The Benefit of the Cost of Patents

ASGCT Clinical Trials and Regulatory Affairs Symposium

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Access to Life-Saving Technologies

Patents Fund Further Innovation

The Story of WARF

- $10,900 in 1925, WARF patented Dr. Steenbock's Vitamin D invention and the royalties funded further research
- By 1945, when Steenbock's patent expired, it had brought WARF some $8 million in net royalties
- After the 1929 Stock Market crash, WARF gave:
  - 1931 $18k grants
  - 1933 $147k research fellows and faculty
  - 1951 $2.8M for housing for students
  - 1969 $3M grants
- By mid 1980's $8M in grants annually
- By 2004, $40M in grants annually
- 2010-11 $51M in grants
- Since its inception WARF has contributed over $1 BILLION to UW
- Resulted in high-yielding strains of penicillin, Warfarin, organ transplant storage medium, MRI, and stem cells

Patent Royalties

Fund Further Research

- Since its founding, the UVA Patent Foundation has funneled more than $17.5 million into research
- University of California
- Northwestern University
- SUNY
- Iowa State University
- Yale
- DePaul University
- Washington Research Foundation
- Other research institutions
  - Cystic fibrosis

Patent Licensing

Creates New Jobs

- According to AUTM, university technology generated nearly $700 million in royalties in FY1997 with academic licensing responsible for nearly 246,000 jobs and $29 BILLION of economic activity over the past 20 years

Percent of R&D Funding from Royalties FY2002 From "The Axel Patents" by Colaianni	
City of Hope National Medical Ctr. & Beckman Research Inst.	42%
Sloan Kettering Inst. for Cancer Res.	41%
Columbia Univ.	41%
New York Univ.	35%
Florida State Univ.	34%
Univ. de Sherbrooke	32%
St. Elizabeth's Medical Ctr. of Boston	23%
Wake Forest Univ.	17%
Univ. of Rochester	16%
Brigham Young Univ.	14%
Emory Univ.	12%

2012 AUTM Report

- Product sales: 58 institutions (31% of the 186 respondents) reported that 2,821 of their licenses paid $662 MILLION
- Total royalty income for all U.S. institutions was $1.5 BILLION
- 10% of 1.5 billion is $150 MILLION = for further research annually

Venture Capital

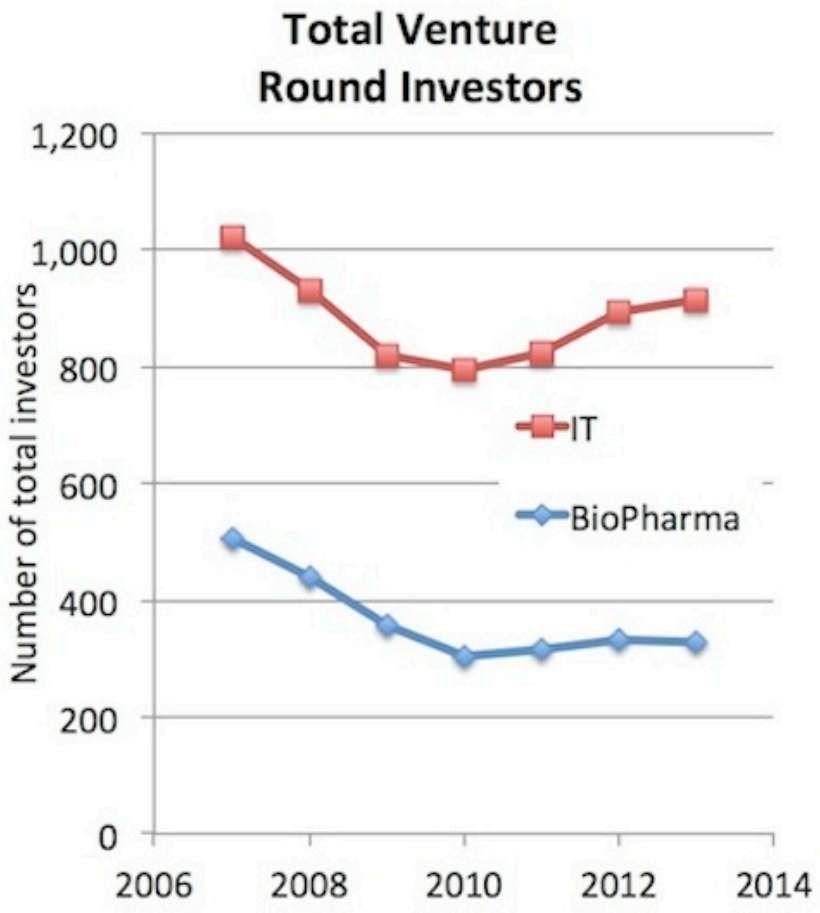
Early Stage Biotech Venture Scarcity

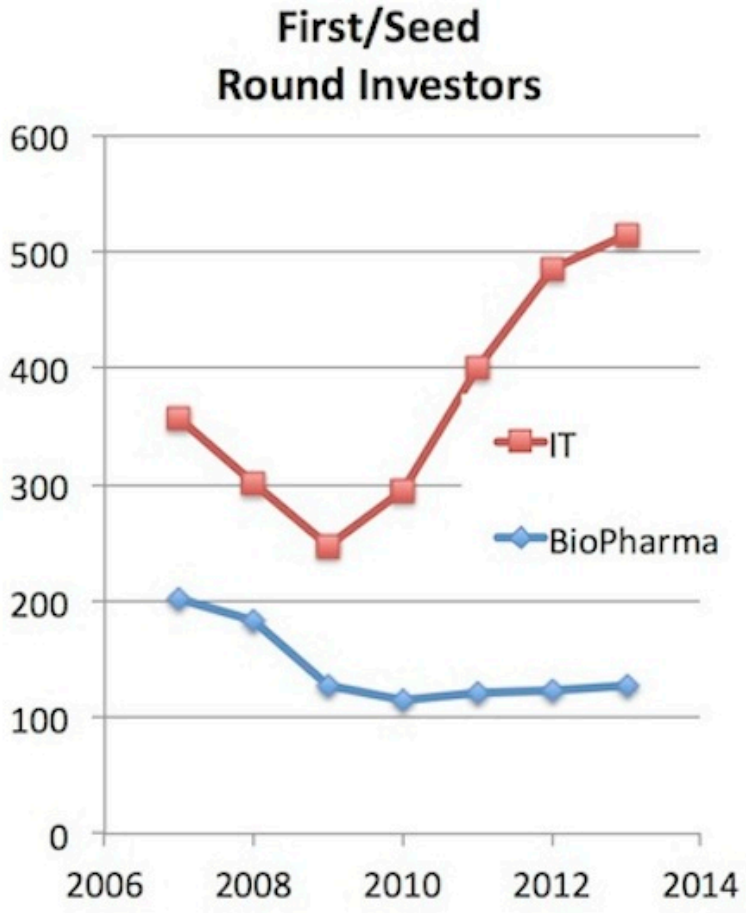
- Active life science investor numbers [ ]dropped by 25% since 2007, and again haven't rebounded; on the contrary, active non-LS (Tech largely) investors have essentially regained their full 2007 ranks
- [O]f the $26B that's been raised to date by venture firms in 2014 – only $3.5B is for healthcare funds – a far smaller percentage than in recent years (15% vs 20-23% of venture fundraisings in 2011-2013)
- [T]here remains a limited pool of capital flowing into life science venture, and even smaller into early stage funds – despite the booming IPO and M&A markets

- http://www.forbes.com/sites/brucebooth/2014/09/22/early-stage-biotech-venture-scarcity-fitness-fear-and-greed/

Venture Capital

Early Stage Biotech Venture Scarcity

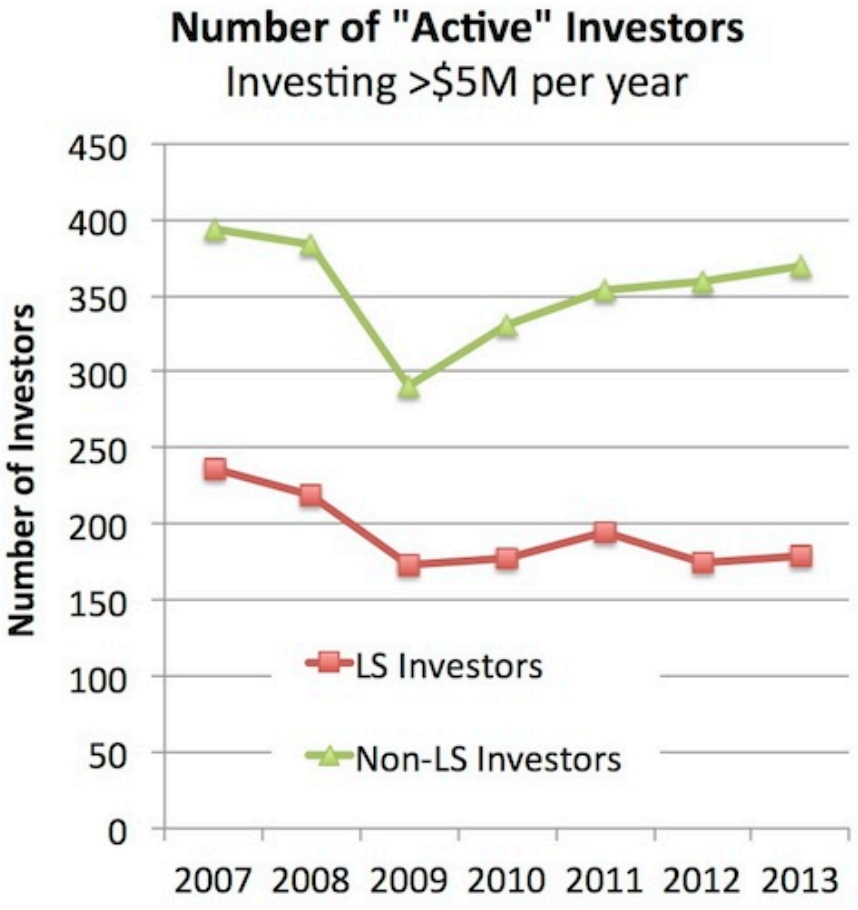




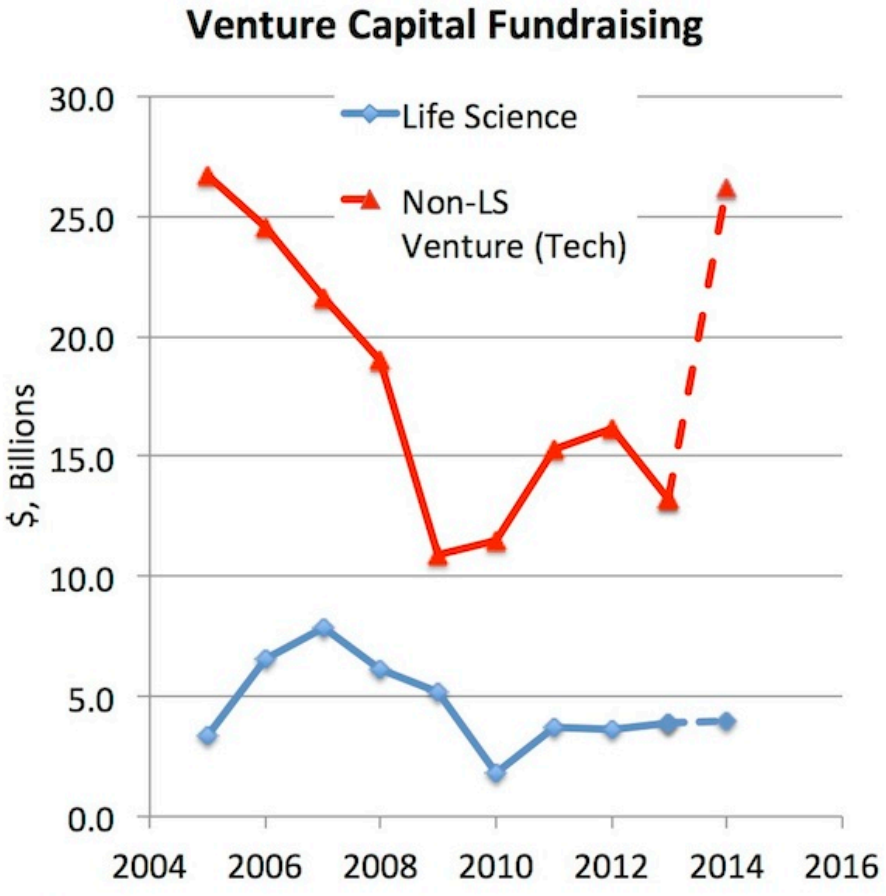
Source: Dow Jones VentureSource

Venture Capital

Early Stage Biotech Venture Scarcity



Source: NVCA Yearbook 2014, Figure 1.05



Dotted lines are annualized extrapolations/estimates
Source: Thomson Reuters/NVCA; SVB analysis

Patent Protection

Process and Costs

US Provisional Application

Priority Placeholder

- File before public disclosure to preserve absolute novelty
- Only as good as what is disclosed and how written
- Can be informal
  - Abstract, Poster Session, Manuscript
- Best if looks and feels like real utility application
- USPTO Filing Fee = $260/$130
- Atty Fee
  - Can range from $500-$15,000+
  - Again, only as good as what is disclosed and how its written

US Utility Application

Can Result in a Granted US Patent

- MUST file within 1 year from provisional filing date
- Can file instead of a Provisional
- Formal requirements
  - Specification format, drawings, claims, abstract, sequence listing, etc.
- Substantive requirements
  - Eligibility and Patentability (novel, unobvious, written description, enablement, and best mode)
- Can not amend/fix the disclosure after filing
- USPTO Filing Fee $1600/$800 not incl. other fees
- Atty Fee
  - ~40 hrs @ $400-500/hr = $16,000-$20,000+
    - *I'm cheap and give a discounted rate to preferred academic clients*
  - Again, only as good as what is disclosed and how its written

PCT Application

Placeholder for Most Foreign and US Protection

- MUST file within 1 year from filing date of first application
- Can file instead of a Provisional or US Utility
- Formal requirements – Like US Utility
- Substantive requirements – Like US Utility
  - Still need best mode for US
- Can not amend/fix the disclosure after filing
- PCT Filing Fee – US/RO and US/ISA
  - $4,056/$2,896 (assumes 35 extra pages)
- Atty Fee
  - ~40 hrs @ $400-500/hr = $16,000-$20,000+
    - *I'm cheap and give a discounted rate to preferred academic clients*
  - Again, only as good as what is disclosed and how its written

Foreign Filings

National Phase Entry or File Directly

- If filing directly in foreign country, generally 1 yr from priority app
- If PCT = National Phase Entry at 30 mos from priority app
- Gov't fees vary
  - ~$800-$2,000, but EPO is ~$5,000
- Foreign atty fees vary
  - ~$800-$3,000
- US atty fee
  - ~$500-$1,000
- Translation Fees are extremely expensive
- Total Cost
  - Anywhere from ~$2,000 if just US and up to $100k+

EPO Regional Phase

Like a PCT Application

- Once allowed and granted, must validate in EU member states
- Gov't and foreign associate fees vary
  - ~$500-$4,000
- Translation Fees are extremely expensive
- An example (validation in all available):
  - 51 pages, 4 claims ~$65,000
  - 146 pages, 27 claims ~$112,000

Costs Do Not Include

Prosecution, Annuities, Grant Fees, etc.

- Usually 2-3 Office Actions
  - In US, atty fees can be ~1,500-3,000 each, not including extension fees
  - Foreign countries, atty fees = US + foreign atty fees + translations
- Foreign annuities
  - Usually each year, range from ~500-$2,500 even when not yet granted
  - For example, for one *limited* family of cases annual annuities are ~20k+
- Grant Fees
  - US $960/$480 + atty fees
  - Foreign countries vary, e.g., EU ~$3,000+
- US Maintenance Fees
  - 3.5 years $1,600/$800
  - 7.5 years $3,600/$1,800
  - 11.5 years $7,400/$3,700

Patent Requirements

Patentability and Eligibility

Patentability

Novelty - 35 U.S.C. 102

- The exact same invention being claimed must not be anticipated by the prior art
  - For example, the prior art discloses Compound X
  - One cannot obtain a granted patent claim on Compound X
  - However, the prior art does not disclose a method of using Compound X for treating Disease Y
  - Inventor shows that Compound X can be used to treat Disease Y and can therefore claim a method of treating Disease Y which comprises administering Compound X
- Remember: Actions by the inventor can destroy novelty, e.g., abstracts, poster session, online publications, etc., before filing at least a provisional

Patentability

Novelty - 35 U.S.C. 102

- A species anticipates a genus
  - Compound X falls within the scope of broad genus of compounds having the general structural formula A
  - Compound X is in the prior art
  - Claims to compounds having the general structural formula A are anticipated
  - Note: A genus doesn't necessarily anticipate a species
- Anticipation by Inherency
  - Prior art discloses method for treating a tumor by administering Compound X
  - Inventors discover that Compound X induces apoptosis in tumor cells
  - A claim to a method for treating a tumor which comprises inducing apoptosis by the administration of Compound X is anticipated because it is inherent in the prior art that Compound X induces apoptosis in tumor cells

Patentability

Unobvious - 35 U.S.C. 103

- The claimed invention must be unobvious to a person of ordinary skill in the art
  - Inventors are not ordinary
- There must be some suggestion or motivation to modify or combine the prior art to obtain the claimed invention with a reasonable expectation of success
- The combination must result in the claimed invention as a whole, i.e., all the claim limitations

Patentability

Unobvious - 35 U.S.C. 103

- Examples of good arguments
  - The prior art is incapable of being combined
  - The combination renders the invention of the primary reference inoperable
  - The combination changes the principle mode of operation of the invention of the primary reference
  - The prior art teaches away from the claimed invention
  - The prior art does not teach or suggest the unexpected superior results, e.g., synergistic results.

Patentability

Written Description, Enablement, Best Mode

- The specification must:
  - Contain a WRITTEN DESCRIPTION of the invention
  - ENABLE a person skilled in the art to make and use the invention
  - Disclose the BEST MODE of the invention
- After filing the application, the specification cannot be fixed!
- Problems arise during prosecution and amending the claims to overcome art and other rejections

Patentability

Claims – Clear and Definite

- The claims must clearly set forth the subject matter that the Applicant regards as the invention
- These claim requirements are generally fairly easy for a patent attorney to address
- However, just in case, ensure that there is proper information
  - Terms are used consistently in the specification
  - Definitions are provided for terms that do not have one accepted meaning recognized by others in the art

Eligibility

35 U.S.C. 101 – Oh what a mess…

- Statutory Subject Matter
  - Processes
  - Machines
  - Articles of Manufacture
  - Compositions of Matter
- Judicial Exceptions to Statutory SM
  - Laws of Nature (includes Products of Nature)
  - Natural Phenomena
  - Abstract Ideas

INEligibility

Mayo v. Prometheus

- 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
  - (a) administering a drug providing 6-thioguanine to a subject having [the disorder]; and
  - (b) determining the level of 6-thioguanine in [the] subject [ ],
  - wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of [the drug administered to the subject] and
  - wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of [the drug administered to the subject].
- Simply appending conventional steps to laws of nature, natural phenomena, and abstract ideas does not confer patent eligibility
  - Pre-solution activity = post-solution activity

INEligibility

AMP v. Myriad

- 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
- 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.
- Held: A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring.
- "We merely hold that genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material."

INEligibility

Alice v. CLS Bank

- All about Abstract Ideas
- Claimed matter has nothing to do with biotech
- 33. A method of exchanging obligations as between parties, each party holding a credit record and a debit record with an exchange institution, the credit records and debit records for exchange of predetermined obligations, the method comprising the steps of…
- "We hold that the claims at issue are drawn to the abstract idea of intermediated settlement, and that merely requiring generic computer implementation fails to transform that abstract idea into a patent-eligible invention."

INEligibility

Mayo/Alice Test

- For product claims
  - Is the claimed product markedly different in structure, function, or other characteristic from the naturally occurring counterpart?
  - If no marked difference, does the claim recite something significantly more than the judicial exception?
- For method claims
  - Does the claim recite something significantly more?

INEligibility

Nature Based Products – Marked Difference?

- A composition comprising pomelo juice and an effective amount of an added preservative. – Yes
- An isolated nucleic acid comprising SEQ ID NO: 1. – No
- A pair of single-stranded DNA primers. – No
- An isolated man-made human pacemaker cell. – No
- An isolated nucleic acid having a non-naturally occurring mutation. – Yes
- An isolated nucleic acid having a fluorescent label attached thereto. – Yes
- A composition comprising a population of isolated man-made human pacemaker cells in a container. – No
- An isolated man-made human pacemaker cell expressing marker Z. – Yes
- A kit for preparing goat milk yogurt comprising: S. thermophilus and L. alexandrinus. – No
- A yogurt starter culture comprising: goat milk mixed with S. thermophilus and L. alexandrinus. – Yes

INEligibility

Method Claims – Significantly More?

- A method comprising providing a pomelo fruit. – No
- A method of treating breast or colon cancer, comprising: administering an effective amount of purified amazonic acid to a patient suffering from breast or colon cancer. – Yes

No Diagnostic Assay Examples… yet

INEligibility

Myriad's Ineligible Method Claims

- 1. A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which
  - comprises analyzing a sequence of a BRCA1 gene [ ] from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184–4187 of SEQ ID NO: 1.
- 1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises [ ]
  - comparing a first sequence [from the tumor sample] with a second sequence [from a nontumor sample],
  - wherein a difference [ ] indicates a somatic alteration in the BRCA1 gene in said tumor sample.

INEligibility

Myriad's Ineligible Method Claims (Ambry)

- 7. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises
  - comparing germline sequence of a BRCA1 gene [with the wildtype, and]
  - wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.
- 8. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises
  - comparing germline sequence of a BRCA1 gene [with the wildtype, and]
  - wherein a germline nucleic acid sequence is compared by amplifying all or part of a BRCA1 gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.

INEligibility

Myriad's Eligible Method Claim 20

- 20. A method for screening potential cancer therapeutics which comprises:
  - growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic,
  - growing said transformed eukaryotic host cell in the absence of said compound,
  - determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells,
  - wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

Commercial Viability?

Granted Diagnostic Assay Claims

Narrow Ranges

A method for detecting sepsis in canine subjects comprising the steps of:

- obtaining a blood serum sample from a canine subject;
- obtaining the concentration of CRP [ ] and assigning a first discrete value to said CRP concentration, wherein said first discrete value is assigned a value: zero (0) when the concentration of CRP is less than 40 mg/l, one (1) when the concentration of CRP is between 40.1 mg/l and 56.4 mg/l, or two (2) when the concentration of CRP is greater than 56.5 mg/l;
- obtaining the concentration of CNP [ ] and assigning a second discrete value to said CNP concentration, wherein said second discrete value is assigned the value: zero (0) when said concentration of CNP is less than 3.8 picomole/l, one (1) when the concentration of CNP is between 3.9 picomole/l and 13.3 picomole/l, two (2) when the concentration of CNP is between 13.4 picomole/l and 20 picomole/l, or three (3) when the concentration of CNP is greater than 20.1 picomole/l;
- computing an index value by adding: the first discrete value multiplied by a CRP weighing coefficient of value 1.43, and the second discrete value multiplied by a CNP weighing coefficient of value 1.17, and
- determining that the canine subject is a carrier of sepsis if said index value is above a criterion value of 2.86.

Change to a Treatment

A diagnostic method to determine probability of an oral disease state comprising

- (a) determining the levels of two or more biomarkers in a sample collected from a first individual, wherein a first biomarker is a bone-specific marker and a second biomarker is a plaque biofilm pathogen marker, said levels of said two or more biomarkers indicating the probability of said oral disease state, wherein the first biomarker is not type I collagen pyridinoline cross-linked telopeptide (ICTP); wherein elevated levels of said two or more biomarkers from said first individual compared to levels of identical biomarkers from a second, healthy individual, or compared to biomarker levels of said first individual measured at an earlier time point are indicative of occurrence of oral disease in said first individual with a probability of diagnosing the disease state equal to or greater than 70%; and
- (b) treating said oral disease by administering an amount of a therapeutic or prophylactic composition sufficient to reduce activity of said two or more biomarkers.

Make it a Specific Disease

A method for early stage detecting and treating a renal disease, which method comprises:

- (i) determining a human megalin level in a urine sample;
- (ii) screening for a patient who suffers from or is at high risk of the renal disease indicated by an increased level of human megalin in a urine sample in comparison to the human megalin level in a healthy subject; and
- (iii) treating the patient identified by step (ii),
- wherein the renal disease is selected from the group consisting of nephritis, nephropathy, and a renal tubular disorder.

Make it a Specific Treatment

A method for treating impaired fluid homeostasis in a subject having symptoms of, being diagnosed with, or being at risk of developing heart failure, wherein the method comprises:

- a) identifying the subject as in need of treatment for impaired fluid homeostasis by a method comprising:
  - (i) providing a sample from the subject;
  - (ii) measuring the quantity of circulating melanoma cell adhesion molecule (MCAM) in the sample from the subject;
  - (iii) comparing the quantity of circulating MCAM measured in (ii) with a reference value of the quantity of circulating MCAM, said reference value representing normal fluid homeostasis, and finding a deviation of the quantity of circulating MCAM measured in (ii) from said reference value so as to identify the subject as in need of the treatment,
  - wherein an increased quantity of circulating MCAM in the sample from the subject compared to a reference value representing normal fluid homeostasis identifies the subject as in need of treatment of impaired fluid homeostasis; and
- b) treating the subject having the deviation, with a treatment or therapy that restores fluid homeostasis by decreasing the fluid content, selected from the group consisting of treatment with exogenous and/or endogenous diuretic agents, ultrafiltration, and treatment with exogenous and/or endogenous vasopressive antagonists.

Add a Device Structure

A method of screening for increased risk of developing fatal prostate cancer in a human male subject in need thereof, comprising:

- providing a blood sample collected from said subject; and
- detecting the presence or absence of an increased level of serum calcium in said sample, an increased level of serum calcium indicating said subject is at increased risk of fatal prostate cancer;
- wherein said serum calcium is total serum calcium and said increased level is greater than 2.3 mmol/L, and said detecting step is carried out by absorption spectrometry.

Make it a Specific Device

An in vitro method for predicting the risk of heart failure in a human subject [ ], said method comprising the steps of:

- (i) measuring the level of troponin T phosphorylated on serine 207 in the troponin T pool in a blood sample obtained from the subject by an ELISA immunoassay consisting of: providing a microtiter plate coated with a set of antibodies specific for troponin T phosporylated on serine 207 [ ],
- (ii) comparing said measured level of troponin T phosphorylated on serine 207 to a control level of troponin T phosphorylated on serine 207 obtained from a healthy subject,
- (iii) wherein when the level of troponin T phosphorylated on serine 207 determined at step i) is lower than the control level of troponin T phosphorylated on serine 207, it is indicative of a high risk of heart failure.

Add an Unconventional Reagent

A method of screening for interstitial cystitis in a patient, said method comprising the steps of:

- (a) obtaining a fluid sample from a patient;
- (b) applying the sample to a detector device, wherein the detector device is a dipstick device, wherein the detector device comprises at least one detection reagent, wherein the detection reagent is a fragment of CKAP4 which comprises a polyhistidine tag at the end of said fragment of CKAP4, and wherein the detection reagent specifically binds antiproliferative factor (APF), further wherein the detection reagent is detectably labeled, wherein the binding of APF to the detection reagent provides detection of a threshold level of APF in the sample in the form of a visual indication that provides correlation with the presence of interstitial cystitis, and wherein the threshold level is above about 10 fMolar; and,
- (c) visualizing the dipstick device to ascertain a positive screen for interstitial cystitis.

Use a Useless Control

A method for determining if a subject has thyroid cancer, the method comprising

- (a) contacting a thyroid aspirate derived from the subject comprising galectin-3 with trypsin to digest galectin-3 and produce one or more biomarkers selected from the group consisting of SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, and any combination thereof,
- (b) adding a control biomarker to the thyroid aspirate, wherein the control biomarker is SEQ ID NO 5 or SEQ ID NO 6,
- (c) quantifying the amount of the biomarker in the thyroid aspirate by multiple reaction monitoring, and
- (d) comparing the amount of the biomarker in the thyroid aspirate to the amount of the same biomarker from a second thyroid aspirate from a subject that does not have thyroid cancer,
- wherein an increase in the amount of the biomarker in the thyroid aspirate as compared to the amount of the same biomarker from the second thyroid aspirate from the subject that does not have thyroid cancer is an indication of the presence of thyroid cancer in the subject.

Unduly Narrow Limitations Work

Most May Be Commercially Worthless

- Narrow ranges
- Treatment steps
- Treat a specific subset of diseases/afflictions
- Particular type of assay format, e.g., ELISA
- Device/structure limitations
- Unconventional reagents
  - Need not be patentable reagents

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