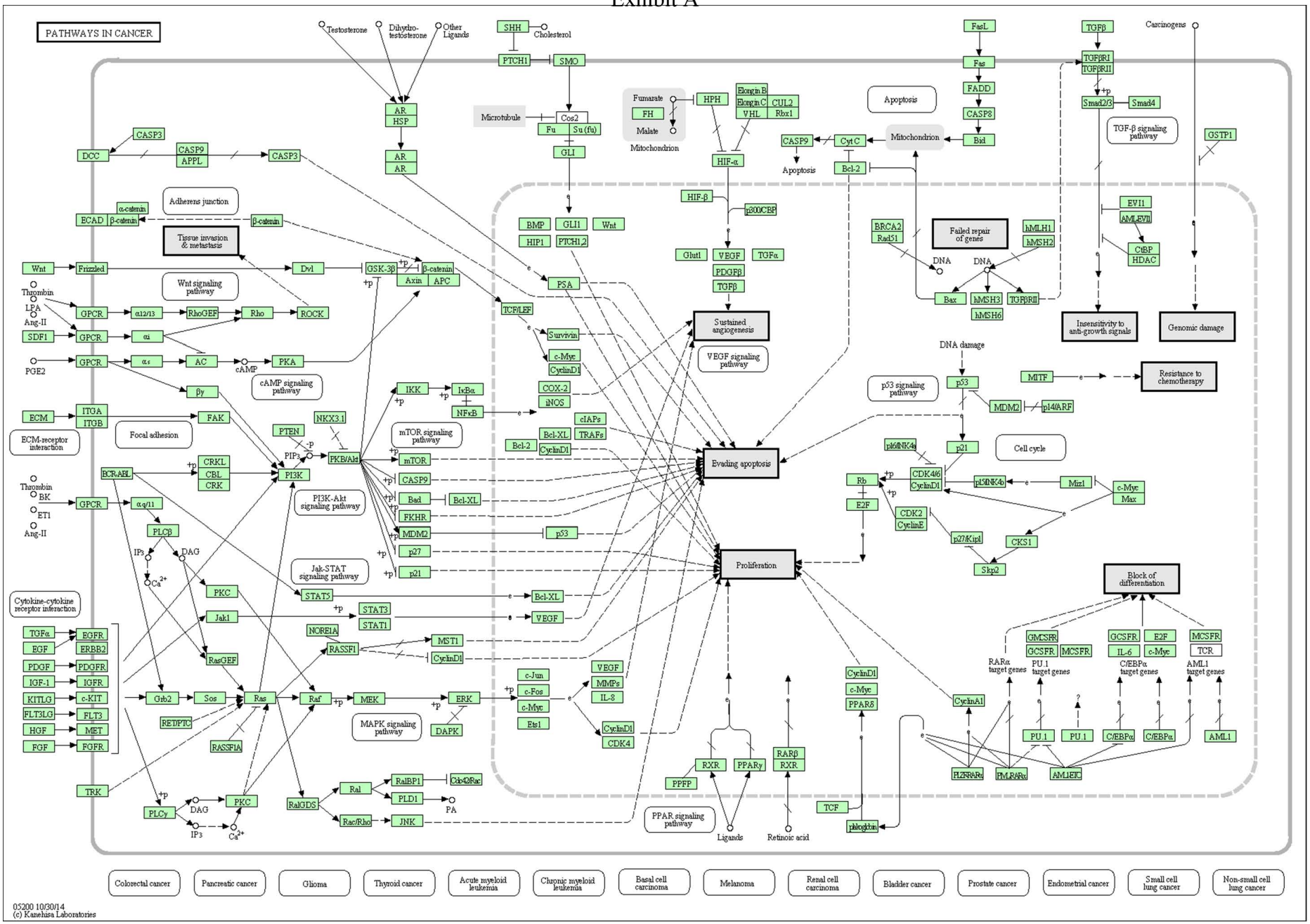
Many claims that have been granted since the 2014 IEG are seemingly similar to other claims being rejected as patent ineligible. Unfortunately, too often nowhere in the prosecution histories of the granted claims is there any indication as to why the claims were considered patent eligible. I appreciate the streamlined analysis of the 2014 IEG, however, I believe it would benefit the public, patentees, applicants, and practitioners if examiners were required to succinctly state in a sentence or two in the Notices of Allowability why the allowed claims are patent eligible subject matter. Therefore, in the next iteration, the USPTO should instruct examiners to set forth in Notices of Allowability a brief explanation as to why the claimed invention is patent eligible.

Again, thank you for this opportunity to comment on the July 2015 IEG. Feel free to contact me for further information or clarification.

Sincerely,

Suzannah K. Sundby

Exhibit A


PATHWAYS IN CANCER
Testosterone
Dihydro-testosterone
Other Ligands
AR
HSP
AR
AR
SHH
Cholesterol
PTCH1
SMO
Microtubule
Cos2
Fu
Su (fu)
GLI
Fumarate
FH
Malate
Mitochondrion
HPH
Elongin B
Elongin C
CUL2
VHL
Rbx1
HIF-α
HIF-β
p300/CBP
Glut1
VEGF
TGFα
PDGFβ
TGFβ
BMP
GLI1
Wnt
HIP1
PTCH1,2
PSA
TCF/LEF
Survivin
c-Myc
CyclinD1
COX-2
iNOS
cIAPs
Bcl-XL
TRAFs
Bcl-2
CyclinD1
Sustained angiogenesis
VEGF signaling pathway
Evading apoptosis
Proliferation
FasL
Fas
FADD
CASP8
Bid
Apoptosis
CASP9
Cyt C
Bcl-2
Apoptosis
Mitochondrion
TGFβ
TGFβRI
TGFβRII
Smad2/3
Smad4
TGF-β signaling pathway
GSTP1
EVI1
AML/EVI1
CtBP
HDAC
Insensitivity to anti-growth signals
Genomic damage
BRCA2
Rad51
Failed repair of genes
hMLH1
hMSH2
DNA
DNA
Bax
hMSH3
TGFβRII
hMSH6
DNA damage
p53 signaling pathway
p53
MDM2
p14/ARF
MITF
Resistance to chemotherapy
p16/INK4a
p21
Cell cycle
Rb
E2F
CDK4/6
CyclinD1
p15/INK4b
Mizl
c-Myc
Max
CDK2
CyclinE
p27/Kipl
CKS1
Skp2
Block of differentiation
GMCSFR
GCSFR
MCSFR
GCSFR
IL-6
E2F
c-Myc
MCSFR
TCR
RARα target genes
PU.1 target genes
C/EBPα target genes
AML1 target genes
CyclinA1
PU.1
PU.1
C/EBPα
C/EBPα
AML1
PLZF/RARα
PML/RARα
AML1/ETO
CyclinD1
c-Myc
PPARδ
TCF
β-catenin
Adherens junction
α-catenin
ECAD
β-catenin
Tissue invasion & metastasis
Wnt
Frizzled
Dvl
GSK-3β
β-catenin
Axin
APC
Wnt signaling pathway
Thrombin
LPA
Ang-II
SDF1
PGE2
GPCR
α12/13
RhoGEF
Rho
ROCK
GPCR
αi
GPCR
αs
AC
cAMP
PKA
cAMP signaling pathway
βγ
ECM
ITGA
ITGB
FAK
Focal adhesion
ECM-receptor interaction
PTEN
NKX3.1
PIP3
PKB/Akt
IKK
IκBα
NFκB
mTOR signaling pathway
mTOR
CASP9
Bad
Bcl-XL
FKHR
MDM2
p53
p27
p21
CRKL
CBL
CRK
PI3K
BCR-ABL
PI3K-Akt signaling pathway
Thrombin
BK
ET1
Ang-II
GPCR
α q/11
PLCβ
IP3
DAG
Ca2+
PKC
Jak-STAT signaling pathway
STAT5
STAT3
STAT1
Bcl-XL
VEGF
Jak1
Cytokine-cytokine receptor interaction
TGFα
EGF
PDGF
IGF-1
KITLG
FLT3LG
HGF
FGF
EGFR
ERBB2
PDGFR
IGFR
c-KIT
FLT3
MET
FGFR
NORE1A
MST1
CyclinD1
RASSF1
RasGEF
Grb2
Sos
Ras
Raf
MEK
ERK
DAPK
MAPK signaling pathway
RASSF1A
RET/PTC
TRK
PLCγ
DAG
IP3
Ca2+
PKC
RalGDS
Ral
RalBP1
Cdc42/Rac
PLD1
PA
Rac/Rho
JNK
c-Jun
c-Fos
c-Myc
Ets1
VEGF
MMPs
IL-8
CyclinD1
CDK4
RXR
PPARγ
PPFP
PPAR signaling pathway
Ligands
RARβ
RXR
Retinoic acid
Colorectal cancer
Pancreatic cancer
Glioma
Thyroid cancer
Acute myeloid leukemia
Chronic myeloid leukemia
Basal cell carcinoma
Melanoma
Renal cell carcinoma
Bladder cancer
Prostate cancer
Endometrial cancer
Small cell lung cancer
Non-small cell lung cancer
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