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(54) **NUCLEIC ACID BASED FLUORESCENT SENSOR FOR MERCURY DETECTION**

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(57) **ABSTRACT**

A nucleic acid enzyme comprises an oligonucleotide containing thymine bases. The nucleic acid enzyme is dependent on both $Hg^{2+}$and a second ion as cofactors, to produce a product from a substrate. The substrate comprises a ribonucleotide, a deoxyribonucleotide, or both.

28 Claims, 6 Drawing Sheets

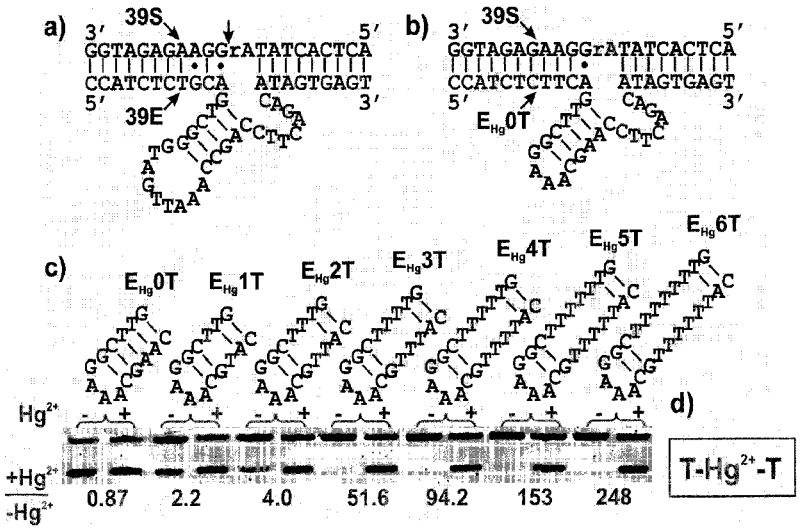

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FIGURE 1

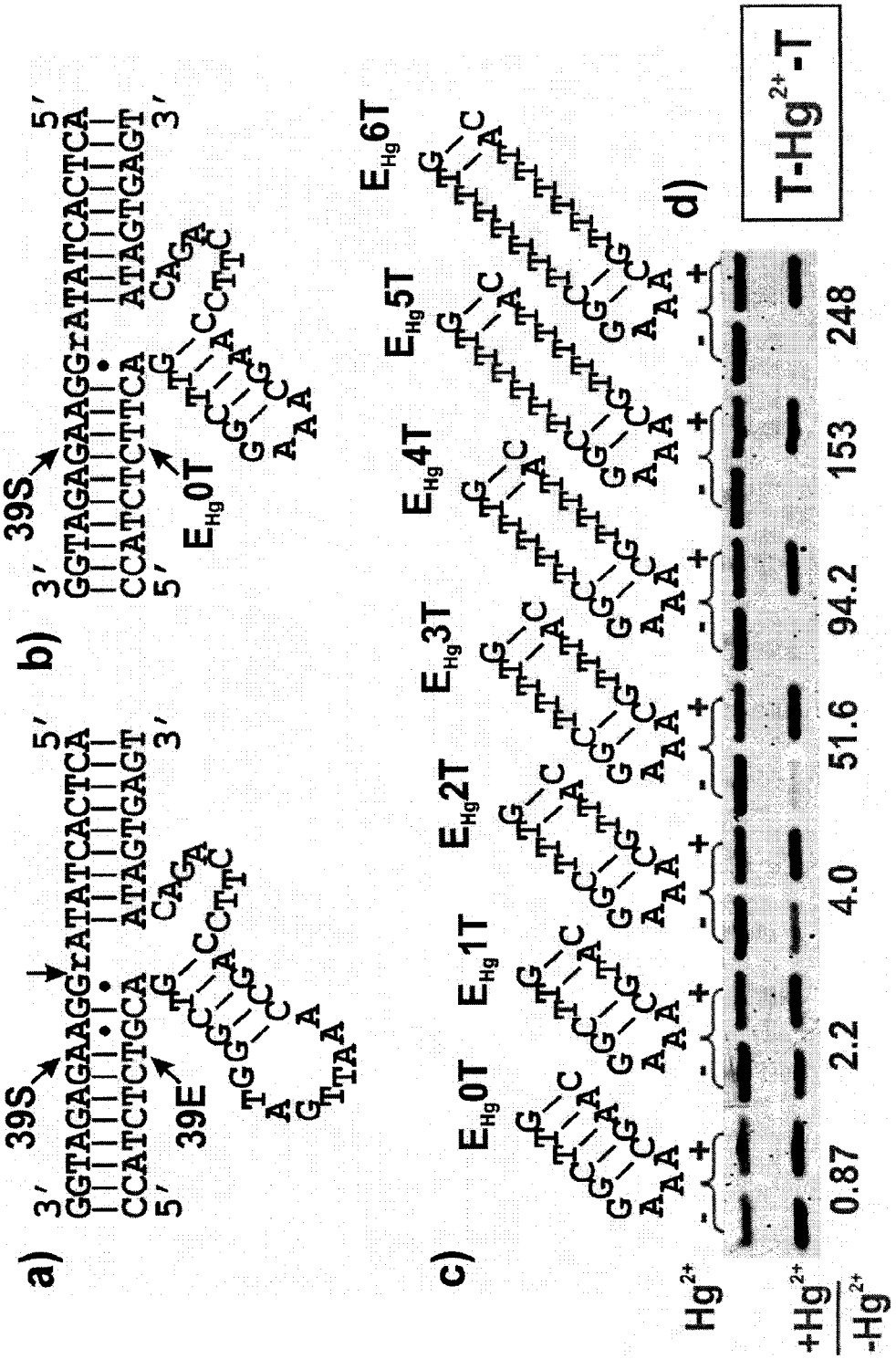

a)
b)
c)
d)
39S
39E
E_{Hg}0T
E_{Hg}1T
E_{Hg}2T
E_{Hg}3T
E_{Hg}4T
E_{Hg}5T
E_{Hg}6T
Hg^{2+}
$+Hg^{2+}$ / $-Hg^{2+}$
0.87
2.2
4.0
51.6
94.2
153
248
T-Hg^{2+}-T

FIGURE 2

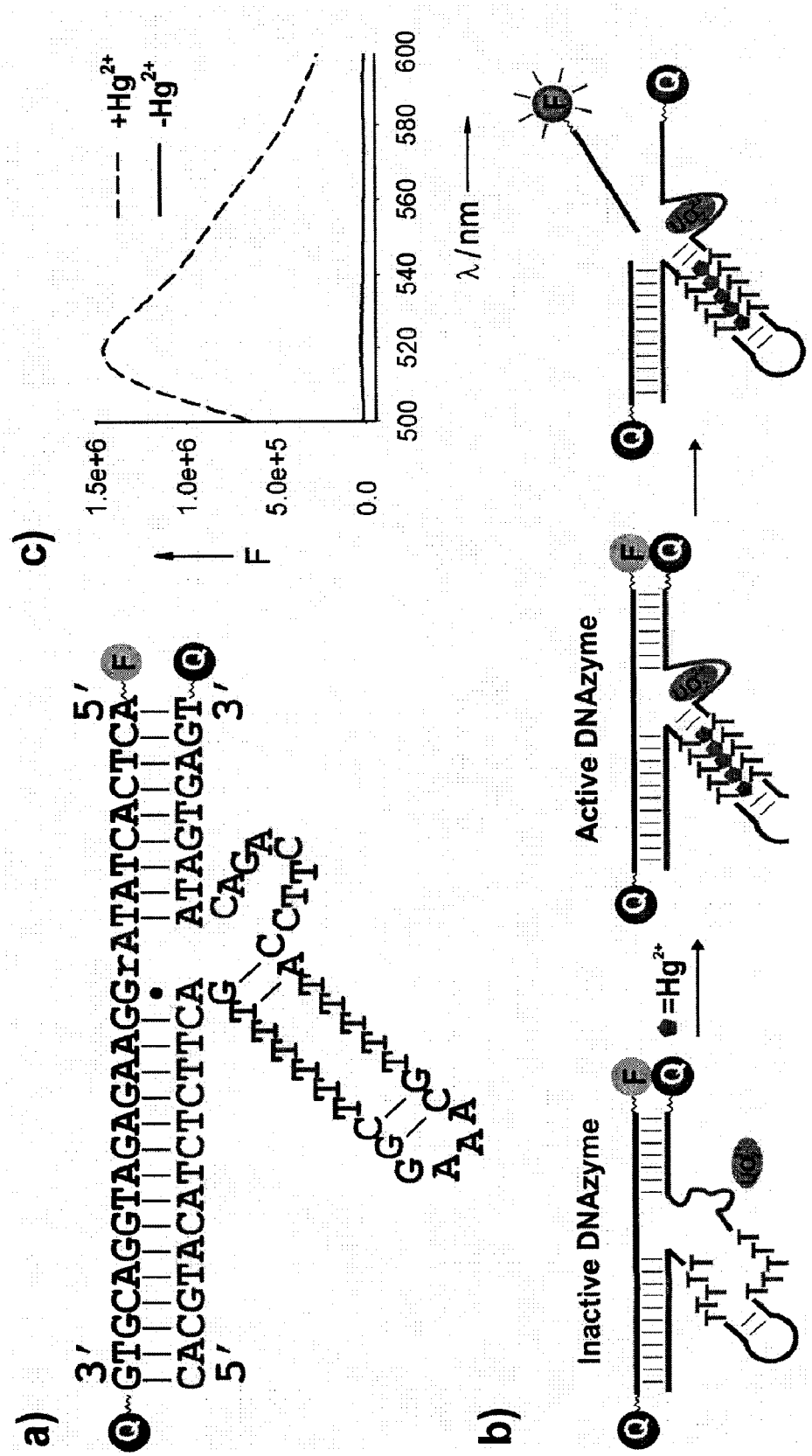

a)
3′
GTGCAGGTAGAGAAGGrATATCACTCA
CACGTACATCTCTTCA
5′
5′
ATAGTGAGT
3′
b)
Inactive DNAzyme
Active DNAzyme
=Hg2+
c)
+Hg2+
-Hg2+
1.5e+6
1.0e+6
5.0e+5
0.0
F
500
520
540
560
580
600
λ/nm

FIGURE 3

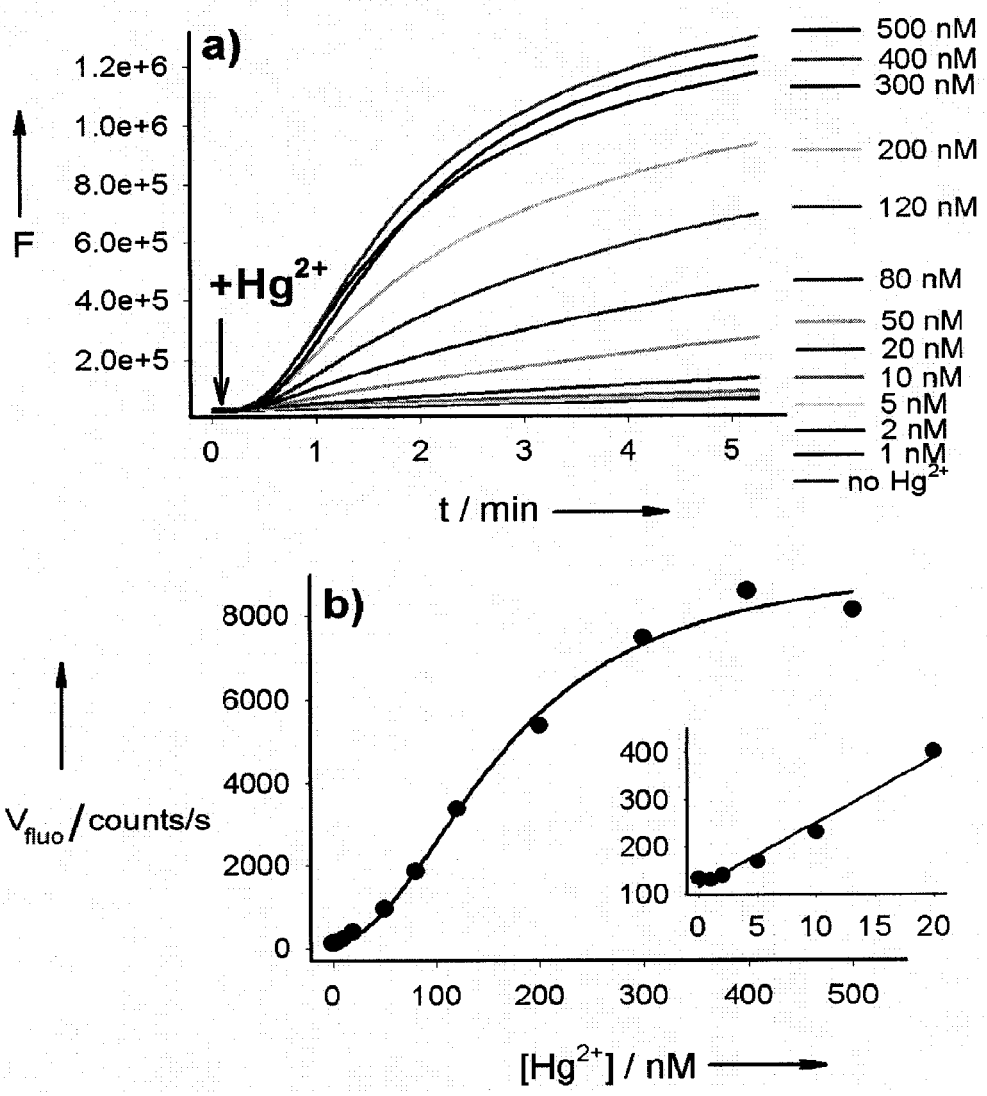

a)
1.2e+6
1.0e+6
8.0e+5
6.0e+5
4.0e+5
2.0e+5
F
+Hg2+
0
1
2
3
4
5
t / min
500 nM
400 nM
300 nM
200 nM
120 nM
80 nM
50 nM
20 nM
10 nM
5 nM
2 nM
1 nM
no Hg2+
b)
8000
6000
4000
2000
0
Vfluo / counts/s
0
100
200
300
400
500
[Hg2+] / nM
400
300
200
100
0
5
10
15
20

FIGURE 4

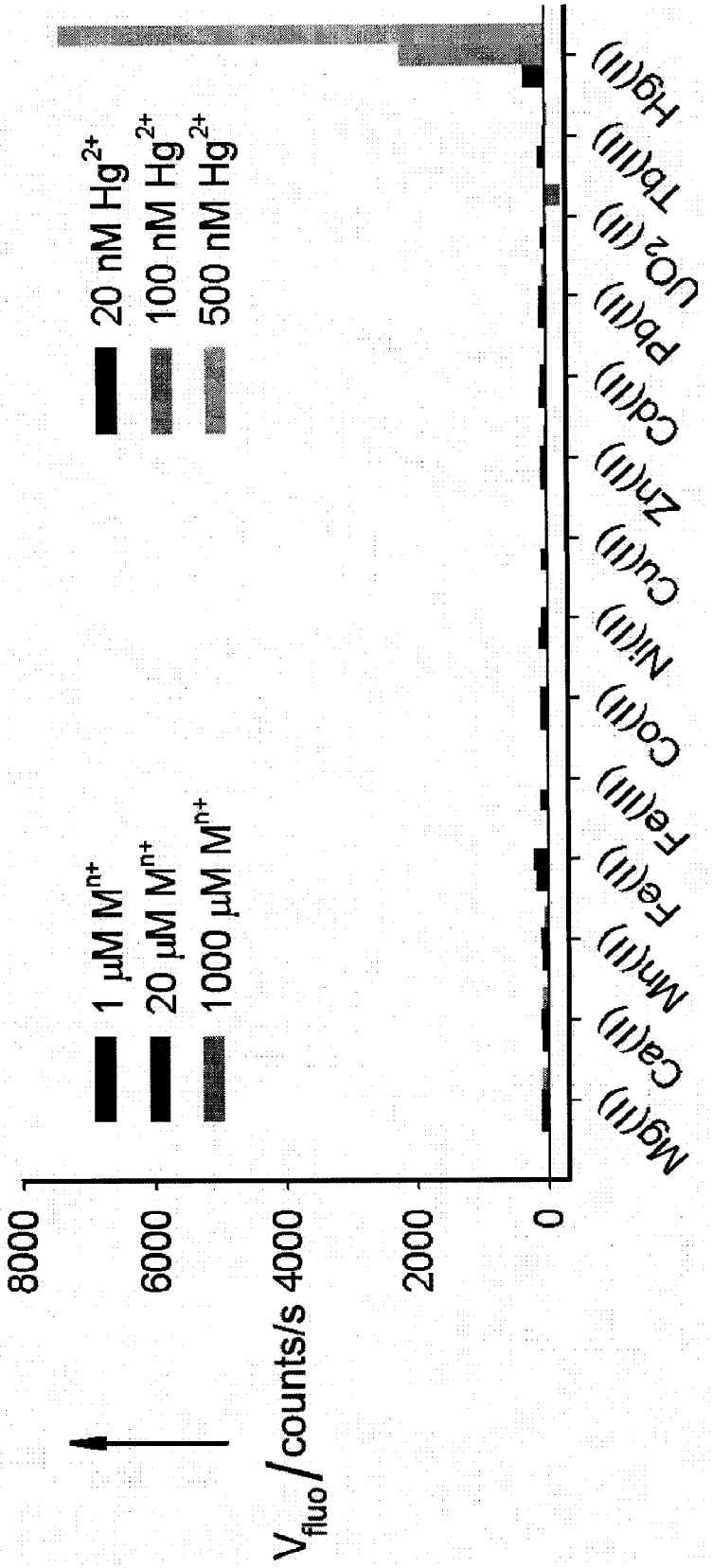

20 nM Hg2+
100 nM Hg2+
500 nM Hg2+
1 µM Mn+
20 µM Mn+
1000 µM Mn+
Vfluo / counts/s
8000
6000
4000
2000
0
Mg(II)
Ca(II)
Mn(II)
Fe(II)
Fe(III)
Co(II)
Ni(II)
Cu(II)
Zn(II)
Cd(II)
Pb(II)
UO2 (II)
Tb(III)
Hg(II)

FIGURE 5

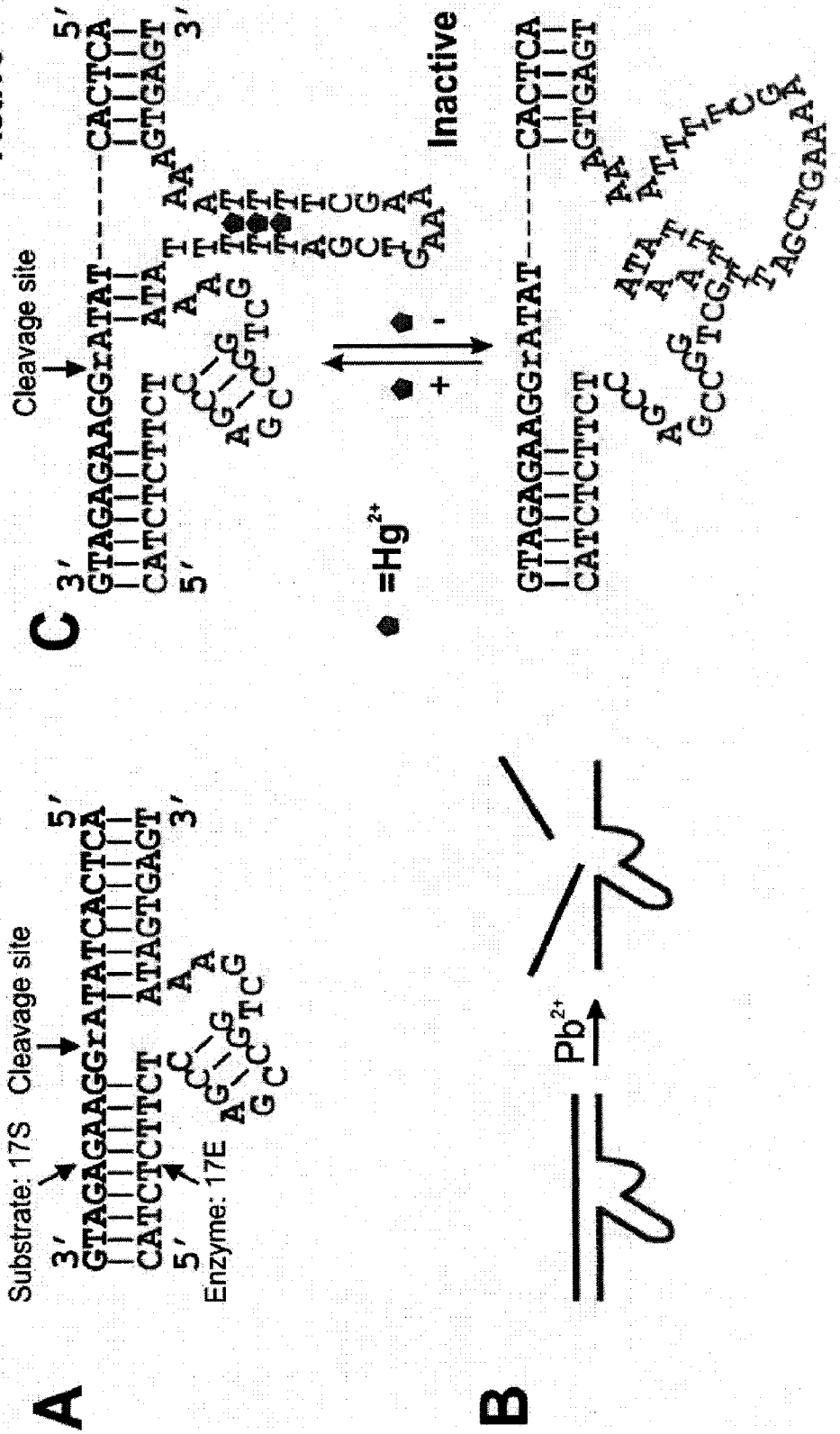
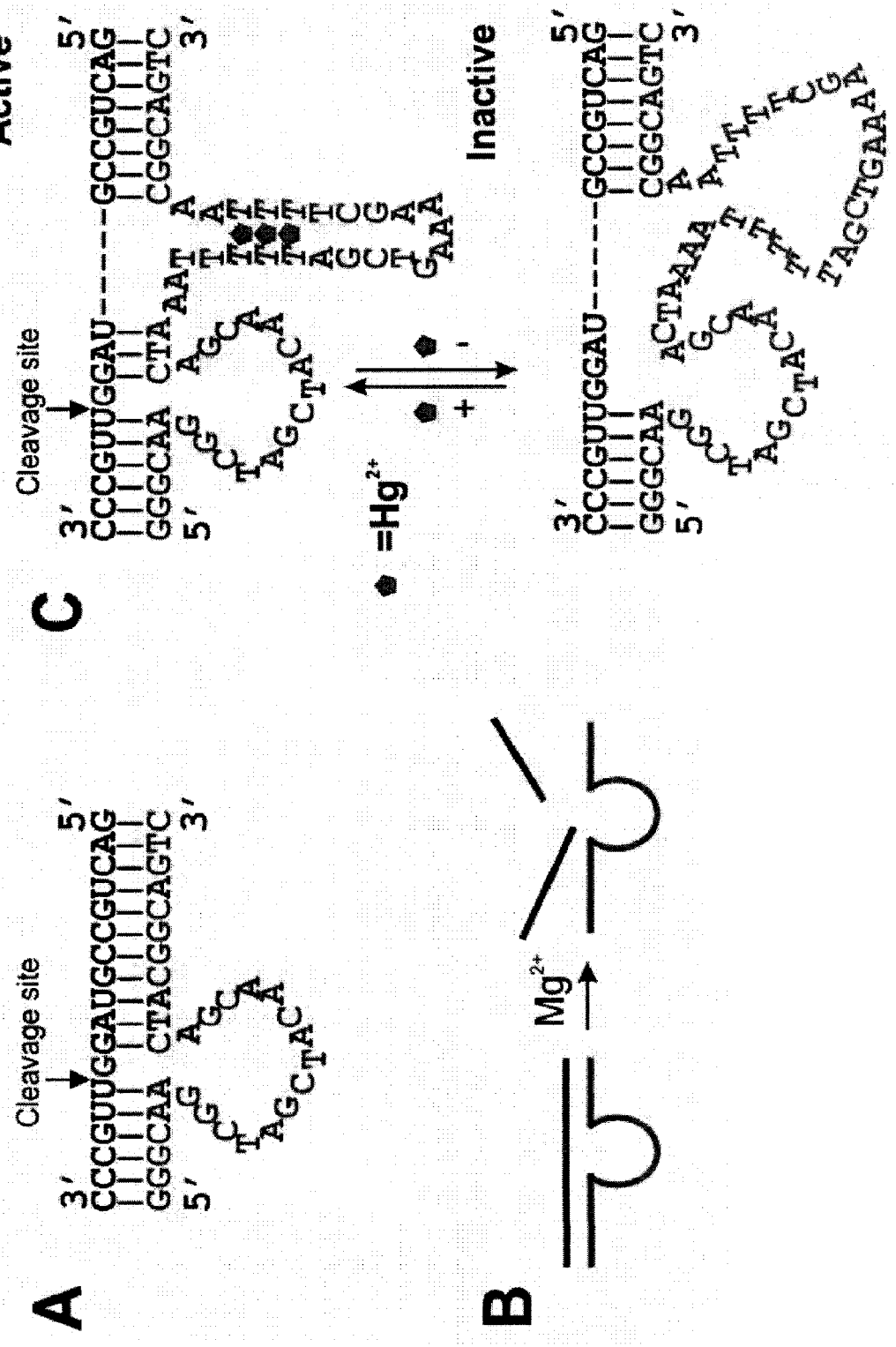

A
Substrate: 17S
Cleavage site
Enzyme: 17E
B
Pb2+
C
Active
Inactive
Cleavage site
=Hg2+
+
-

FIGURE 6


A
Cleavage site
3′
5′
5′
3′
B
Mg2+
C
Active
Inactive
Cleavage site
=Hg2+
-
+

NUCLEIC ACID BASED FLUORESCENT SENSOR FOR MERCURY DETECTION

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to provisional application No. 60/955,316 entitled "Nucleic Acid Based Fluorescent Sensor For Mercury Detection" filed 10 Aug. 2007, the entire contents of which are hereby incorporated by reference, except where inconsistent with the present application.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This subject matter of this application may have been funded in part under the following research grants and contracts: National Science Foundation Contract Numbers CTS-0120978 and DMI-0328162, and U.S. Department of Energy Contract Number DE-FG02-01-ER63179. The U.S. Government may have rights in this invention.

BACKGROUND

Mercury is a highly toxic heavy metal in the environment. Mercury exposure can cause a number of severe adverse health effects, such as damages in the brain, nerve system, immune system, kidney, and many other organs.[1] Mercury contamination comes from both nature and human activities, and an annual releasing of 4,400 to 7,500 metric tons of mercury to the environment was estimated by the United Nations Environment Programme (UNEP).[2] Therefore, highly sensitive and selective mercury sensors are very useful in understanding its distribution and pollution and in preventing mercury poisoning. Towards this goal, many fluorescent small organic molecule-based Hg^{2+} sensors have been reported, which change their emission properties upon binding to Hg^{2+}. Most of these sensors, however, require the involvement of organic solvent, show quenched emissions, and suffer from poor selectivity.[3-11] Only a few such sensors can detection Hg^{2+} in water with high sensitivity and selectivity.[12-17] Hg^{2+} sensors based on foldamers,[18, 19] oligonucleotides,[20] genetically engineered cells,[21] enzymes,[22] antibodies,[23] transcriptional regulatory proteins,[24,25] DNAzymes,[26] and chemically modified optical fibers[27,28] capillary optode,[29,30] membranes,[31] electrodes,[32,33] mesoporous silica,[34] and nanoparticles[35] are also known. For environmental monitoring applications, such as detection of Hg^{2+} in drinking water, a detection limit of lower than 10 nM (the toxic level defined by the US Environmental Protection Agency (EPA)) is required. However, few reported mercury sensors can reach such sensitivity.[11,21,25] We are interested in using catalytic DNA or DNAzymes to design metal sensors that can achieve the goal.[36,37]

DNAzymes are DNA-based biocatalysts.[38-42] Similar to protein enzymes or ribozymes, DNAzymes can also catalyze many chemical and biological transformations, and some of the reactions require specific metal ions as cofactors. Highly effective fluorescent and colorimetric sensors have been demonstrated for Pb^{2+} and UO_2^{2+} with DNAzymes.[36,37,43] These sensors showed picomolar to low nanomolar sensitivity and thousand to million-fold selectivity. In the presence of target metal ions, the fluorescence enhancement was generally greater than 10-fold, and signal generation took only 2 min or less. These sensors can be used at room temperature in aqueous solutions and no organic solvents are needed. Recently, DNAzyme-based electrochemical metal sensors

are also reported.[44] Compared to protein or RNA, DNA is relatively more cost-effective to produce and more stable. DNAzymes can be denatured and renatured many times without losing their activities.[39] Therefore, DNAzymes are useful in metal detection.

It was reported that Hg^{2+} can specifically bind in between two DNA thymine bases and promote such T-T mismatches into stable base pairs (FIG. **1***d*).[20,45,46] This property was applied by Ono and co-workers to design a fluorescent sensor for Hg^{2+} detection.[20] The sensor consisted of a single-stranded thymine rich DNA with the two ends labeled with a fluorophore and a quencher, respectively. In the presence of Hg^{2+}, the two ends were brought close to each other, resulting in decreased fluorescence. A detection limit of 40 nM was reported.[20] Being sensitive and selective, this sensor is a "turn-off" sensor and fluorescence intensity decreased in the presence of Hg^{2+}, which may give false positive results caused by external quenchers or other environmental factors that can also induce fluorescence decrease. The Hg^{2+} stabilization effects on T-T mismatches have also been applied to design colorimetric sensors with DNA-functionalized gold nanoparticles and a detection limit of 100 nM was achieved.[35] In previous DNAzyme work, a signaling method called catalytic beacon was designed in which the metal binding site in DNAzymes and the fluorescence signaling part are spatially separated.[36,37,47]

SUMMARY

In a first aspect, the present invention is a nucleic acid enzyme, comprising an oligonucleotide containing thymine bases. The nucleic acid enzyme is dependent on both Hg^{2+} and a second ion as cofactors, to produce a product from a substrate comprising a ribonucleotide, a deoxyribonucleotide, or both.

In a second aspect, the present invention is a method of detecting Hg^{2+} in a sample comprising forming a mixture comprising (1) a nucleic acid enzyme, (2) the sample, (3) a substrate, and (4) a second ion, to produce a product from the mixture; and determining the presence of the product. The enzyme comprises at least one quencher and is dependent on both the Hg^{2+} and the second ion as cofactors to produce the product from the substrate. Furthermore, the substrate comprises a ribonucleotide, a deoxyribonucleotide, or both, and the substrate comprises at least one fluorophore and at least one quencher.

In a third aspect, the present invention is a method of determining the concentration of Hg^{2+} in the presence of other ions, in a sample, comprising forming a mixture comprising (1) a nucleic acid enzyme, (2) the sample, (3) a substrate, and (4) a second ion, to produce a product from the mixture; determining the presence of the product; and determining the concentration of the Hg^{2+} by measuring an amount of the product produced. The enzyme comprises at least one quencher and is dependent on the Hg^{2+} and the second ion as cofactors to produce the product from the substrate. Furthermore, the substrate comprises a ribonucleotide, a deoxyribonucleotide, or both, and the substrate comprises at least one fluorophore and at least one quencher.

In a fourth aspect, the present invention is a sensor for Hg^{2+}, comprising (1) a nucleic acid enzyme, (2) a substrate, and (3) a second ion. The enzyme comprises at least one quencher and is dependent on both the Hg^{2+} and the second ion as cofactors to produce a product from the substrate. Furthermore, the substrate comprises a ribonucleotide, a deoxyribonucleotide, or both, and the substrate comprises at least one fluorophore and at least one quencher.

A "nucleic acid enzyme" is a nucleic acid molecule that catalyzes a chemical reaction. The nucleic acid enzyme may be covalently linked with one or more other molecules yet remain a nucleic acid enzyme. Examples of other molecules include dyes, quenchers, proteins, and solid supports. The nucleic acid enzyme may be entirely made up of ribonucleotides, deoxyribonucleotides, or a combination of ribo- and deoxyribonucleotides.

A "sample" may be any solution that may contain an ion (before or after pre-treatment). The sample may contain an unknown concentration of an ion. For example, the sample may be paint that is tested. The sample may be diluted yet still remain a sample. The sample may be obtained from the natural environment, such as a lake, pond, or ocean, an industrial environment, such as a pool or waste stream, a research lab, a common household, or a biological environment, such as blood. Of course, sample is not limited to the taking of an aliquot of solution but also includes the solution itself. For example, a biosensor may be placed into a body of water to measure for contaminants. In such instance, the sample may comprise the body of water or a particular area of the body of water. Alternatively, a solution may be flowed over the biosensor without an aliquot being taken. Furthermore, the sample may contain a solid or be produced by dissolving a solid to produce a solution. For example, the solution may contain soil from weapon sites or chemical plants.

"Measuring an amount of the product produced" includes measuring the result of the production of a product by an enzyme. For example, in an embodiment where the substrate comprises a quencher and fluorophore and the enzyme comprises a second quencher, and cleavage of the substrate by the enzyme leads to dissociation of the product from the enzyme, "measuring an amount of the product produced" includes detecting the increase of fluorescence. Thus, the product is measured by detecting its inability to quench fluorescence.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. (a) The secondary structure of the originally reported UO_2^{2+}-specific DNAzyme (SEQ ID NO: 1 (bottom strand) and SEQ ID NO: 2 (top strand)). (b) The new UO_2^{2+}-specific DNAzyme with the replaced stem loop. One of the A·G mismatches was also replaced by an A-T base pair (SEQ ID NO: 2 (top strand) and SEQ ID NO: 3 (bottom strand)). (c) The stem loop part of DNAzymes with zero to six T-T mismatches (top) (SEQ ID NOS: 25-31, respectively, in order of appearance from left to right). Gel image showing the fraction of cleavage after 1 min reaction time in the absence or presence of 10 μM Hg^{2+} (middle). The ratio of cleavage fraction after 1 min in the presence or absence of Hg^{2+} (bottom). (d) Schematics of a T-T mismatch stabilized by a Hg^{2+} ion.

FIG. **2**. (a) The secondary structure and modification of the Hg^{2+} sensor DNAzyme (SEQ ID NO: 33 (top strand) and SEQ ID NO: 32 (bottom strand)). (b) Schematic presentation of the sensor design. (c) Fluorescence spectra of the sensor (with the DNAzyme and 1 μM UO_2^{2+}) in the absence and 8 min after addition of 0.5 μM Hg^{2+}.

FIG. **3**. Sensitivity of the Hg^{2+} sensor. (a) Kinetics of fluorescence increase in the presence of varying concentrations of Hg^{2+}. (b) Hg^{2+} dependent fluorescence increase rate. Rates were calculated in the time window of 1-2 min in (a). Inset: sensor responses at low Hg^{2+} concentrations. The y-axis is the fluorescence counts increase per second. The DNAzyme and UO_2^{2+} concentrations were 100 nM and 1 μM, respectively.

FIG. **4**. Selectivity of the Hg^{2+} sensor. All competing metal ions were tested at 1, 20, and 1000 μM. For comparison, sensor responses to 20, 100, and 500 nM of Hg^{2+} were also presented. The DNAzyme and UO_2^{2+} concentrations were 100 nM and 1 μM, respectively.

FIG. **5**. Rational design of an allosteric Hg^{2+} DNAzyme based on the 8-17 DNAzyme. (A) the secondary structure of the 8-17 DNAzyme (SEQ ID NO: 11 (top strand) and SEQ ID NO: 10, (bottom strand)). (B) Schematics of cleavage of the 8-17 DNAzyme by Pb^{2+}. (C) Insertion of a stem in the enzyme strand with T-T mismatches can make the DNAzyme into a Hg^{2+} dependent enzyme (SEQ ID NO: 13 (top strand) and SEQ ID NO: 12 (bottom strand)).

FIG. **6**. Rational design of an allosteric Hg^{2+} DNAzyme based on the 10-23 DNAzyme. (A) the secondary structure of the 10-23 DNAzyme (SEQ ID NO: 15 (top strand) and SEQ ID NO: 14 (bottom strand)). (B) Schematics of cleavage of the 10-23 DNAzyme by Mg^{2+}. (C) Insertion of a stem in the enzyme strand with T-T mismatches can make the DNAzyme into a Hg^{2+} dependent enzyme (SEQ ID NO: 17 (top strand) and 16 (bottom strand)).

DETAILED DESCRIPTION

The present invention makes use of the discovery of new nucleic acid enzymes, which may be used in a sensor system for Hg^{2+}, and in a method of determining the concentration of mercury in a sample, especially in the presence of other ions. These new nucleic acid enzymes are designed from existing nucleic acid enzymes. The existing nucleic acid enzymes typically have a secondary structure necessary for activity, maintained by hybridization between bases within the nucleic acid enzyme. By introducing one or more thymine-thymine mismatches, opposite each other and within those hybridized portions of the nucleic acid enzyme which maintain the secondary structure, the secondary structure is destabilized. When Hg^{2+} is present, however, it causes the T-T mismatches to form stable base pairs, stabilizing the secondary structure and restoring activity. These new nucleic acid enzymes require two different ions as cofactors: the original ion and Hg^{2+}.

It is also possible to artificially create such secondary structure stabilizing bases in the nucleic acid enzyme by introducing a stem loop having at least two consecutive pairs of hybridizing nucleotides in the stem loop and at least three nucleotides in between; one or two additional nucleotides may also be included at each end of the introduced section. The nucleic acid enzyme can then be made response to Hg^{2+} by introducing one or more pairs of thymine bases, opposite each other and within those hybridized portions of the nucleic acid enzyme which maintain the secondary structure. Again, the result is a nucleic acid enzyme having two different ions as cofactors: the original ion and Hg^{2+}.

The present invention provides a simple, rapid, inexpensive, selective and sensitive method for detecting the presence of Hg^{2+}, with background fluorescence signal near zero, and is an important and useful tool in preventing or at least lowering health and environmental risks associated with the environmental contaminant Hg^{2+}. A nucleic acid enzyme that catalyzes the cleavage of a nucleic acid in the presence of two ions, Hg^{2+} and a second ion, is used. The nucleic acid enzyme may be RNA (ribozyme), DNA (deoxyribozyme), a DNA/RNA hybrid enzyme, or a peptide nucleic acid (PNA) enzyme. PNAs comprise a polyamide backbone and the bases found in naturally occurring nucleosides and are commercially available, e.g., from Biosearch, Inc. (Bedford, Mass.). Nucleic acids including nucleotides containing modified bases, phosphate, or sugars may be used in the compositions and methods of the present invention. Modified bases are well

known in the art and include inosine, nebularine, 2-aminopurine riboside, N^7-denzaadenosine, and O^6-methylguanosine.[55] Modified sugars and phosphates are also well known and include 2'-deoxynucleoside, abasic, propyl, phosphorothioate, and 2'-O-allyl nucleoside.[55] DNA/RNA hybrids and PNAs may be used in the compositions and methods of the present invention.

A highly sensitive and selective catalytic beacon for mercury was rationally designed based on a uranium-specific DNAzyme, shown in FIG. **2**(*a*). Hg^{2+} enhanced the DNAzyme activity through allosteric interactions, and a series of allosteric DNAzymes with varying number of thymine-thymine mismatches were tested. The optimal DNAzymes was labeled with fluorophore and quenchers to construct a catalytic beacon. The sensor has a detection limit of 2.4 nM, which is lower than the EPA limit of Hg^{2+} in drinking water. It is also highly selective and is silent to any other metal ions with up to millimolar concentration levels. The catalytic beacon performance may be further improved by incorporation of in vitro selections to optimize the allosteric interactions.[52] This work further demonstrated that DNAzymes are a great platform for metal sensing. Additional nucleic acid enzymes, using the same strategy, have also been designed, and their sequences are shown in the table along with nucleic acid enzyme used to design the highly sensitive and selective catalytic beacon for mercury.

The nucleic acid enzymes and their substrates may be used in a "turn-on" sensor for Hg^{2+}. These sensors are similar to those described in U.S. Pat. No. 6,890,719, except that the nucleic acid enzyme requires Hg^{2+} and a second ion as cofactors. For the sensor to be responsive to Hg^{2+}, the second ion is included with the sensor. The second ion may be monovalent, divalent, trivalent, or polyvalent. Examples of monovalent cations include K^+, Na^+, Li^+, Tl^+, NH_4^+ and Ag^+. Examples of divalent cations include Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Pb^{2+}, Pt^{2+}, Ra^{2+}, Ba^{2+}, UO_2^{2+} and Sr^{2+}. Examples of trivalent cations include Co^{3+}, Cr^{3+}, and lanthanide ions (Ln^{3+}). Polyvalent cations include Ce^{4+}, and Cr^{6+}. The second ion also includes ions having a metal in a variety of oxidation states. Examples include K(I), Na(I), Li(I), Tl(I), Ag(I), Hg(I), Mg(II), Ca(II), Mn(II), Co(II), Ni(II), Zn(II), Cd(II), Pb(II), Pt(II), Ra(II), Ba(II), Sr(II), Co(III), Cr(III), Ln(III), Ce(IV), Cr(VI) and U(VI).

The sequences of nucleic acid enzymes are indicated in the table below, along with specific examples, and substrates for the enzymes. R, Y, r and n represent purine, pyrimidine, a ribonucleotide and any nucleotide, respectively. F indicates a fluorophore, and Q indicates a quencher. The cofactor(s) for the enzyme is (are) included in the first column. Preferably, the nucleic acid enzyme contains 38 to 100 bases.

Nucleic acid enzyme 39E (UO_2^{2+})(FIG. 1(a))	5' CCA TCT CTG CA G TCG G GT AGT TAA A CC GAC CTT CAG AC A TAG TGA GT 3'	SEQ ID NO: 1
39S (substrate for 39E; FIG. 1(a))	3' GGT AGA GAA GGr ATA TCA CTC A 5'	SEQ ID NO: 2
Nucleic acid enzyme E_{Hg}0T (UO_2^{2+}; FIG. 1(b))	5' CCA TCT CTT CA G TTC G GA AA C GAA C CT TCA GAC ATA GTG AGT 3'	SEQ ID NO: 3
Nucleic acid enzyme E_{Hg}1T (UO_2^{2+} and Hg^{2+}; FIG. 1(c))	5' CCA TCT CTT CA G TTC G GA AA C GTA C CT TCA GAC ATA GTG AGT 3'	SEQ ID NO: 4
Nucleic acid enzyme E_{Hg}2T (UO_2^{2+} and Hg^{2+}; FIG. 1(c))	5' CCA TCT CTT CA G TTTC G GA AA C GTT A C CT TCA GAC ATA GTG AGT 3'	SEQ ID NO: 5
Nucleic acid enzyme E_{Hg}3T (UO_2^{2+} and Hg^{2+}; FIG. 1(c))	5' CCA TCT CTT CA G TTT TC G GA AA C GTT TA C CT TCA GAC ATA GTG AGT 3'	SEQ ID NO: 6
Nucleic acid enzyme E_{Hg}4T (UO_2^{2+} and Hg^{2+}; FIG. 1(c))	5' CCA TCT CTT CA G TTT TTC G GA AA C GTT TTA C CT TCA GAC ATA GTG AGT 3'	SEQ ID NO: 7
Nucleic acid enzyme E_{Hg}5T (UO_2^{2+} and Hg^{2+}; FIG. 1(c))	5' CCA TCT CTT CA G TTT TTT C G GA AA C GTT TTT A C CT TCA GAC ATA GTG AGT 3'	SEQ ID NO: 8
Nucleic acid enzyme E_{Hg}6T (UO_2^{2+} and Hg^{2+}; FIG. 1(c))	5' CCA TCT CTT CA G TTT TTT TC G GA AA C GTT TTT TA C CT TCA GAC ATA GTG AGT 3'	SEQ ID NO: 9
Nucleic acid enzyme 17E (Pb^{2+}; FIG. 5A)	5' CAT CTC TTC TCC GAG CCG GTC GAA ATA GTG AGT 3'	SEQ ID NO: 10
17S (substrate for 17E; FIG. 5A)	3' GTA GAG AAG GrA TAT CAC TCA 5'	SEQ ID NO: 11
Nucleic acid enzyme $17E_{Hg}$ (Pb^{2+} and Hg^{2+}; FIG. 5C)	5' CAT CTC TTC TCC GAG CCG GTC GAA ATA TTT TTA GCT GAA AAG CTT TTA AAA GTG AGT 3'	SEQ ID NO: 12
$17S_{Hg}$ (substrate for $17E_{Hg}$; FIG. 5C)	3' GTA GAG AAG GrA TAT nnn CAC TCA 5'	SEQ ID NO: 13

-continued

Nucleic acid enzyme 6E (Mg^{2+}; FIG. 6A)	5' GGG CAA GGC TAG CTA CAA CGA CTA CGG CAG TC 3'	SEQ ID NO: 14
6S (substrate for 6E; FIG. 6A)	3' CCC GUU G GAU GCC GUC AG 5'	SEQ ID NO: 15
Nucleic acid enzyme $6E_{Hg}$ (Mg^{2+} and Hg^{2+}; FIG. 6C)	5' GGG CAA GGC TAG CTA CAA CGA CTA AAT TTT TAG CTG AAA AGC TTT TAA CGG CAG TC 3'	SEQ ID NO: 16
$6S_{Hg}$ (substrate for $6E_{Hg}$; FIG. 6C)	3' CCC GUU G GAU nnn GCC GUC AG 5'	SEQ ID NO: 17
Nucleic acid enzyme E2112 (Mn^{2+}) [53]	5' GAA TCG AAC T GTC AGT GAC TCG AAA GCA CGG A 3'	SEQ ID NO: 18
S2112 (substrate for E2112) [53]	3' CTT AGC TTGG n nr TCG TGCCT 5'	SEQ ID NO: 19
Nucleic acid enzyme $E2112_{Hg(a)}$ (Mn^{2+} and Hg^{2+})	5' GAA TCG AAC T GTTTTC AGT GTTATC TCG AAA GCA CGG A 3'	SEQ ID NO: 20
Nucleic acid enzyme $E2112_{Hg(b)}$ (Mn^{2+} and Hg^{2+})	5' GAA TCG AAC T GTTTTTC AGT GTTATTC TCG AAA GCA CGG A 3'	SEQ ID NO: 21
Nucleic acid enzyme $E_{Hg}XT$ (UO_2^{2+} and Hg^{2+}) (consensus sequence)	5' nnn YYY YYY Y AGT T_m YR nnnn YR T_m AC CT TCA GAC A YRR YRR nn 3' (m = 1-6)	SEQ ID NO: 22
Nucleic acid enzyme $17E_{Hg(x)}$ (Pb^{2+} and Hg^{2+}) (consensus sequence)	5' nnY YYY YYY TCC Gnn nCG GTC GAA A TA TT T_p A GC T nnnn AG CT T_p A A nn RYR RRY 3' (p = 1-6)	SEQ ID NO: 23
Nucleic acid enzyme $6E_{Hg(x)}$ (Mg^{2+} and Hg^{2+}) (consensus sequence)	5' RRR YR A GGC TAG CTA CAA CGA C TA AAT T T_q AG CT nnnn AGC TT_q AA YRR YRR nn 3' (q = 1-6)	SEQ ID NO: 24

F indicates a fluorophore, and Q indicates a quencher. Essentially any fluorophore may be used, including BODIPY, fluoroscein, fluoroscein substitutes (Alexa Fluor dye, Oregon green dye), long wavelength dyes, and UV-excited fluorophores. These and additional fluorophores are listed in Fluorescent and Luminescent Probes for Biological Activity. A Practical Guide to Technology for Quantitative Real-Time Analysis, Second Ed. W. T. Mason, ed. Academic Press (1999)[56]. In preferred embodiments, the fluorophore is 6-carboxyfluorescein (FAM). FAM has an excitation range of 460-500 nm.

Other fluorophores included quantum dots and silica nanoparticles. Each type of quantum dot displays a unique emission wavelength. Preferred quantum dot particles include quantum dot semiconductors, such as CdS, CdSe, CdTe, ZnS, ZnSe, ZnTe, PIn, and PbSe. Additional preferred quantum dots may include ternary quantum dots, such as $Cd_xZn_{1-x}Se$ or CdS_xSe_{1-x}. Additional preferred quantum dots may include core-shell quantum dots, such as those having a CdSe core and ZnS shell. The quantum dots can also have different morphologies, including dots, rods, tetrapods, and the like. In a preferred aspect, the particles are quantum dot semiconductors having average diameter from 2 to 50 nanometers.

A quencher is a molecule that absorbs the energy of the excited fluorophore. Close proximity of a fluorophore and a quencher allow for the energy to be transferred from the fluorophore to the quencher. By absorbing this energy, the quencher prevents the fluorophore from releasing the energy in the form of a photon, thereby preventing fluorescence.

Quenchers may be categorized as non-fluorescent and fluorescent quenchers. Non-fluorescent quenchers are capable of quenching the fluorescence of a wide variety of fluorophores. Generally, non-fluorescent quenchers absorb energy from the fluorophore and release the energy as heat. Examples of non-fluorescent quenchers include 4-(4'-dimethylaminophenylazo)benzoic acid) (Dabcyl), QSY-7, and QSY-33.

Fluorescent quenchers tend to be specific to fluorophores that emit at a specific wavelength range. Fluorescent quenchers often involve fluorescence resonance energy transfer (FRET). In many instances the fluorescent quencher molecule is also a fluorophore. In such cases, close proximity of the fluorophore and fluorescent quencher is indicated by a decrease in fluorescence of the "fluorophore" and an increase in fluorescence of the fluorescent quencher. Commonly used fluorescent fluorophore pairs (fluorophore/fluorescent quencher) include fluorescein/tetramethylrhodamine, IAEDANS/fluorescein, fluorescein/fluorescein, and BODIPY FL/BODIPY FL.

When choosing a fluorophore, a quencher, or where to position these molecules, it is important to consider, and preferably to test, the effect of the fluorophore or quencher on the enzymatic activity of the nucleic acid enzyme. Also, it is preferable that the fluorophore display a high quantum yield and energy transfer efficiency. Long-wavelength (excitation and emission) fluorophores are preferred because of less interference from other absorbing species. The fluorophore should also be less sensitive to pH change or to non-specific quenching by metal ions or other species.

Methods and devices for detecting fluorescence are well developed. Essentially any instrument or method for detecting fluorescent emissions may be used. For example, WO 99/27351 describes a monolithic bioelectrical device comprising a bioreporter and an optical application specific inte-

grated circuit (OASIC).[57] The device allows remote sampling for the presence of substances in solution. Furthermore, the fluorescence may be measured by a number of different modes. Examples include fluorescence intensity, lifetime, and anisotropy in either steady state or kinetic rate change modes.[58]

Sometimes other factors in a solution such as pH, salt concentration or ionic strength, or viscosity will have an effect on fluorescence, and may even affect the hybridization of the substrate and enzyme. Therefore, in preferred methods, controls are run to determine if the solution itself, regardless of enzymatic activity, is altering the fluorescence. Such controls include the use of non-cleavable substrates and or substrate without the presence of enzyme.

The sensor system may be used to determine an amount of mercury in a sample, such as a water sample, a biological sample (such as blood or serum), or a solid sample, such as soil or paint. Preferably, a solid sample is first dissolved into solution. The samples may be diluted or concentrated prior to testing, and may also be buffered. The sensor system is able to determine an amount of mercury in the presence of other ions, preferably other metal ions, such as Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, UO_2^{2+} and Tb^{3+}, or in the presence of other ions.

In light of the present disclosure, one of ordinary skill in the art would know how to modify the nucleic acid biosensors to include nucleic acid enzymes. For example, a biosensor of the present invention may comprise a nucleic acid enzyme labeled with a fluorescent quencher, a substrate labeled with a fluorophore and a second fluorescent quencher, and a device to detect fluorescence such as a fluorescence microscope or a fluorometer. In a method using this embodiment, the enzyme and substrate are contacted with a sample suspected of containing an ion to which the enzyme is sensitive. Fluorescence is measured and compared to a control wherein the ion is absent. Change in fluorescence is indicative of the presence of the ion.

Of course, many variants of even this simple embodiment are included within the scope of the invention. Such variants include placing the enzyme, substrate, and sample in the well of a microtiter plate and measuring fluorescence with a microtiter plate reader. In another variation, the enzyme is attached to a solid support. When the enzyme is attached to a solid support, it is preferable that a linker is used. An exemplary linking system is biotin/streptavidin. For example, the biotin molecule may be linked to the enzyme and a plate may be coated with streptavidin. When linking an enzyme to a solid support, it is important to determine the effect of linkage on the enzymatic activity of the enzyme.

In an alternative embodiment, the solid support may be a bead and fluorescence measured using a flow cytometer. In embodiments having the enzyme attached to a solid support, the biosensor may be reusable. Old substrate and sample is removed, leaving the enzyme in place. New substrate and sample may then be added.

Recently, a UO_2^{2+}-specific DNAzyme was isolated by in vitro selection.[37] The secondary structure of the DNAzyme is shown in FIG. **1***a*, which contained a substrate strand (39S) and an enzyme strand (39E). 39S has a single RNA linkage (rA) that serves as the cleavage site. 39E binds 39S through two substrate binding arms. The catalytic core in 39E contains a stem loop and an eight-nucleotide bulge. Further studies indicated that the exact nucleotide sequence in the stem loop was unimportant for activity, as long as such a structure was maintained. For example, by replacing the stem loop to that shown in FIG. **1***b*, the DNAzyme was still active. In addition to the change made to the stem loop, one of the A·G mismatches in the left substrate binding arm away from the cleavage site in FIG. **1***a* was replaced by a A-T Watson-Crick base pair, while the other A·G mismatch close to the cleavage site was maintained. The new enzyme strand was then named $E_{Hg}0T$ (FIG. **1***b*), which was used as a scaffold to engineer allosteric DNAzymes that can detect Hg^{2+}. In addition to having such a replaceable stem loop, the uranium DNAzyme was chosen for Hg^{2+} sensing also for the following reasons. First, this DNAzyme is active only in the presence of UO_2^{2+} and 1 μM UO_2^{2+} is sufficient to saturate its activity.[37] Unlike other common metal ions, UO_2^{2+} does not present in high concentrations in most environmental samples. Therefore, if the sensor system is saturated with UO_2^{2+}, external metals are unlikely to interfere with the detection. Even though uranium is a radionuclide, 1 μM UO_2^{2+} does not cause health or environmental concerns because uranium is ubiquitous in the environment, and even in drinking water, 130 nM uranium is allowed, according to the US EPA. Since the sensing application requires only 500 μL or less sensor samples, the environmental impact is negligible. Second, the enzyme kinetics is fast. The $E_{Hg}0T$ DNAzyme shown in FIG. **1***b* has a rate constant of 2.0 min^{-1} in the presence of 1 μM UO_2^{2+}, which allows fast sensor response. Finally, the DNAzyme is relatively small in size and can be chemically synthesize and modified with high yield.

To incorporate Hg^{2+} recognition elements into the DNAzyme, using rational design methods by introducing one to six T-T mismatches in stem region of $E_{Hg}0T$ (FIG. **1***c*). All other nucleotides were kept the same. The sequence of $E_{Hg}0T$ was designed in such a way that no stable secondary structures in the catalytic cores of all the DNAzymes (from $E_{Hg}1T$ to $E_{Hg}6T$) involving the thymine insertions were predicted by the Mfold program.[48] As a result, the DNAzymes cannot fold into their active structures in the absence of Hg^{2+}. Addition of Hg^{2+} should quickly fold the DNAzymes into their active conformations without kinetic traps. Because the effect of Hg^{2+} is spatially away from the UO_2^{2+} binding site, such DNAzymes belongs to allosteric DNAzymes.[49]

Experimental Details

To test whether Hg^{2+} can enhance the activity of these thymine rich

DNAzymes, 1 μM of the DNAzyme complexes were incubated with 10 μM Hg^{2+} for 10 min. at room temperature. The substrate strand was labeled with a FAM fluorophore on the 5'-end. UO_2^{2+} was added to initiate the cleavage reaction. After 1 min, the reaction was stopped and the samples were loaded onto a 20% denaturing polyacrylamide gel to separate the cleaved and uncleaved substrate. As shown in FIG. **1***c*, in all the DNAzymes with T-T mismatches, the fraction of cleavage was higher in the presence of Hg^{2+}, suggesting that Hg^{2+} indeed helped to stabilize the stem loop structure and made the DNAzymes more active. For the $E_{Hg}1T$, $E_{Hg}2T$, and $E_{Hg}3T$ DNAzymes, the cleavage bands in the absence of Hg^{2+} were also quite clear, suggesting that the DNAzymes may transiently fold into their active conformations even with several T-T mismatches. Such tolerability, however, dropped very quickly as the number of mismatches increases. For each DNAzyme, the ratio of cleavage fraction in the presence and absence of Hg^{2+} was determined (bottom of FIG. **1***c*), which approximately represents the fold of activity enhancement caused by Hg^{2+}, and this value positively correlates with signal-to-background ratio for sensing applications.

In the above experiment, the DNAzymes were first allowed to equilibrate with Hg^{2+}, and UO_2^{2+} was added to initiate the reaction. To detect Hg^{2+}, it is more desirable to add Hg^{2+} to the DNAzyme/UO_2^{2+} mixture to initiate the cleavage reaction. Because $E_{Hg}5T$ and $E_{Hg}6T$ showed the highest activity

enhancement by Hg^{2+}, the rates of cleavage initiated by adding 10 μM Hg^{2+} to the mixture of 1 μM DNAzyme and 1 μM UO_2^{2+} was calculated. Compared to the original DNAzyme $E_{Ng}0T$, which had a rate constant of 2.0 min^{-1}, the values for $E_{Hg}5T$ and $E_{Hg}6T$ were 0.61 and 0.45 min^{-1}, respectively. Therefore, DNAzymes with more T-T mismatches had lower rates, which could be explained by that it took more time for longer DNA to find the right conformation. As a compromise between the rate of the reaction and the fold of activity enhancement, $E_{Hg}5T$ was chosen for further studies.

The Hg^{2+} catalytic beacon is shown in FIG. **2***a*. The original $E_{Hg}5T$ enzyme strand was extended on the 5'-end by five nucleotides, and the substrate was also extended accordingly to form base pairs with the extended enzyme. Such extensions were made to increase the hybridization efficiency between the two strands. To generate signal, a fluorophore (FAM) was labeled on the 5'-end of the substrate, a quencher was labeled on the 3'-end of the enzyme, and an additional quencher was attached on the 3'-end of the substrate. Both quenchers were black hole quenchers. Such dual quencher labeling method gave very low background fluorescence and therefore allowed high signal enhancement.[50] The DNAzyme was mixed with UO_2^{2+} to become a mercury sensor (FIG. **2***b*). In the absence of Hg^{2+}, the DNAzyme was incapable of binding UO_2^{2+} because of the active secondary structure cannot form. Addition of Hg^{2+} quickly restored the stem loop structure and activated the DNAzyme to cleave the substrate, releasing the fluorophore-labeled piece and giving increased fluorescence. The fluorescence spectra of the sensor before and 8 min after addition of 500 nM Hg^{2+} is shown in FIG. **2***c*, and ~50-fold increase in the 520 nm peak was observed. Such level of fluorescence increase is among the highest in functional nucleic acid based sensors.[51]

Given the very high fluorescence enhancement, the DNAzyme was titrated with varying concentrations of Hg^{2+} and the kinetics of fluorescence enhancement at 520 nm was monitored. As shown in FIG. **3***a*, higher concentrations of Hg^{2+} produced higher rates of emission enhancement. All the kinetic traces showed a roughly linear increase in 1-2 min time window after addition of Hg^{2+} and therefore the rate of fluorescence increase in this window was calculated to quantify Hg^{2+} concentration (FIG. **3***b*). The Hg^{2+}-dependent response had a sigmoid shape and was fit to a Hill plot with a Hill coefficient of 2.1. This result suggests that Hg^{2+} binding to the DNAzyme is a cooperative process. Although the DNAzyme has five Hg^{2+} binding sites, the DNAzyme is stable enough to cleave its substrate after binding ~2 Hg^{2+} ions. The detection limit was determined to be 2.4 nM based on 3σ/slope (inset of FIG. **3***b*), which was a ~16-fold improvement compared to the previous oligonucleotide folding based sensor.[20] Among all the reported Hg^{2+} sensors made from small and macro-molecules, this catalytic beacon has the best detection limit. The US EPA defined the toxic level of Hg^{2+} in drinking water to be 2 parts-per-billion or 10 nM, which can be covered by the beacon.

To test selectivity, the catalytic beacon responses in the presence of 13 competing metal ions were assayed (FIG. **4**). Each metal was tested at three concentrations (1, 20, and 1000 μM). None of the metal ions gave responses higher than half of that produced by 20 nM Hg^{2+}, and the selectivity was determined to be at least 100,000-fold higher for Hg^{2+} over any other metal ions (10 nM Hg^{2+} versus 1 mM competing metal ions).

Materials: All DNA samples were purchased from Integrated DNA Technologies Inc. (Coralville, IA, USA) and were purified by HPLC by the company. Uranium acetate dihydrate was purchased from Fisher Scientific (Hampton, N.H., USA) and other metal salts used in this work include: $MgCl_2$, $CaCl_2$, $Mn(OAc)_2$, $Fe(NH_4)_2(SO_4)_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$, $Cu(NO_3)_2$, $ZnCl_2$, $Cd(OAc)_2$, $Hg(ClO_4)_2$, $Pb(NO_3)_2$, and $TbCl_3$.

Gel based assay: 1 μM 5'-FAM labeled 39S and 1 μM enzyme were annealed in 10 mM MES buffer pH 5.5 with 300 mM $NaNO_3$ by heating at 65° C. for 1 min and subsequently cooling slowly to room temperature in 30 min. For the experiment shown in FIG. **1***c*, 8 μL of the annealed DNAzymes were placed in microcentrifuge tubes and 1 μL of 100 μM $Hg(ClO_4)_2$ was added. The system was allowed to incubate at room temperature for 10 min and 1 μL of 10 μM UO_2^{2+} was added to initiate the cleavage reaction. The reaction was stopped after 1 min by adding 10 μL of stop buffer containing 8 M urea and 50 mM EDTA. For $E_{Hg}3T$, $E_{Hg4}T$, $E_{Hg}5T$, and $E_{Hg}6T$ DNAzymes, a 20 min time point was also taken for the samples without Hg^{2+}, because the fractions of cleavage for these enzymes were too low at 1 min to allow accurate calculation. The reaction mixture was then loaded to a denaturing 20% polyacrylamide gel and the gel was imaged with a Molecular Dynamics STORM 840 fluorescence imager with excitation wavelength set at 450 nm.

Hg^{2+} detection: The catalytic beacon sensor was prepared by annealing 2 μM of the substrate and enzyme strand shown in FIG. **2***a* in 10 mM MES, pH 5.5 and 300 mM $NaNO_3$. A large volume of the same buffer was also prepared. For each detection, 25 μL of the annealed sensor was mixed with 475 μL of buffer and the final sensor concentration was 100 nM. The fluorometer (Fluoromax-P, Horiba Jobin Yvon, Edison, N.J.) was set at the kinetics mode with 15 sec intervals. The excitation was set at 490 nm and emission at 520 nm. The temperature was set at 24° C. UO_2^{2+} (0.5 μL of 1 mM) was added to the DNAzyme to make a final concentration of 0.5 μM, and this mixture was used as the sensor for Hg^{2+}. The sensor was vortexed and placed into the fluorometer to start the kinetics reading. After the first reading, the cuvette was taken out and a small volume of $Hg(ClO_4)_2$ or other metals was added. After vortexing, the cuvette was placed back to the fluorometer to continue the reading.

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gggcaaggct agctacaacg actaaatttt tagctgaaaa gcttttaacg gcagtc 56

<210> SEQ ID NO 17
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<400> SEQUENCE: 17

gacugccgnn nuagguugcc c 21

<210> SEQ ID NO 18
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<400> SEQUENCE: 18

gaatcgaact gtcagtgact cgaaagcacg ga 32

<210> SEQ ID NO 19
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<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 19

tccgtgctrn nggttcgatt c 21

<210> SEQ ID NO 20
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 20

gaatcgaact gttttcagtg ttatctcgaa agcacgga 38

<210> SEQ ID NO 21
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<212> TYPE: DNA
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<400> SEQUENCE: 21

gaatcgaact gtttttcagt gttattctcg aaagcacgga 40

<210> SEQ ID NO 22
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<222> LOCATION: (1)..(3)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<222> LOCATION: (14)..(19)
<223> OTHER INFORMATION: /replace=" "
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: /note="Nucleotides given in the sequence have
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<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(25)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: Variation
<222> LOCATION: (28)..(33)
<223> OTHER INFORMATION: /replace=" "
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (28)..(33)
<223> OTHER INFORMATION: /note="Nucleotides given in the sequence have
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<220> FEATURE:
<221> NAME/KEY: modified_base

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<222> LOCATION: (51)..(52)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 22

nnnyyyyyyy agttttttty rnnnnyrttt tttaccttca gacayrryrr nn 52

<210> SEQ ID NO 23
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<220> FEATURE:
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<223> OTHER INFORMATION: /replace=" "
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<221> NAME/KEY: misc_feature
<222> LOCATION: (30)..(35)
<223> OTHER INFORMATION: /note="Nucleotides given in the sequence have
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 23

nnyyyyyyyt ccgnnncggt cgaaatattt tttttagctn nnnagctttt tttaannryr 60

rry 63

<210> SEQ ID NO 24
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<223> OTHER INFORMATION: /note="Nucleotides given in the sequence have
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<222> LOCATION: (39)..(42)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: /replace=" "
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: /note="Nucleotides given in the sequence have no preference with respect to those in the annotation for said positions"
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (61)..(62)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 24

rrryraggct agctacaacg actaaatttt ttttagctnn nnagcttttt ttaayrryrr 60

nn 62

<210> SEQ ID NO 25
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 25

gttcggaaac gaac 14

<210> SEQ ID NO 26
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 26

gttcggaaac gtac 14

<210> SEQ ID NO 27
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 27

gtttcggaaa cgttac 16

<210> SEQ ID NO 28
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 28

gttttcggaa acgtttac 18

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<210> SEQ ID NO 29
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 29

gtttttcgga aacgttttac 20

<210> SEQ ID NO 30
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 30

gttttttcgg aaacgttttt ac 22

<210> SEQ ID NO 31
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 31

gttttttttcg gaaacgtttt ttac 24

<210> SEQ ID NO 32
<211> LENGTH: 55
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 32

cacgtacatc tcttcagttt tttcggaaac gtttttacct tcagacatag tgagt 55

<210> SEQ ID NO 33
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> SEQUENCE: 33

actcactata rggaagagat ggacgtg 27

What is claimed is:

1. A nucleic acid enzyme, comprising:

an oligonucleotide substrate strand;

an oligonucleotide enzyme strand comprising at least one stem loop, wherein at least one of the stem loops of the enzyme strand comprises one or more thymine-thymine (T-T) mismatches opposite each other, wherein the T-T mismatches form stable base pairs in the presence of Hg^{2+},

wherein the nucleic acid enzyme is dependent on both Hg^{2+} and a second ion as cofactors, to produce a product from the substrate strand comprising a ribonucleotide, a deoxyribonucleotide, or both.

2. The nucleic acid enzyme of claim 1, wherein the oligonucleotide enzyme strand comprises at least 4 T-T mismatches.

3. The nucleic acid enzyme of claim 1, wherein the oligonucleotide enzyme strand comprises at least 6 T-T mismatches.

4. The nucleic acid enzyme of claim 1, further comprising a quencher.

5. The nucleic acid enzyme of claim 1, wherein the second ion is selected from the group consisting of UO_2^{2+}, Pb^{2+}, Mg^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+} and Mn^{2+}.

6. The nucleic acid enzyme of claim 1, wherein the second ion is UO_2^{2+}.

7. The nucleic acid enzyme of claim 1, wherein the oligonucleotide enzyme strand comprises at least 38 bases.

8. A method of detecting Hg^{2+} in a sample, comprising:

providing a mixture comprising:

the nucleic acid enzyme of claim 1,

the sample, and

a second ion,

producing a product from the mixture if Hg^{2+} is present in the sample; and

determining the presence of the product, wherein the presence of the product indicates the presence of Hg^{2+} in the sample.

9. The method of claim 8, wherein the second ion is selected from the group consisting of UO_2^{2+}, Pb^{2+}, Mg^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+} and Mn^{2+}.

10. The method of claim 8, wherein the second ion is UO_2^{2+}.

11. The method of claim 8, wherein the method determines the concentration of Hg^{2+} in the presence of other ions in the sample by measuring an amount of the product produced.

12. The method of claim 11, wherein the substrate strand comprises a fluorophore and a first quencher, and the enzyme strand comprises a second quencher.

13. The method of claim 8, wherein the substrate strand comprises a fluorophore and a first quencher, and the enzyme strand comprises a second quencher.

14. A sensor for Hg^{2+}, comprising:

(1) an oligonucleotide enzyme strand comprising at least one stem loop, wherein at least one of the stem loops of the enzyme strand comprises one or more thymine-thymine (T-T) mismatches opposite each other, wherein the T-T mismatches form stable base pairs in the presence of Hg^{2+}, and wherein the enzyme strand comprises at least one quencher,

(2) an oligonucleotide substrate strand comprising at least one fluorophore and at least one quencher, and

(3) a second ion,

wherein the sensor is dependent on both the Hg^{2+} and the second ion as cofactors to produce a product from the substrate strand.

15. The sensor of claim 14, wherein the enzyme strand comprises at least 2 T-T mismatches.

16. The sensor of claim 15, wherein the enzyme strand comprises at least 4 T-T mismatches.

17. The sensor of claim 15, wherein the enzyme strand comprises at least 6 T-T mismatches.

18. The sensor of claim 14, wherein the second ion is selected from the group consisting of UO_2^{2+}, Pb^{2+}, Mg^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+} and Mn^{2+}.

19. The sensor of claim 14, wherein the second ion is UO_2^{2+}.

20. The sensor of claim 15, wherein the enzyme strand comprises at least 38 bases.

21. The nucleic acid enzyme of claim 1, wherein the nucleic acid enzyme is a ribozyme (RNAzyme), deoxyribozyme (DNAzyme), a DNA/RNA hybrid enzyme, or a peptide nucleic acid enzyme (PNAzyme).

22. The nucleic acid enzyme of claim 1, wherein the substrate strand comprises a fluorophore and a first quencher, and the enzyme strand comprises a second quencher.

23. The nucleic acid enzyme of claim 22, wherein the fluorophore is 6-carboxyfluorescein.

24. The nucleic acid enzyme of claim 1, wherein the first and/or second quencher is 4-(4-dimethylaminophenylazo) benzoic acid) (Dabcyl), QSY-7, or QSY-33.

25. The nucleic acid enzyme of claim 1, wherein the oligonucleotide enzyme strand comprises one to six T-T mismatches.

26. A solid support comprising the nucleic acid enzyme of claim 1.

27. The solid support of claim 26, wherein the solid support comprises a microtiter plate or a bead.

28. The method of claim 8, wherein the sample is a water sample, biological sample, soil sample, or paint sample.

* * * * *