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(72) NYCE, Jonathan W., US
(71) EAST CAROLINA UNIVERSITY, US

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(54) **AGENT ET METHODE DE TRAITEMENT DE MALADIES ET D'ETATS PATHOLOGIQUES ASSOCIES A DES MALAISES RESPIRATOIRES ET A UNE INFLAMMATION PULMONAIRE**

(54) **AGENT AND METHOD OF TREATMENT FOR DISEASES AND CONDITIONS ASSOCIATED WITH RESPIRATORY AILMENTS AND LUNG INFLAMMATION**

(57) L'invention concerne un agent comprenant des oligos anti-sens agissant sur des récepteurs d'adénosine en vue de soulager les malaises respiratoires et de réduire les inflammations respiratoires. Cet agent qui se présente sous la forme d'une composition et de différentes formulations, figure aussi dans un nécessaire. Les agents de l'invention peuvent être administrés en une dose efficace du point de vue anti-bronchoconstrictif et/ou anti-inflammatoire, et ceci, afin de réduire la bronchoconstriction et l'inflammation dont souffre le patient. Les agents préférés contiennent un oligonucléotide anti-sens ciblant les récepteurs d'adénosine A_1, A_{2a}, A_{2b} et/ou A_3 et le récepteur de bradykinine B_2. La méthode est utile dans le traitement de patients souffrant d'asthme et d''utres problèmes respiratoires. L'invention concerne également des formulations à usage pharmaceutique.

(57) An agent comprises anti-sense oligos directed to adenosine receptors for allevation of respiratory ailments and inflammation. The agent is provided as a composition, various formulations, and kit. The present agents may be administered in an anti-bronchoconstriction and/or anti-inflammation effective amount to alleviate the bronchoconstriction and inflammation afflicting a subject. Preferred agents contain anti-sense oligonucleotide targeting the adenosine A_1, A_{2a}, A_{2b} and/or A_3 receptors and bradykinin B_2 receptor. The method is useful for treating patients afflicted with asthma and other respiratory problems. Pharmaceutical formulations are also disclosed.

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(71) Applicant *(for all designated States except US)*: EAST CAROLINA UNIVERSITY [US/US]; 210 Spilman Building, Greenville, NC 27858–4353 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: NYCE, Jonathan, W. [US/US]; 302 Harrell Street, Greenville, NC 27858 (US).

(74) Agents: SIBLEY, Kenneth, D. et al.; Myers Bigel Sibley & Sajovec, P.O. Box 37428, Raleigh, NC 27627 (US).

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(54) Title: AGENT AND METHOD OF TREATMENT FOR DISEASES AND CONDITIONS ASSOCIATED WITH RESPIRATORY AILMENTS AND LUNG INFLAMMATION

(57) Abstract

An agent comprises anti–sense oligos directed to adenosine receptors for allevation of respiratory ailments and inflammation. The agent is provided as a composition, various formulations, and kit. The present agents may be administered in an anti–bronchoconstriction and/or anti–inflammation effective amount to alleviate the bronchoconstriction and inflammation afflicting a subject. Preferred agents contain anti–sense oligonucleotide targeting the adenosine A_1, A_{2a}, A_{2b} and/or A_3 receptors and bradykinin B_2 receptor. The method is useful for treating patients afflicted with asthma and other respiratory problems. Pharmaceutical formulations are also disclosed.

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AGENT & METHOD OF TREATMENT FOR DISEASES & CONDITIONS ASSOCIATED WITH RESPIRATORY AILMENTS & LUNG INFLAMMATION

BACKGROUND OF THE INVENTION

This invention was made at least partially with United States Government support under Grant No. ROl-CA47217 from the National Cancer Institute. The United States Government may have certain rights to this invention.

Field of the Invention

This invention relates to oligonucleotide agents which are anti-sense to mRNAs corresponding to genes associated with certain types of lung diseases or conditions. The agents of the invention are effective in the treatment of lung diseases and conditions, such as asthma, and the like, which are associated with lung inflammation, bronchconstriction, impeded air flow through the lung's airways, and general breathing difficulties. Particularly important are agents of the invention comprising oligonucleotides which are anti-sense to the adenosine A_1, A_{2b} and A_3 and bradykinin B_2 receptors.

DESCRIPTION OF THE BACKGROUND

Respiratory ailments, associated with a variety of diseases and conditions, are extremely common in the general population, and more so in certain ethnic groups, such as black Americans. In some cases "these ailments" are accompanied by inflammation, which aggravates the condition of the lungs. Asthma, for example, is one of the most common diseases in industrialized countries. In the United States it accounts for about 1% of all health care costs. An alarming increase in both the prevalence and mortality of asthma over the past decade has been reported, and asthma is predicted to be the preeminent occupational lung disease in the next decade. While the increasing mortality of asthma in industrialized countries could be attributable to the increased reliance upon beta agonists in the treatment of this disease, the underlying causes of asthma remain poorly understood.

Adenosine may constitute an important natural mediator of bronchial asthma. Its potential role in human asthma has been supported by an experimental finding that, in contrast to normal individuals, asthmatic individuals responded to aerosolized adenosine with marked bronchoconstriction. Similar responses were reported in an experimental rabbit model for human asthma ("the allergic rabbit") produced by administration of the dust mite. Recent work using the allergic rabbit has suggested that bronchoconstriction and bronchial

hyperresponsiveness in asthma may be mediated, at least in part, through the stimulation of adenosine receptors.

The adenosine A_1 receptor appears to be overexpressed in the lungs of virtually every asthma patient, and it has been suggested that sensitivity to adenosine may be a better indicator for asthma than the current standard in the art: the methacholine test. Further evidence of the important role adenosine and its receptors play in asthma is garnered from the observation that adenosine levels are highly elevated in the bronchial lavage fluid of asthmatic lungs. This observation indicates that the overexpressed adenosine A_1 receptor may be subjected to continuous stimulation in the asthmatic lung which, in turn, aggravates bronchoconstriction/inflammation in the asthmatic lung. The overexpressed adenosine A_1 receptor, therefore, may be a fundamental mediator of asthma and other respiratory diseases in which bronchoconstriction and inflammation play a role.

A handful of medicaments have been available for the treatment of respiratory diseases and conditions, although in general they all have limitations. Theophylline, an important drug in the treatment of asthma, is a known adenosine receptor antagonist which was reported to eliminate adenosine-mediated bronchoconstriction in asthmatic rabbits. A selective adenosine A_1 receptor antagonist, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX) was also reported to inhibit adenosine-mediated bronchoconstriction and bronchial hyperresponsiveness in allergic rabbits. The therapeutic and preventative applications of currently available adenosine A_1 receptor-specific antagonists are, nevertheless, limited by their toxicity. Theophylline, for example, has been widely used in the treatment of asthma, but is associated with frequent, significant toxicity resulting from its narrow therapeutic dose range. DPCPX is far too toxic to be useful clinically. The fact that despite decades of extensive research, no specific adenosine receptor antagonist is available for clinical use attests to the general toxicity of these agents.

Other adenosine receptors and the bradykinin B_2 receptor are known to be associated with respiratory and inflammatory conditions. Amongst these are the A_{2a}, A_{2b}, and A_3 adenosine receptors. The adenosine A_1, A_{2a}, A_{2b}, and A_3 receptors are members of the G-protein coupled family of cell surface receptors having 7-transmembrane segments. There is extensive sequence homology between the A_{2a} and A_{2b} receptors, with variation occurring primarily in their carboxy terminal domains. The adenosine A_{2a} receptor is considered to be a high affinity receptor and the adenosine A_{2b} a lower affinity receptor. Whereas the

adenosine A_1 receptor is reported to inhibit adenyl cyclase activity, both A_{2a} and A_{2b} receptors are reported to stimulate adenyl cyclase activity.

Anti-sense oligonucleotides have received considerable consideration for their potential use as pharmacological agents in human disease. Finding practical and effective applications of these agents in actual models of human disease, however, have been few and far between, particularly because they had to be administered in large doses. Another important consideration in the pharmacologic application of these molecules is their route of administration. Many in vivo applications have involved the direct administration of anti-sense oligonucleotides to limited regions of the brain. Such applications, however, have limited clinical utility due to their invasive nature.

The systemic administration of anti-sense oligonucleotides as pharmacological agents has been found to also have significant problems, not the least of which is a difficulty in targeting disease-involved tissues. That is, the necessary dilution of the anti-sense oligonucleotide in the circulatory system makes it extremely difficult to attain a therapeutic dose at the target tissue by intravenous or oral administration. The bioavailability of orally administered anti-sense oligonucleotides is very low, on the order of less than about 5%.

Accordingly, there is still a need for novel agents which are effective in the treatment of diseases and conditions of the lung that are associated with inflammation and airway obstruction. Of particular importance, for long term preventative and therapeutic applications, are agents which are sufficiently specific, and/or are directly administered to their site of action, to be devoid of undesirable side effects or whose side effects are substantially low to permit their long term administration.

SUMMARY OF THE INVENTION

The present invention relates to an agent suitable for reducing bronchoconstriction and/ or lung inflammation which comprises an oligonucleotide which is anti-sense to one or more adenosine, bradykinin and related receptors in the lung. Adenosine and bradykinin receptors which have been associated with these conditions are the adenosine A_1, A_{2a}, A_{2b} and A_3 receptors and bradykinin B_2 receptor. The present agents may be safely administered for the long term prevention, control and therapy of all types of diseases and conditions associated with lung inflammation, bronchoconstriction, airway obstruction and respiratory ailments. The agent of the present invention is also provided as a pharmaceutical

composition, comprising a carrier, preferably a pharmaceutically acceptable carrier, and one or more oligonucleotides which is(are) anti-sense to receptors associated with bronchoconstriction, respiratory problems such as impeded respiration, obstructed airways, mucous buildup and/or lung inflammation, among others. The present agents are also provided as medicament in the form of various formulations for reducing bronchoconstriction and/or inflammation, as well as treating diseases and conditions associated with those symptoms, such as asthma and the like, and as a kit, along with instructions for its administration.

The present agents may be applied to the treatment of ailments which are associated with the described symptoms, including asthma, adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, cystic fibrosis, allergy, emphysema, and the like. The present agents may be administered in an anti-bronchoconstriction and/or anti-inflammatory and/or a respiratory distress alleviating effective amount for either preventative, maintenance or therapeutic applications. Their use is generally indicated for both acute and chronic conditions because of their safety and substantial lack of side effects.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the effect of A_1 adenosine receptor anti-sense oligonucleotides and mismatch control anti-sense oligonucleotides on the dynamic compliance of the bronchial airway in a rabbit model. The two stars represent significant difference at $p < 0.01$, Student's t-test.

Figure 2 illustrates the specificity of A_1 adenosine receptor anti-sense oligonucleotides as indicated by the A_1 and A_2 adenosine receptor number present in airway tissue treated with A_1 adenosine receptor anti-sense oligonucleotides.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention arose from a desire by the inventor to improve on available prior art technology for the prevention, control and acute and chronic treatment of diseases and conditions which are associated with respiratory difficulties, such as bronchoconstriction, airway obstruction, mucous buildup, allergies, inflammatory responses, and the like. He undertook the search for an agent that could be selectively targeted to specific receptors associated with the observed symptomatology, and at the same time administered to the site

of action. He surmised that the combination of these two strategies would provide a class of medications which are highly effective while resulting in negligible undesirable side effects, which are observed with other agents presently available. He deduced that anti-sense oligonucleotides (oligos) would fulfill these criteria. However, most such anti-sense oligos, as indicated above, had been administered directly to the brain or systemically, the earlier having limited application in humans, and the latter requiring elevated doses which generally bring about untoward toxicity and/or side effects. Both those classes of drugs are of limited utility, mostly in acute occurrences, whereas their long term administration is contraindicated. In contrast, the inventor postulated that the lung would be an excellent target for the direct administration of an agent and that, in this manner, he would circumvent a large number of possibilities for interaction of the drug with other tissues and/or fluids which might reasonably be expected to result in a variety of undesired effects. In addition, the inventor contemplated the utilization of anti-sense oligonucleotides to sequences specific to genes and/or messengerRNAs (mRNAs) associated with the conditions or diseases targeted. He thus set out to pursue the search of oligonucleotides having sequences specific to pre-determined targets which, if hybridized by the oligos, would reduce production of a gene product involved in an undesirable effect, and administered the anti-sense oligos locally, thereby avoiding their dissemination throughout the body of the recipient. Such application represents a non-invasive and tissue-specific approach, never before reported for anti-sense oligonucleotides.

Nucleotide sequences are presented herein by single strand only, in the 5' to 3' direction, from left to right. Nucleotide and amino acids are represented herein in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission, or (for amino acids) by three letter code, in accordance with 37 CFR § 1.822 and established usage. See, e.g., Patent In User Manual, 99-102 (Nov. 1990); U.S. Patent and Trademark Office, Office of the Assistant Commissioner for Patents, Washington, DC 20231; US Patent No. 4,871,670 to Hudson et al. at col. 3, lines 20-43, the relevant portions of their disclosure and of all other patents and publications referenced in this patent are incorporated herein by reference.

The method of the present invention may be used to reduce bronchoconstriction and/or inflammation, particularly adenosine-mediated bronchoconstriction and/or inflammation, of a subject's lungs, resulting from a variety of causes including, but not limited to, asthma, COPD, pulmonary hypertension, allergy and emphysema, among others. Anti-sense

oligonucleotides to the mRNA of the adenosine A_1, A_{2a}, A_{2b} and A_3 receptors and bradykinin B_2 receptor, for example, have been shown by the inventor to be effective in the downregulation of adenosine A_1, A_{2a}, A_{2b} and A_3 and bradykinin B_2 receptor molecules, respectively, in the cell. One novel feature of the present agents when compared to more traditional treatments for bronchoconstriction and inflammation, particularly adenosine-mediated and/or bradykinin-mediated respiratory difficulties, bronchoconstriction and/or inflammation, is their ability to specifically target a desired gene product by designing the oligos to be anti-sense to mRNAs encoding a desired product. In one preferred embodiment the agents of the invention are administered directly into the respiration, preferably directly to the lung(s), by inhalation or into the respiratory airways. The present agents, thus, reduce the amount of, for example, a receptor protein itself rather than merely interacting with it, as prior art agents do. In this manner, the mere reduction of the requisite protein intermediary reduces the undesirable symptomatology, e.g., bronchoconstriction, airway obstruction, mucous buildup, significantly reduced respiratory capacity and/or inflammation. The fact that the present agents are specifically targeted rather than generally acting reduces toxicity which results from the generalized interaction of a drug with diverse tissues and receptors.

As used herein, the term "treat" or "treating" a disease or conditions associated with bronchoconstriction, reduced respiratory capacity and/or inflammation, such as is the case in asthma, among others, refers to the administration of the present agents to a subject, preferably directly to the lung or through the respiration or via inhalation, to decrease the likelihood that the subject will manifest symptoms of bronchoconstriction, decreased respiratory capacity or ability and/or inflammation. The term "downregulate" refers to inducing a decrease in inducing production, secretion and/or availability and, thus, a decrease in concentration, of the intracellular level of, for example, adenosine A_1, A_{2a}, A_{2b} and/or A_3 and/or bradykinin B_2 receptors. The downregulation of other proteins and/or receptors via inhalation of anti-sense oligonucleotides is also encompassed.

Although the present invention is primarily concerned with the treatment of human subjects it is also intended for the treatment of other vertebrates, including mammalian subjects, such as wild and domesticated animals, farm and marine animals, including horses, zoo animals and pets, e.g. dogs and cats, among other animals. Of particular interest are applications intended for use by a veterinary in the treatment of large and small animals.

The term "anti-sense" generally refers to the use of small, synthetic oligonucleotides,

resembling single-stranded DNA, which are designed to inhibit expression of a specific target gene by inhibiting the function of the corresponding target messenger RNA (mRNA), as described by Milligan et al. See, Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993). The present invention is generally intended to attain the inhibition of the expression of genes associated with bronchoconstriction, inflammation, reduced respiratory ability, and associated symptoms, such as the adenosine A_1, A_{2a}, A_{2b} and A_3 and bradykinin B_2 receptors. The present agents inhibit gene expression by hybridizing either to the coding (sense), regulatory and/or intron sequences present in the messenger RNA (mRNA) corresponding to the targeted gene. The hybridization or binding of the present agents to fragments of the mRNA target is believed to occur by hydrogen bonding according to Watson-Crick base pairing rules. Although no claim is hereby made to a specific mechanism of action for the present agents, it is presently believed that the exogenously administered anti-sense oligonucleotides decrease the amount of targeted mRNA available for translation and, thereby, decrease the level of the encoded protein and/or cause changes in the growth characteristics or shapes of the cells. Id. See also Helene, C. and Toulme, J., Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S. D., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987).

"Adenosine receptor anti-sense oligonucleotide" is defined within this patent as a short nucleotide sequence, mostly of synthetic origin, that (1) is complementary to at least a portion of the mRNA, including introns and exon borders corresponding to the 5' and 3' ends, and the intron/exon junction between coding and non-coding regions, and to all segments of the coding and regulatory regions of the mRNA and/or gene which encode the gene product, including the adenosine A_1, A_{2a}, A_{2b} and A_3 and bradykinin B_2 receptors, and (2) upon hybridization causes a decrease or loss of target mRNA template or template function and/or decreased amounts of the protein encoded by the target mRNA.

The mRNA sequence corresponding to the target gene, e. g. the adenosine A_1, A_{2a}, A_{2b} or A_3, or bradykinin B_2 receptor genes, is generally derived from the DNA base sequence of the gene expressing the target protein which exercises a detrimental role in the disease or condition to be treated. The sequences of all genomic targets exemplified in this patent are in the public domain, and the technology is generally available and widely applied for determining the sequence of any target gene or of its corresponding mRNA so that this technology may easily be applied to other targets. The human A_1 adenosine receptor, for

example, is known and is disclosed in US Patent No. 5,320,962 to Stiles et al. The rat and human adenosine A_3 receptors have been cloned, sequenced and expressed. See, Zhou et al., P.N.A.S. USA 89 :7432 (1992); Jacobson et al., UK Patent Application No. 9304582.1 (1993). The sequence of the adenosine A_{2b} gene is known as well. See, Pierce, K.D. et al., Biochem. Biophys. Res. Commun. 187(1):86-93 (1992); Also known is the sequence of the bradykinin B_2 gene. See, Eggerickx, D. et al., Biochem. Biophys. Res. Commun. 187(3):1306-1313 (1992). Thus, anti-sense oligonucleotides that hybridize to mRNA corresponding to the adenosine A_1, A_{2a}, A_{2b} and A_3 and bradykinin B_2 genes, and down-regulate the production of the A_1, A_{2b} and/or A3 receptors may be designed and produced in accordance with standard techniques based on the inventor's teachings provided herein.

This invention, thus, provides an anti-sense oligonucleotide having a sequence selectively binding or hybridizing to any targeted mRNA. Preferred are those oligos that hybridize to any segment of the mRNA which encode the adenosine A_1, A_{2b} and A3 receptors so as to prevent its translation. In one embodiment of the present invention, the anti-sense oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 7, and fragments thereof about 8 to about 40 nucleotides long, preferably about 15 to 25 nucleotides long, and more preferably about 18 to 22 nucleotides long starting at different sites of each of the sequences encoding the target genes. Examples of the fragments are provided below, where each one was given a specific fragment number.

In another embodiment of the invention, the sequence of the anti-sense oligonucleotide brackets the initiation codon of the human adenosine A_1 receptor. Such an anti-sense oligonucleotide may have a sequence disclosed herein as follows:

5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' **(SEQ. ID NO: 7)**

5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 1) **(SEQ. ID NO: 11)**

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 2) **(SEQ. ID NO: 12)**

5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 3) **(SEQ. ID NO: 13)**

5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 4) **(SEQ. ID NO: 14)**

5'-C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 5) **(SEQ. ID NO: 15)**

5'-CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 6) **(SEQ. ID NO: 16)**

5'-TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 7) **(SEQ. ID NO: 17)**

5'-G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 8) **(SEQ. ID NO: 18)**

5'-GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 9) **(SEQ. ID NO: 19)**

5'-AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 10) **(SEQ. ID NO: 20)**

5'-A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 11) **(SEQ. ID NO: 21)**

5'-AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 12) **(SEQ. ID NO: 22)**

5'-GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 13) **(SEQ. ID NO: 23)**
5'-C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 14) **(SEQ. ID NO: 24)**
5'-TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 15) **(SEQ. ID NO: 25)**
5'-GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 16) **(SEQ. ID NO: 26)**
5'-A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 17) **(SEQ. ID NO: 27)**
5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 18) **(SEQ. ID NO: 28)**
5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 19) **(SEQ. ID NO: 29)**
5'-T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 20) **(SEQ. ID NO: 30)**
5'-GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 21) **(SEQ. ID NO: 31)**
5'-GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 22) **(SEQ. ID NO: 32)**
5'-A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 23) **(SEQ. ID NO: 33)**
5'-GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 24) **(SEQ. ID NO: 34)**
5'-GG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 25) **(SEQ. ID NO: 35)**
5'-G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 26) **(SEQ. ID NO: 36)**
5'-CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 27) **(SEQ. ID NO: 37)**
5'-GG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 28) **(SEQ. ID NO: 38)**
5'-G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 29) **(SEQ. ID NO: 39)**
5'-CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 30) **(SEQ. ID NO: 40)**
5'-AT GGC GGG CAC AGG CTG GGC-3' (FRAG 31) **(SEQ. ID NO: 41)**
5'-T GGC GGG CAC AGG CTG GGC-3' (FRAG 32) **(SEQ. ID NO: 42)**
5'-GGC GGG CAC AGG CTG GGC-3' (FRAG 33) **(SEQ. ID NO: 43)**
5'-GC GGG CAC AGG CTG GGC-3' (FRAG 34) **(SEQ. ID NO: 44)**
5'-C GGG CAC AGG CTG GGC-3' (FRAG 35) **(SEQ. ID NO: 45)**
5'-GGG CAC AGG CTG GGC-3' (FRAG 36) **(SEQ. ID NO: 46)**
5'-GG CAC AGG CTG GGC-3' (FRAG 37) **(SEQ. ID NO: 47)**
5'-G CAC AGG CTG GGC-3' (FRAG 38) **(SEQ. ID NO: 48)**
5'-CAC AGG CTG GGC-3' (FRAG 39) **(SEQ. ID NO: 49)**
5'-AC AGG CTG GGC-3' (FRAG 40) **(SEQ. ID NO: 50)**
5'-C AGG CTG GGC-3' (FRAG 41) **(SEQ. ID NO: 51)**
5'-AGG CTG GGC-3' (FRAG 42) **(SEQ. ID NO: 52)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 43) **(SEQ. ID NO: 53)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 44) **(SEQ. ID NO: 54)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 45) **(SEQ. ID NO: 55)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 46) **(SEQ. ID NO: 56)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 47) **(SEQ. ID NO: 57)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 48) **(SEQ. ID NO: 58)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 49) **(SEQ. ID NO: 59)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 50) **(SEQ. ID NO: 60)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 51) **(SEQ. ID NO: 61)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 52) **(SEQ. ID NO: 62)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 53) **(SEQ. ID NO: 63)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 54) **(SEQ. ID NO: 64)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 55) **(SEQ. ID NO: 65)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 56) **(SEQ. ID NO: 66)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3'(FRAG 57) **(SEQ. ID NO: 67)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 58) **(SEQ. ID NO: 68)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 59) **(SEQ. ID NO: 69)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 60) **(SEQ. ID NO: 70)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 61) **(SEQ. ID NO: 71)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 62) **(SEQ. ID NO: 72)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 63) **(SEQ. ID NO: 73)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 64) **(SEQ. ID NO: 74)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 65) **(SEQ. ID NO: 75)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 66) **(SEQ. ID NO: 76)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 67) **(SEQ. ID NO: 77)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 68) **(SEQ. ID NO: 78)**

5'-GGC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 69) **(SEQ. ID NO: 79)**
5'-GGC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 70) **(SEQ. ID NO: 80)**
5'-GGC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 71) **(SEQ. ID NO: 81)**
5'-GGC GGC CTG GAA AGC TGA GAT G -3' (FRAG 72) **(SEQ. ID NO: 82)**
5'-GGC GGC CTG GAA AGC TGA GAT -3' (FRAG 73) **(SEQ. ID NO: 83)**
5'-GGC GGC CTG GAA AGC TGA GA-3' (FRAG 74) **(SEQ. ID NO: 84)**
5'-GGC GGC CTG GAA AGC TGA G-3' (FRAG 75) **(SEQ. ID NO: 85)**
5'-GGC GGC CTG GAA AGC TGA-3' (FRAG 76) **(SEQ. ID NO: 86)**
5'-GGC GGC CTG GAA AGC TG-3' (FRAG 77) **(SEQ. ID NO: 87)**
5'-GGC GGC CTG GAA AGC T-3' (FRAG 78) **(SEQ. ID NO: 88)**
5'-GGC GGC CTG GAA AGC-3' (FRAG 79) **(SEQ. ID NO: 89)**
5'-GGC GGC CTG GAA AG-3' (FRAG 80) **(SEQ. ID NO: 90)**
5'-GGC GGC CTG GAA A-3' (FRAG 81) **(SEQ. ID NO: 91)**
5'-GGC GGC CTG GAA-3' (FRAG 82) **(SEQ. ID NO: 92)**
5'-GGC GGC CTG GA-3' (FRAG 83) **(SEQ. ID NO: 93)**
5'-GGC GGC CTG G-3' (FRAG 84) **(SEQ. ID NO: 94)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 85) **(SEQ. ID NO: 95)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 86) **(SEQ. ID NO: 96)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 87) **(SEQ. ID NO: 97)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 88) **(SEQ. ID NO: 98)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 89) **(SEQ. ID NO: 99)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 90) **(SEQ. ID NO: 100)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 91) **(SEQ. ID NO: 101)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 92) **(SEQ. ID NO: 102)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 93) **(SEQ. ID NO: 103)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 94) **(SEQ. ID NO: 104)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 95) **(SEQ. ID NO: 105)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 96) **(SEQ. ID NO: 106)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 97) **(SEQ. ID NO: 107)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 98) **(SEQ. ID NO: 108)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 99) **(SEQ. ID NO: 109)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 100) **(SEQ. ID NO: 110)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 101) **(SEQ. ID NO: 111)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 102) **(SEQ. ID NO: 112)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 103) **(SEQ. ID NO: 113)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 104) **(SEQ. ID NO: 114)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 105) **(SEQ. ID NO: 115)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 106) **(SEQ. ID NO: 116)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 107) **(SEQ. ID NO: 117)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 108) **(SEQ. ID NO: 118)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 109) **(SEQ. ID NO: 119)**
5'-GC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 110) **(SEQ. ID NO: 120)**
5'-GC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 111) **(SEQ. ID NO: 121)**
5'-GC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 112) **(SEQ. ID NO: 122)**
5'-GC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 113) **(SEQ. ID NO: 123)**
5'-GC GGC CTG GAA AGC TGA GAT G -3' (FRAG 114) **(SEQ. ID NO: 124)**
5'-GC GGC CTG GAA AGC TGA GAT -3' (FRAG 115) **(SEQ. ID NO: 125)**
5'-GC GGC CTG GAA AGC TGA GA-3' (FRAG 116) **(SEQ. ID NO: 126)**
5'-GC GGC CTG GAA AGC TGA G-3' (FRAG 117) **(SEQ. ID NO: 127)**
5'-GC GGC CTG GAA AGC TGA-3' (FRAG 118) **(SEQ. ID NO: 128)**
5'-GC GGC CTG GAA AGC TG-3' (FRAG 119) **(SEQ. ID NO: 129)**
5'-GC GGC CTG GAA AGC T-3' (FRAG 120) **(SEQ. ID NO: 130)**
5'-GC GGC CTG GAA AGC-3' (FRAG 121) **(SEQ. ID NO: 131)**
5'-GC GGC CTG GAA AG-3' (FRAG 122) **(SEQ. ID NO: 132)**
5'-GC GGC CTG GAA A-3' (FRAG 123) **(SEQ. ID NO: 133)**
5'-GC GGC CTG GAA-3' (FRAG 124) **(SEQ. ID NO: 134)**
5'-GC GGC CTG GA-3' (FRAG 125) **(SEQ. ID NO: 135)**

5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 126) **(SEQ. ID NO: 136)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 127) **(SEQ. ID NO: 137)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 128) **(SEQ. ID NO: 138)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 129) **(SEQ. ID NO: 139)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 130) **(SEQ. ID NO: 140)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 131) **(SEQ. ID NO: 141)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 132) **(SEQ. ID NO: 142)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 133) **(SEQ. ID NO: 143)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 134) **(SEQ. ID NO: 144)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 135) **(SEQ. ID NO: 145)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 136) **(SEQ. ID NO: 146)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 137) **(SEQ. ID NO: 147)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 138) **(SEQ. ID NO: 148)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 139) **(SEQ. ID NO: 149)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 140) **(SEQ. ID NO: 150)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 141) **(SEQ. ID NO: 151)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 142) **(SEQ. ID NO: 152)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRA 143) **(SEQ. ID NO: 153)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 144) **(SEQ. ID NO: 154)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 145) **(SEQ. ID NO: 155)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 146) **(SEQ. ID NO: 156)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 147) **(SEQ. ID NO: 157)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 148) **(SEQ. ID NO: 158)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 148) **(SEQ. ID NO: 159)**
5'-C GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 150) **(SEQ. ID NO: 160)**
5'-C GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 151) **(SEQ. ID NO: 161)**
5'-C GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 152) **(SEQ. ID NO: 162)**
5'-C GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 153) **(SEQ. ID NO: 163)**
5'-C GGC CTG GAA AGC TGA GAT GG -3' (FRAG 154) **(SEQ. ID NO: 164)**
5'-C GGC CTG GAA AGC TGA GAT G -3' (FRAG 155) **(SEQ. ID NO: 165)**
5'-C GGC CTG GAA AGC TGA GAT -3' (FRAG 156) **(SEQ. ID NO: 166)**
5'-C GGC CTG GAA AGC TGA GA-3' (FRAG 157) **(SEQ. ID NO: 167)**
5'-C GGC CTG GAA AGC TGA G-3' (FRAG 158) **(SEQ. ID NO: 168)**
5'-C GGC CTG GAA AGC TGA-3' (FRAG 159) **(SEQ. ID NO: 169)**
5'-C GGC CTG GAA AGC TG-3' (FRAG 160) **(SEQ. ID NO: 170)**
5'-C GGC CTG GAA AGC T-3' (FRAG 161) **(SEQ. ID NO: 171)**
5'-C GGC CTG GAA AGC-3' (FRAG 162) **(SEQ. ID NO: 172)**
5'-C GGC CTG GAA AG-3' (FRAG 163) **(SEQ. ID NO: 173)**
5'-C GGC CTG GAA A-3' (FRAG 164) **(SEQ. ID NO: 174)**
5'-C GGC CTG GAA-3' (FRAG 165) **(SEQ. ID NO: 175)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 166) **(SEQ. ID NO: 176)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 167) **(SEQ. ID NO: 177)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 168) **(SEQ. ID NO: 178)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 169) **(SEQ. ID NO: 179)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 170) **(SEQ. ID NO: 180)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 171) **(SEQ. ID NO: 181)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 172) **(SEQ. ID NO: 182)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 173) **(SEQ. ID NO: 183)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 174) **(SEQ. ID NO: 184)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 175) **(SEQ. ID NO: 185)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 176) **(SEQ. ID NO: 186)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 177) **(SEQ. ID NO: 187)**

5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 178) **(SEQ. ID NO: 188)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 179) **(SEQ. ID NO: 189)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 180) **(SEQ. ID NO: 190)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 181) **(SEQ. ID NO: 191)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 182) **(SEQ. ID NO: 192)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 183) **(SEQ. ID NO: 193)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 184) **(SEQ. ID NO: 194)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 185) **(SEQ. ID NO: 195)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 186) **(SEQ. ID NO: 196)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 187) **(SEQ. ID NO: 197)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 188) **(SEQ. ID NO: 198)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 189) **(SEQ. ID NO: 199)**
5'- GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 190) **(SEQ. ID NO: 200)**
5'- GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 191) **(SEQ. ID NO: 201)**
5'- GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 192) **(SEQ. ID NO: 202)**
5'- GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 193) **(SEQ. ID NO: 203)**
5'- GGC CTG GAA AGC TGA GAT GG -3' (FRAG 194) **(SEQ. ID NO: 204)**
5'- GGC CTG GAA AGC TGA GAT G -3' (FRAG 195) **(SEQ. ID NO: 205)**
5'- GGC CTG GAA AGC TGA GAT -3' (FRAG 196) **(SEQ. ID NO: 206)**
5'- GGC CTG GAA AGC TGA GA-3' (FRAG 197) **(SEQ. ID NO: 207)**
5'- GGC CTG GAA AGC TGA G-3' (FRAG 198) **(SEQ. ID NO: 208)**
5'- GGC CTG GAA AGC TGA-3' (FRAG 199) **(SEQ. ID NO: 209)**
5'- GGC CTG GAA AGC TG-3' (FRAG 200 **(SEQ. ID NO: 210)**
5'- GGC CTG GAA AGC T-3' (FRAG 201) **(SEQ. ID NO: 211)**
5'- GGC CTG GAA AGC-3' (FRAG 202) **(SEQ. ID NO: 212)**
5'- GGC CTG GAA AG-3' (FRAG 203) **(SEQ. ID NO: 213)**
5'- GGC CTG GAA A-3' (FRAG 204) **(SEQ. ID NO: 214)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 205) **(SEQ. ID NO: 215)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 206) **(SEQ. ID NO: 216)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 207) **(SEQ. ID NO: 217)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 208) **(SEQ. ID NO: 218)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 209) **(SEQ. ID NO: 219)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 210) **(SEQ. ID NO: 220)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 211) **(SEQ. ID NO: 221)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 212) **(SEQ. ID NO: 222)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 213) **(SEQ. ID NO: 223)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 214) **(SEQ. ID NO: 224)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 215) **(SEQ. ID NO: 225)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 216) **(SEQ. ID NO: 226)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 217) **(SEQ. ID NO: 227)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 218) **(SEQ. ID NO: 228)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 219) **(SEQ. ID NO: 229)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 220) **(SEQ. ID NO: 230)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 221) **(SEQ. ID NO: 231)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 222) **(SEQ. ID NO: 232)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 223) **(SEQ. ID NO: 233)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 224) **(SEQ. ID NO: 234)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 225) **(SEQ. ID NO: 235)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 226) **(SEQ. ID NO: 236)**
5'- GC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 227) **(SEQ. ID NO: 237)**
5'- GC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 228) **(SEQ. ID NO: 238)**
5'- GC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 229) **(SEQ. ID NO: 239)**
5'- GC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 230) **(SEQ. ID NO: 240)**
5'- GC CTG GAA AGC TGA GAT GGA G -3' (FRAG 231) **(SEQ. ID NO: 241)**
5'- GC CTG GAA AGC TGA GAT GGA -3' (FRAG 232) **(SEQ. ID NO: 242)**
5'- GC CTG GAA AGC TGA GAT GG -3' (FRAG 233) **(SEQ. ID NO: 243)**
5'- GC CTG GAA AGC TGA GAT G -3' (FRAG 234) **(SEQ. ID NO: 244)**
5'- GC CTG GAA AGC TGA GAT -3' (FRAG 235) **(SEQ. ID NO: 245)**
5'- GC CTG GAA AGC TGA GA-3' (FRAG 236) **(SEQ. ID NO: 246)**

5'- GC CTG GAA AGC TGA G-3' (FRAG 237) **(SEQ. ID NO: 247)**
5'- GC CTG GAA AGC TGA-3' (FRAG 238) **(SEQ. ID NO: 248)**
5'- GC CTG GAA AGC TG-3' (FRAG 239) **(SEQ. ID NO: 249)**
5'- GC CTG GAA AGC T-3' (FRAG 240) **(SEQ. ID NO: 250)**
5'- GC CTG GAA AGC-3' (FRAG 241) **(SEQ. ID NO: 251)**
5'- GC CTG GAA AG-3' (FRAG 242) **(SEQ. ID NO: 252)**
5'- C CTG GAA AGC TGA GAT GG A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 243) **(SEQ. ID NO: 253)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 244) **(SEQ. ID NO: 254)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 245) **(SEQ. ID NO: 255)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 246) **(SEQ. ID NO: 256)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 247) **(SEQ. ID NO: 257)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 248) **(SEQ. ID NO: 258)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 249) **(SEQ. ID NO: 259)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 250) **(SEQ. ID NO: 260)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 251) **(SEQ. ID NO: 261)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 252) **(SEQ. ID NO: 262)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 253) **(SEQ. ID NO: 263)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 254) **(SEQ. ID NO: 264)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 255) **(SEQ. ID NO: 265)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 256) **(SEQ. ID NO: 266)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 257) **(SEQ. ID NO: 267)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 258) **(SEQ. ID NO: 268)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 259) **(SEQ. ID NO: 269)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 260) **(SEQ. ID NO: 270)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 261) **(SEQ. ID NO: 271)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 262) **(SEQ. ID NO: 272)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 263) **(SEQ. ID NO: 273)**
5'- C CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 264) **(SEQ. ID NO: 274)**
5'- C CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 265) **(SEQ. ID NO: 275)**
5'- C CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 266) **(SEQ. ID NO: 276)**
5'- C CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 267) **(SEQ. ID NO: 277)**
5'- C CTG GAA AGC TGA GAT GGA GG -3' (FRAG 268) **(SEQ. ID NO: 278)**
5'- C CTG GAA AGC TGA GAT GGA G -3' (FRAG 269) **(SEQ. ID NO: 279)**
5'- C CTG GAA AGC TGA GAT GGA -3' (FRAG 270) **(SEQ. ID NO: 280)**
5'- C CTG GAA AGC TGA GAT GG -3' (FRAG 271) **(SEQ. ID NO: 281)**
5'- C CTG GAA AGC TGA GAT G -3' (FRAG 272) **(SEQ. ID NO: 282)**
5'- C CTG GAA AGC TGA GAT -3' (FRAG 273) **(SEQ. ID NO: 283)**
5'- C CTG GAA AGC TGA GA-3' (FRAG 274) **(SEQ. ID NO: 284)**
5'- C CTG GAA AGC TGA G-3' (FRAG 275) **(SEQ. ID NO: 285)**
5'- C CTG GAA AGC TGA-3' (FRAG 276) **(SEQ. ID NO: 286)**
5'- C CTG GAA AGC TG-3' (FRAG 277) **(SEQ. ID NO: 287)**
5'- C CTG GAA AGC T-3' (FRAG 278) **(SEQ. ID NO: 288)**
5'- C CTG GAA AGC-3' (FRAG 279) **(SEQ. ID NO: 289)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 280) **(SEQ. ID NO: 290)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 281) **(SEQ. ID NO: 291)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 282) **(SEQ. ID NO: 292)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 283) **(SEQ. ID NO: 293)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 284) **(SEQ. ID NO: 294)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 285) **(SEQ. ID NO: 295)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 286) **(SEQ. ID NO: 296)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 287) **(SEQ. ID NO: 297)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 288) **(SEQ. ID NO: 298)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 289) **(SEQ. ID NO: 299)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 290) **(SEQ. ID NO: 300)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 291) **(SEQ. ID NO: 301)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 292) **(SEQ. ID NO: 302)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 293) **(SEQ. ID NO: 303)**

5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 294) **(SEQ. ID NO: 304)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 295) **(SEQ. ID NO: 305)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 296) **(SEQ. ID NO: 306)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 297) **(SEQ. ID NO: 307)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 298) **(SEQ. ID NO: 308)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 299) **(SEQ. ID NO: 309)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 300) **(SEQ. ID NO: 310)**
5'- CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 301) **(SEQ. ID NO: 311)**
5'- CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 302) **(SEQ. ID NO: 312)**
5'- CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 303) **(SEQ. ID NO: 313)**
5'- CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 304) **(SEQ. ID NO: 314)**
5'- CTG GAA AGC TGA GAT GGA GG -3' (FRAG 305) **(SEQ. ID NO: 315)**
5'- CTG GAA AGC TGA GAT GGA G -3' (FRAG 306) **(SEQ. ID NO: 316)**
5'- CTG GAA AGC TGA GAT GGA -3' (FRAG 307) **(SEQ. ID NO: 317)**
5'- CTG GAA AGC TGA GAT GG -3' (FRAG 308) **(SEQ. ID NO: 318)**
5'- CTG GAA AGC TGA GAT G -3' (FRAG 309) **(SEQ. ID NO: 319)**
5'- CTG GAA AGC TGA GAT -3' (FRAG 310) **(SEQ. ID NO: 320)**
5'- CTG GAA AGC TGA GA-3' (FRAG 311) **(SEQ. ID NO: 321)**
5'- CTG GAA AGC TGA G-3' (FRAG 312) **(SEQ. ID NO: 322)**
5'- CTG GAA AGC TGA-3' (FRAG 313) **(SEQ. ID NO: 323)**
5'- CTG GAA AGC TG-3' (FRAG 314) **(SEQ. ID NO: 324)**
5'- CTG GAA AGC T-3' (FRAG 315) **(SEQ. ID NO: 325)**

5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 316) **(SEQ. ID NO: 326)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 317) **(SEQ. ID NO: 327)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 318) **(SEQ. ID NO: 328)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 319) **(SEQ. ID NO: 329)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 320) **(SEQ. ID NO: 330)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 321) **(SEQ. ID NO: 331)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 322) **(SEQ. ID NO: 332)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 323) **(SEQ. ID NO: 333)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 324) **(SEQ. ID NO: 334)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 325) **(SEQ. ID NO: 335)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 326) **(SEQ. ID NO: 336)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 327) **(SEQ. ID NO: 337)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 328) **(SEQ. ID NO: 338)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 329) **(SEQ. ID NO: 339)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 330) **(SEQ. ID NO: 340)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 331) **(SEQ. ID NO: 341)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 332) **(SEQ. ID NO: 342)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 333) **(SEQ. ID NO: 343)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 334) **(SEQ. ID NO: 344)**
5'- TG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 335) **(SEQ. ID NO: 345)**
5'- TG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 336) **(SEQ. ID NO: 346)**
5'- TG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 337) **(SEQ. ID NO: 347)**
5'- TG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 338) **(SEQ. ID NO: 348)**
5'- TG GAA AGC TGA GAT GGA GGG C -3' (FRAG 339) **(SEQ. ID NO: 349)**
5'- TG GAA AGC TGA GAT GGA GGG -3' (FRAG 340) **(SEQ. ID NO: 350)**
5'- TG GAA AGC TGA GAT GGA GG -3' (FRAG 341) **(SEQ. ID NO: 351)**
5'- TG GAA AGC TGA GAT GGA G -3' (FRAG 342) **(SEQ. ID NO: 352)**
5'- TG GAA AGC TGA GAT GGA -3' (FRAG 343) **(SEQ. ID NO: 353)**
5'- TG GAA AGC TGA GAT GG -3' (FRAG 344) **(SEQ. ID NO: 354)**
5'- TG GAA AGC TGA GAT G -3' (FRAG 345) **(SEQ. ID NO: 355)**
5'- TG GAA AGC TGA GAT -3' (FRAG 346) **(SEQ. ID NO: 356)**
5'- TG GAA AGC TGA GA-3' (FRAG 347) **(SEQ. ID NO: 357)**
5'- TG GAA AGC TGA G-3' (FRAG 348) **(SEQ. ID NO: 358)**
5'- TG GAA AGC TGA-3' (FRAG 349) **(SEQ. ID NO: 359)**
5'- TG GAA AGC TG-3' (FRAG 350) **(SEQ. ID NO: 360)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 351) **(SEQ. ID NO: 361)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 352) **(SEQ. ID NO: 362)**

5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 353) **(SEQ. ID NO: 363)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 354) **(SEQ. ID NO: 364)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 355) **(SEQ. ID NO: 365)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 356) **(SEQ. ID NO: 366)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 357) **(SEQ. ID NO: 367)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 358) **(SEQ. ID NO: 368)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 359) **(SEQ. ID NO: 369)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 360) **(SEQ. ID NO: 370)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 361) **(SEQ. ID NO: 371)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 362) **(SEQ. ID NO: 372)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 363) **(SEQ. ID NO: 373)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 364) **(SEQ. ID NO: 374)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 365) **(SEQ. ID NO: 375)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 366) **(SEQ. ID NO: 376)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 367) **(SEQ. ID NO: 377)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 368) **(SEQ. ID NO: 378)**
5'- G GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 369) **(SEQ. ID NO: 379)**
5'- G GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 370) **(SEQ. ID NO: 380)**
5'- G GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 371) **(SEQ. ID NO: 381)**
5'- G GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 372) **(SEQ. ID NO: 382)**
5'- G GAA AGC TGA GAT GGA GGG CG -3' (FRAG 373) **(SEQ. ID NO: 383)**
5'- G GAA AGC TGA GAT GGA GGG C -3' (FRAG 374) **(SEQ. ID NO: 384)**
5'- G GAA AGC TGA GAT GGA GGG -3' (FRAG 375) **(SEQ. ID NO: 385)**
5'- G GAA AGC TGA GAT GGA GG -3' (FRAG 376) **(SEQ. ID NO: 386)**
5'- G GAA AGC TGA GAT GGA G -3' (FRAG 377) **(SEQ. ID NO: 387)**
5'- G GAA AGC TGA GAT GGA -3' (FRAG 378) **(SEQ. ID NO: 388)**
5'- G GAA AGC TGA GAT GG -3' (FRAG 379) **(SEQ. ID NO: 389)**
5'- G GAA AGC TGA GAT G -3' (FRAG 380) **(SEQ. ID NO: 390)**
5'- G GAA AGC TGA GAT -3' (FRAG 381) **(SEQ. ID NO: 391)**
5'- G GAA AGC TGA GA-3' (FRAG 382) **(SEQ. ID NO: 392)**
5'- G GAA AGC TGA G-3' (FRAG 383) **(SEQ. ID NO: 393)**
5'- G GAA AGC TGA-3' (FRAG 384) **(SEQ. ID NO: 394)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 385) **(SEQ. ID NO: 395)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 386) **(SEQ. ID NO: 396)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 387) **(SEQ. ID NO: 397)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 388) **(SEQ. ID NO: 398)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 389) **(SEQ. ID NO: 399)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 390) **(SEQ. ID NO: 400)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 391) **(SEQ. ID NO: 401)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 392) **(SEQ. ID NO: 402)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 393) **(SEQ. ID NO: 403)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 394) **(SEQ. ID NO: 404)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 395) **(SEQ. ID NO: 405)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 396) **(SEQ. ID NO: 406)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 397) **(SEQ. ID NO: 407)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 398) **(SEQ. ID NO: 408)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 399) **(SEQ. ID NO: 409)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 400) **(SEQ. ID NO: 410)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 401) **(SEQ. ID NO: 411)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 402) **(SEQ. ID NO: 412)**
5'- GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 403) **(SEQ. ID NO: 413)**
5'- GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 404) **(SEQ. ID NO: 414)**
5'- GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 405) **(SEQ. ID NO: 415)**
5'- GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 406) **(SEQ. ID NO: 416)**
5'- GAA AGC TGA GAT GGA GGG CG -3' (FRAG 407) **(SEQ. ID NO: 417)**
5'- GAA AGC TGA GAT GGA GGG C -3' (FRAG 408) **(SEQ. ID NO: 418)**
5'- GAA AGC TGA GAT GGA GGG -3' (FRAG 409) **(SEQ. ID NO: 419)**
5'- GAA AGC TGA GAT GGA GG -3' (FRAG 410) **(SEQ. ID NO: 420)**
5'- GAA AGC TGA GAT GGA G -3' (FRAG 411) **(SEQ. ID NO: 421)**
5'- GAA AGC TGA GAT GGA -3' (FRAG 412) **(SEQ. ID NO: 422)**
5'- GAA AGC TGA GAT GG -3' (FRAG 413) **(SEQ. ID NO: 423)**
5'- GAA AGC TGA GAT G -3' (FRAG 414) **(SEQ. ID NO: 424)**
5'- GAA AGC TGA GAT -3' (FRAG 415) **(SEQ. ID NO: 425)**

5'- GAA AGC TGA GA-3' (FRAG 416) **(SEQ. ID NO: 426)**
5'- GAA AGC TGA G-3' (FRAG 417) **(SEQ. ID NO: 427)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 418) **(SEQ. ID NO: 428)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 419) **(SEQ. ID NO: 429)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 420) **(SEQ. ID NO: 430)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 421) **(SEQ. ID NO: 431)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 422) **(SEQ. ID NO: 432)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 423) **(SEQ. ID NO: 433)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3'(FRAG 424) **(SEQ. ID NO: 434)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 425) **(SEQ. ID NO: 435)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 426) **(SEQ. ID NO: 436)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 427) **(SEQ. ID NO: 437)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 428) **(SEQ. ID NO: 438)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 429) **(SEQ. ID NO: 439)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 430) **(SEQ. ID NO: 440)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 431) **(SEQ. ID NO: 441)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 432) **(SEQ. ID NO: 442)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 433) **(SEQ. ID NO: 443)**
5'- AA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 434) **(SEQ. ID NO: 444)**
5'- AA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 435) **(SEQ. ID NO: 445)**
5'- AA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 436) **(SEQ. ID NO: 446)**
5'- AA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 437) **(SEQ. ID NO: 447)**
5'- AA AGC TGA GAT GGA GGG CGG C-3' (FRAG 438) **(SEQ. ID NO: 448)**
5'- AA AGC TGA GAT GGA GGG CGG -3' (FRAG 439) **(SEQ. ID NO: 449)**
5'- AA AGC TGA GAT GGA GGG CG -3' (FRAG 440) **(SEQ. ID NO: 450)**
5'- AA AGC TGA GAT GGA GGG C -3' (FRAG 441) **(SEQ. ID NO: 451)**
5'- AA AGC TGA GAT GGA GGG -3' (FRAG 442) **(SEQ. ID NO: 452)**
5'- AA AGC TGA GAT GGA GG -3' (FRAG 443) **(SEQ. ID NO: 453)**
5'- AA AGC TGA GAT GGA G -3' (FRAG 444) **(SEQ. ID NO: 454)**
5'- AA AGC TGA GAT GGA -3' (FRAG 445) **(SEQ. ID NO: 455)**
5'- AA AGC TGA GAT GG -3' (FRAG 446) **(SEQ. ID NO: 456)**
5'- AA AGC TGA GAT G -3' (FRAG 447) **(SEQ. ID NO: 457)**
5'- AA AGC TGA GAT -3' (FRAG 448) **(SEQ. ID NO: 458)**
5'- AA AGC TGA GA-3' (FRAG 449) **(SEQ. ID NO: 459)**
5'- A AGC TGA GAT GGA GGG CG G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 450) **(SEQ. ID NO: 460)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 451) **(SEQ. ID NO: 461)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 452) **(SEQ. ID NO: 462)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 453) **(SEQ. ID NO: 463)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 454) **(SEQ. ID NO: 464)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 455) **(SEQ. ID NO: 465)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 456) **(SEQ. ID NO: 466)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 457) **(SEQ. ID NO: 467)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 458) **(SEQ. ID NO: 468)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 459) **(SEQ. ID NO: 469)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 460) **(SEQ. ID NO: 470)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 461) **(SEQ. ID NO: 471)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 462) **(SEQ. ID NO: 472)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 463) **(SEQ. ID NO: 473)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 464) **(SEQ. ID NO: 474)**
5'- A AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 465) **(SEQ. ID NO: 475)**
5'- A AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 466) **(SEQ. ID NO: 476)**
5'- A AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 467) **(SEQ. ID NO: 477)**
5'- A AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 468) **(SEQ. ID NO: 478)**
5'- A AGC TGA GAT GGA GGG CGG CA-3' (FRAG 469) **(SEQ. ID NO: 479)**
5'- A AGC TGA GAT GGA GGG CGG C-3' (FRAG 470) **(SEQ. ID NO: 480)**
5'- A AGC TGA GAT GGA GGG CGG -3' (FRAG 471) **(SEQ. ID NO: 481)**
5'- A AGC TGA GAT GGA GGG CG -3' (FRAG 472) **(SEQ. ID NO: 482)**
5'- A AGC TGA GAT GGA GGG C -3' (FRAG 473) **(SEQ. ID NO: 483)**
5'- A AGC TGA GAT GGA GGG -3' (FRAG 474) **(SEQ. ID NO: 484)**
5'- A AGC TGA GAT GGA GG -3' (FRAG 475) **(SEQ. ID NO: 485)**
5'- A AGC TGA GAT GGA G -3' (FRAG 476) **(SEQ. ID NO: 486)**
5'- A AGC TGA GAT GGA -3' (FRAG 477) **(SEQ. ID NO: 487)**
5'- A AGC TGA GAT GG -3' (FRAG 478) **(SEQ. ID NO: 488)**

5'- A AGC TGA GAT G -3' (FRAG 479) **(SEQ. ID NO: 489)**
5'- A AGC TGA GAT -3' (FRAG 480) **(SEQ. ID NO: 490)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 481) **(SEQ. ID NO: 491)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 482) **(SEQ. ID NO: 492)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 483) **(SEQ. ID NO: 493)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 484) **(SEQ. ID NO: 494)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 485) **(SEQ. ID NO: 495)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 486) **(SEQ. ID NO: 496)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 487) **(SEQ. ID NO: 497)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 488) **(SEQ. ID NO: 498)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 489) **(SEQ. ID NO: 499)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 490) **(SEQ. ID NO: 500)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 491) **(SEQ. ID NO: 501)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 492) **(SEQ. ID NO: 502)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 493) **(SEQ. ID NO: 503)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 494) **(SEQ. ID NO: 504)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 495) **(SEQ. ID NO: 505)**
5'- AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 496) **(SEQ. ID NO: 506)**
5'- AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 497) **(SEQ. ID NO: 507)**
5'- AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 498) **(SEQ. ID NO: 508)**
5'- AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 499) **(SEQ. ID NO: 509)**
5'- AGC TGA GAT GGA GGG CGG CA-3' (FRAG 500) **(SEQ. ID NO: 510)**
5'- AGC TGA GAT GGA GGG CGG C-3' (FRAG 501) **(SEQ. ID NO: 511)**
5'- AGC TGA GAT GGA GGG CGG -3' (FRAG 502) **(SEQ. ID NO: 512)**
5'- AGC TGA GAT GGA GGG CG -3' (FRAG 503) **(SEQ. ID NO: 513)**
5'- AGC TGA GAT GGA GGG C -3' (FRAG 504) **(SEQ. ID NO: 514)**
5'- AGC TGA GAT GGA GGG -3' (FRAG 505) **(SEQ. ID NO: 515)**
5'- AGC TGA GAT GGA GG -3' (FRAG 506) **(SEQ. ID NO: 516)**
5'- AGC TGA GAT GGA G -3' (FRAG 507) **(SEQ. ID NO: 517)**
5'- AGC TGA GAT GGA -3' (FRAG 508) **(SEQ. ID NO: 518)**
5'- AGC TGA GAT GG -3' (FRAG 509) **(SEQ. ID NO: 519)**
5'- AGC TGA GAT G -3' (FRAG 510) **(SEQ. ID NO: 520)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 511) **(SEQ. ID NO: 521)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 512) **(SEQ. ID NO: 522)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 513) **(SEQ. ID NO: 523)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 514) **(SEQ. ID NO: 524)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 515) **(SEQ. ID NO: 525)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 516) **(SEQ. ID NO: 526)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 517) **(SEQ. ID NO: 527)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 518) **(SEQ. ID NO: 528)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 519) **(SEQ. ID NO: 529)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 520) **(SEQ. ID NO: 530)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 521) **(SEQ. ID NO: 531)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 522) **(SEQ. ID NO: 532)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 523) **(SEQ. ID NO: 533)**
5'- GC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 524) **(SEQ. ID NO: 534)**
5'- GC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 525) **(SEQ. ID NO: 535)**
5'- GC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 526) **(SEQ. ID NO: 536)**
5'- GC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 527) **(SEQ. ID NO: 537)**
5'- GC TGA GAT GGA GGG CGG CAT G -3' (FRAG 528) **(SEQ. ID NO: 538)**
5'- GC TGA GAT GGA GGG CGG CAT -3' (FRAG 529) **(SEQ. ID NO: 539)**
5'- GC TGA GAT GGA GGG CGG CA-3' (FRAG 530) **(SEQ. ID NO: 540)**
5'- GC TGA GAT GGA GGG CGG C-3' (FRAG 531) **(SEQ. ID NO: 541)**
5'- GC TGA GAT GGA GGG CGG -3' (FRAG 532) **(SEQ. ID NO: 542)**
5'- GC TGA GAT GGA GGG CG -3' (FRAG 533) **(SEQ. ID NO: 543)**
5'- GC TGA GAT GGA GGG C -3' (FRAG 534) **(SEQ. ID NO: 544)**
5'- GC TGA GAT GGA GGG -3' (FRAG 535) **(SEQ. ID NO: 545)**
5'- GC TGA GAT GGA GG -3' (FRAG 536) **(SEQ. ID NO: 546)**
5'- GC TGA GAT GGA G -3' (FRAG 537) **(SEQ. ID NO: 547)**
5'- GC TGA GAT GGA -3' (FRAG 538) **(SEQ. ID NO: 548)**
5'- GC TGA GAT GG -3' (FRAG 539) **(SEQ. ID NO: 549)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 540) **(SEQ. ID NO: 550)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 541) **(SEQ. ID NO: 551)**

5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 542) **(SEQ. ID NO: 552)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 543) **(SEQ. ID NO: 553)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 544) **(SEQ. ID NO: 554)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 545) **(SEQ. ID NO: 555)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 546) **(SEQ. ID NO: 556)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 547) **(SEQ. ID NO: 557)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 548) **(SEQ. ID NO: 558)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 549) **(SEQ. ID NO: 559)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 550) **(SEQ. ID NO: 560)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 551) **(SEQ. ID NO: 561)**
5'- C TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 552) **(SEQ. ID NO: 562)**
5'- C TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 553) **(SEQ. ID NO: 563)**
5'- C TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 554) **(SEQ. ID NO: 564)**
5'- C TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 555) **(SEQ. ID NO: 565)**
5'- C TGA GAT GGA GGG CGG CAT GG -3' (FRAG 556) **(SEQ. ID NO: 566)**
5'- C TGA GAT GGA GGG CGG CAT G -3' (FRAG 557) **(SEQ. ID NO: 567)**
5'- C TGA GAT GGA GGG CGG CAT -3' (FRAG 558) **(SEQ. ID NO: 568)**
5'- C TGA GAT GGA GGG CGG CA-3' (FRAG 559) **(SEQ. ID NO: 569)**
5'- C TGA GAT GGA GGG CGG C-3' (FRAG 560) **(SEQ. ID NO: 570)**
5'- C TGA GAT GGA GGG CGG -3' (FRAG 561) **(SEQ. ID NO: 571)**
5'- C TGA GAT GGA GGG CG -3' (FRAG 562) **(SEQ. ID NO: 572)**
5'- C TGA GAT GGA GGG C -3' (FRAG 563) **(SEQ. ID NO: 573)**
5'- C TGA GAT GGA GGG -3' (FRAG 564) **(SEQ. ID NO: 574)**
5'- C TGA GAT GGA GG -3' (FRAG 565) **(SEQ. ID NO: 575)**
5'- C TGA GAT GGA G -3' (FRAG 566) **(SEQ. ID NO: 576)**
5'- C TGA GAT GGA -3' (FRAG 567) **(SEQ. ID NO: 577)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 568) **(SEQ. ID NO: 578)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 569) **(SEQ. ID NO: 579)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 570) **(SEQ. ID NO: 580)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 571) **(SEQ. ID NO: 581)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 572) **(SEQ. ID NO: 582)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 573) **(SEQ. ID NO: 583)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 574) **(SEQ. ID NO: 584)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 575) **(SEQ. ID NO: 585)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 576) **(SEQ. ID NO: 586)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 577) **(SEQ. ID NO: 587)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 578) **(SEQ. ID NO: 588)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 579) **(SEQ. ID NO: 589)**
5'- TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 580) **(SEQ. ID NO: 590)**
5'- TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 581) **(SEQ. ID NO: 591)**
5'- TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 582) **(SEQ. ID NO: 592)**
5'- TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 583) **(SEQ. ID NO: 593)**
5'- TGA GAT GGA GGG CGG CAT GG -3' (FRAG 584) **(SEQ. ID NO: 594)**
5'- TGA GAT GGA GGG CGG CAT G -3' (FRAG 585) **(SEQ. ID NO: 595)**
5'- TGA GAT GGA GGG CGG CAT -3' (FRAG 586) **(SEQ. ID NO: 596)**
5'- TGA GAT GGA GGG CGG CA-3' (FRAG 587) **(SEQ. ID NO: 597)**
5'- TGA GAT GGA GGG CGG C-3' (FRAG 588) **(SEQ. ID NO: 598)**
5'- TGA GAT GGA GGG CGG -3' (FRAG 589) **(SEQ. ID NO: 599)**
5'- TGA GAT GGA GGG CG -3' (FRAG 590) **(SEQ. ID NO: 600)**
5'- TGA GAT GGA GGG C -3' (FRAG 591) **(SEQ. ID NO: 601)**
5'- TGA GAT GGA GGG -3' (FRAG 592) **(SEQ. ID NO: 602)**
5'- TGA GAT GGA GG -3' (FRAG 593) **(SEQ. ID NO: 603)**
5'- TGA GAT GGA G -3' (FRAG 594) **(SEQ. ID NO: 604)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 595) **(SEQ. ID NO: 605)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 596) **(SEQ. ID NO: 606)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 597) **(SEQ. ID NO: 607)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 598) **(SEQ. ID NO: 608)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 599) **(SEQ. ID NO: 609)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 600) **(SEQ. ID NO: 610)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 601) **(SEQ. ID NO: 611)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 602) **(SEQ. ID NO: 612)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 603) **(SEQ. ID NO: 613)**
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 604) **(SEQ. ID NO: 614)**

5'- GA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 605) **(SEQ. ID NO: 615)**
5'- GA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 606) **(SEQ. ID NO: 616)**
5'- GA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 607) **(SEQ. ID NO: 617)**
5'- GA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 608) **(SEQ. ID NO: 618)**
5'- GA GAT GGA GGG CGG CAT GGC G-3' (FRAG 609) **(SEQ. ID NO: 619)**
5'- GA GAT GGA GGG CGG CAT GGC -3' (FRAG 610) **(SEQ. ID NO: 620)**
5'- GA GAT GGA GGG CGG CAT GG -3' (FRAG 611) **(SEQ. ID NO: 621)**
5'- GA GAT GGA GGG CGG CAT G -3' (FRAG 612) **(SEQ. ID NO: 622)**
5'- GA GAT GGA GGG CGG CAT -3' (FRAG 613) **(SEQ. ID NO: 623)**
5'- GA GAT GGA GGG CGG CA-3' (FRAG 614) **(SEQ. ID NO: 624)**
5'- GA GAT GGA GGG CGG C-3' (FRAG 615) **(SEQ. ID NO: 625)**
5'- GA GAT GGA GGG CGG -3' (FRAG 616) **(SEQ. ID NO: 626)**
5'- GA GAT GGA GGG CG -3' (FRAG 617) **(SEQ. ID NO: 627)**
5'- GA GAT GGA GGG C -3' (FRAG 618) **(SEQ. ID NO: 628)**
5'- GA GAT GGA GGG -3' (FRAG 619) **(SEQ. ID NO: 629)**
5'- GA GAT GGA GG -3' (FRAG 620) **(SEQ. ID NO: 630)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 621) **(SEQ. ID NO: 631)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 622) **(SEQ. ID NO: 632)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 623) **(SEQ. ID NO: 633)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 624) **(SEQ. ID NO: 634)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 625) **(SEQ. ID NO: 635)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 626) **(SEQ. ID NO: 636)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 627) **(SEQ. ID NO: 637)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 628) **(SEQ. ID NO: 638)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 629) **(SEQ. ID NO: 639)**
5'- A GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 630) **(SEQ. ID NO: 640)**
5'- A GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 631) **(SEQ. ID NO: 641)**
5'- A GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 632) **(SEQ. ID NO: 642)**
5'- A GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 633) **(SEQ. ID NO: 643)**
5'- A GAT GGA GGG CGG CAT GGC GG-3' (FRAG 634) **(SEQ. ID NO: 644)**
5'- A GAT GGA GGG CGG CAT GGC G-3' (FRAG 635) **(SEQ. ID NO: 645)**
5'- A GAT GGA GGG CGG CAT GGC -3' (FRAG 636) **(SEQ. ID NO: 646)**
5'- A GAT GGA GGG CGG CAT GG -3' (FRAG 637) **(SEQ. ID NO: 647)**
5'- A GAT GGA GGG CGG CAT G -3' (FRAG 638) **(SEQ. ID NO: 648)**
5'- A GAT GGA GGG CGG CAT -3' (FRAG 639) **(SEQ. ID NO: 649)**
5'- A GAT GGA GGG CGG CA-3' (FRAG 640) **(SEQ. ID NO: 650)**
5'- A GAT GGA GGG CGG C-3' (FRAG 641) **(SEQ. ID NO: 651)**
5'- A GAT GGA GGG CGG -3' (FRAG 642) **(SEQ. ID NO: 652)**
5'- A GAT GGA GGG CG -3' (FRAG 643) **(SEQ. ID NO: 653)**
5'- A GAT GGA GGG C -3' (FRAG 644) **(SEQ. ID NO: 654)**
5'- A GAT GGA GGG -3' (FRAG 645) **(SEQ. ID NO: 655)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 646) **(SEQ. ID NO: 656)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 647) **(SEQ. ID NO: 657)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 648) **(SEQ. ID NO: 658)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 649) **(SEQ. ID NO: 659)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 650) **(SEQ. ID NO: 660)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 651) **(SEQ. ID NO: 661)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 652) **(SEQ. ID NO: 662)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 653) **(SEQ. ID NO: 663)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 654) **(SEQ. ID NO: 664)**
5'- GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 655) **(SEQ. ID NO: 665)**
5'- GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 656) **(SEQ. ID NO: 666)**
5'- GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 657) **(SEQ. ID NO: 667)**
5'- GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 658) **(SEQ. ID NO: 668)**
5'- GAT GGA GGG CGG CAT GGC GG-3' (FRAG 659) **(SEQ. ID NO: 669)**
5'- GAT GGA GGG CGG CAT GGC G-3' (FRAG 660) **(SEQ. ID NO: 670)**
5'- GAT GGA GGG CGG CAT GGC -3' (FRAG 661) **(SEQ. ID NO: 671)**
5'- GAT GGA GGG CGG CAT GG -3' (FRAG 662) **(SEQ. ID NO: 672)**
5'- GAT GGA GGG CGG CAT G -3' (FRAG 663) **(SEQ. ID NO: 673)**
5'- GAT GGA GGG CGG CAT -3' (FRAG 664) **(SEQ. ID NO: 674)**
5'- GAT GGA GGG CGG CA-3' (FRAG 665) **(SEQ. ID NO: 675)**
5'- GAT GGA GGG CGG C-3' (FRAG 666) **(SEQ. ID NO: 676)**
5'- GAT GGA GGG CGG -3' (FRAG 667) **(SEQ. ID NO: 677)**

5'- GAT GGA GGG CG -3' (FRAG 668) **(SEQ. ID NO: 678)**
5'- GAT GGA GGG C -3' (FRAG 669) **(SEQ. ID NO: 679)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 670) **(SEQ. ID NO: 680)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 671) **(SEQ. ID NO: 681)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 672) **(SEQ. ID NO: 682)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 673) **(SEQ. ID NO: 683)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 674) **(SEQ. ID NO: 684)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 675) **(SEQ. ID NO: 685)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 676) **(SEQ. ID NO: 686)**
5'- AT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 677) **(SEQ. ID NO: 687)**
5'- AT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 678) **(SEQ. ID NO: 688)**
5'- AT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 679) **(SEQ. ID NO: 689)**
5'- AT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 680) **(SEQ. ID NO: 690)**
5'- AT GGA GGG CGG CAT GGC GGG C-3' (FRAG 681) **(SEQ. ID NO: 691)**
5'- AT GGA GGG CGG CAT GGC GGG -3' (FRAG 682) **(SEQ. ID NO: 692)**
5'- AT GGA GGG CGG CAT GGC GG-3' (FRAG 683) **(SEQ. ID NO: 693)**
5'- AT GGA GGG CGG CAT GGC G-3' (FRAG 684) **(SEQ. ID NO: 694)**
5'- AT GGA GGG CGG CAT GGC -3' (FRAG 685) **(SEQ. ID NO: 695)**
5'- AT GGA GGG CGG CAT GG -3' (FRAG 686) **(SEQ. ID NO: 696)**
5'- AT GGA GGG CGG CAT G -3' (FRAG 687) **(SEQ. ID NO: 697)**
5'- AT GGA GGG CGG CAT -3' (FRAG 688) **(SEQ. ID NO: 698)**
5'- AT GGA GGG CGG CA-3' (FRAG 689) **(SEQ. ID NO: 699)**
5'- AT GGA GGG CGG C-3' (FRAG 690) **(SEQ. ID NO: 700)**
5'- AT GGA GGG CGG -3' (FRAG 691) **(SEQ. ID NO: 701)**
5'- AT GGA GGG CG -3' (FRAG 692) **(SEQ. ID NO: 702)**
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 693) **(SEQ. ID NO: 703)**
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 694) **(SEQ. ID NO: 704)**
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 695) **(SEQ. ID NO: 705)**
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 696) **(SEQ. ID NO: 706)**
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 697) **(SEQ. ID NO: 707)**
5'- T GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 698) **(SEQ. ID NO: 708)**
5'- T GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 699) **(SEQ. ID NO: 709)**
5'- T GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 700) **(SEQ. ID NO: 710)**
5'- T GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 701) **(SEQ. ID NO: 711)**
5'- T GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 702) **(SEQ. ID NO: 712)**
5'- T GGA GGG CGG CAT GGC GGG CA-3' (FRAG 703) **(SEQ. ID NO: 713)**
5'- T GGA GGG CGG CAT GGC GGG C-3' (FRAG 704) **(SEQ. ID NO: 714)**
5'- T GGA GGG CGG CAT GGC GGG -3' (FRAG 705) **(SEQ. ID NO: 715)**
5'- T GGA GGG CGG CAT GGC GG-3' (FRAG 706) **(SEQ. ID NO: 716)**
5'- T GGA GGG CGG CAT GGC G-3' (FRAG 707) **(SEQ. ID NO: 717)**
5'- T GGA GGG CGG CAT GGC -3' (FRAG 708) **(SEQ. ID NO: 718)**
5'- T GGA GGG CGG CAT GG -3' (FRAG 709) **(SEQ. ID NO: 719)**
5'- T GGA GGG CGG CAT G -3' (FRAG 710) **(SEQ. ID NO: 720)**
5'- T GGA GGG CGG CAT -3' (FRAG 711) **(SEQ. ID NO: 721)**
5'- T GGA GGG CGG CA-3' (FRAG 712) **(SEQ. ID NO: 722)**
5'- T GGA GGG CGG C-3' (FRAG 713) **(SEQ. ID NO: 723)**
5'- T GGA GGG CGG -3' (FRAG 714) **(SEQ. ID NO: 724)**
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 715) **(SEQ. ID NO: 725)**
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 716) **(SEQ. ID NO: 726)**
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 717) **(SEQ. ID NO: 727)**
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 718) **(SEQ. ID NO: 728)**
5'- GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 719) **(SEQ. ID NO: 729)**
5'- GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 720) **(SEQ. ID NO: 730)**
5'- GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 721) **(SEQ. ID NO: 731)**
5'- GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 722) **(SEQ. ID NO: 732)**
5'- GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 723) **(SEQ. ID NO: 733)**
5'- GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 724) **(SEQ. ID NO: 734)**
5'- GGA GGG CGG CAT GGC GGG CA-3' (FRAG 725) **(SEQ. ID NO: 735)**
5'- GGA GGG CGG CAT GGC GGG C-3' (FRAG 726) **(SEQ. ID NO: 736)**
5'- GGA GGG CGG CAT GGC GGG -3' (FRAG 727) **(SEQ. ID NO: 737)**
5'- GGA GGG CGG CAT GGC GG-3' (FRAG 728) **(SEQ. ID NO: 738)**
5'- GGA GGG CGG CAT GGC G-3' (FRAG 729) **(SEQ. ID NO: 739)**
5'- GGA GGG CGG CAT GGC -3' (FRAG 730) **(SEQ. ID NO: 740)**

5'- GGA GGG CGG CAT GG -3' (FRAG 731) **(SEQ. ID NO: 741)**
5'- GGA GGG CGG CAT G -3' (FRAG 732) **(SEQ. ID NO: 742)**
5'- GGA GGG CGG CAT -3' (FRAG 733) **(SEQ. ID NO: 743)**
5'- GGA GGG CGG CA-3' (FRAG 734) **(SEQ. ID NO: 744)**
5'- GGA GGG CGG C-3' (FRAG 735) **(SEQ. ID NO: 745)**
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 736) **(SEQ. ID NO: 746)**
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 737) **(SEQ. ID NO: 747)**
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 738) **(SEQ. ID NO: 748)**
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 739) **(SEQ. ID NO: 749)**
5'- GA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 740) **(SEQ. ID NO: 750)**
5'- GA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 741) **(SEQ. ID NO: 751)**
5'- GA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 742) **(SEQ. ID NO: 752)**
5'- GA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 743) **(SEQ. ID NO: 753)**
5'- GA GGG CGG CAT GGC GGG CAC A-3' (FRAG 744) **(SEQ. ID NO: 754)**
5'- GA GGG CGG CAT GGC GGG CAC-3' (FRAG 745) **(SEQ. ID NO: 755)**
5'- GA GGG CGG CAT GGC GGG CA-3' (FRAG 746) **(SEQ. ID NO: 756)**
5'- GA GGG CGG CAT GGC GGG C-3' (FRAG 747) **(SEQ. ID NO: 757)**
5'- GA GGG CGG CAT GGC GGG -3' (FRAG 748) **(SEQ. ID NO: 758)**
5'- GA GGG CGG CAT GGC GG-3' (FRAG 749) **(SEQ. ID NO: 759)**
5'- GA GGG CGG CAT GGC G-3' (FRAG 750) **(SEQ. ID NO: 760)**
5'- GA GGG CGG CAT GGC -3' (FRAG 751) **(SEQ. ID NO: 761)**
5'- GA GGG CGG CAT GG -3' (FRAG 752) **(SEQ. ID NO: 762)**
5'- GA GGG CGG CAT G -3' (FRAG 753) **(SEQ. ID NO: 763)**
5'- GA GGG CGG CAT -3' (FRAG 754) **(SEQ. ID NO: 764)**
5'- GA GGG CGG CA-3' (FRAG 755) **(SEQ. ID NO: 765)**
5'- A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 756) **(SEQ. ID NO: 766)**
5'- A GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 757) **(SEQ. ID NO: 767)**
5'- A GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 758) **(SEQ. ID NO: 768)**
5'- A GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 759) **(SEQ. ID NO: 769)**
5'- A GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 760) **(SEQ. ID NO: 770)**
5'- A GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 761) **(SEQ. ID NO: 771)**
5'- A GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 762) **(SEQ. ID NO: 772)**
5'- A GGG CGG CAT GGC GGG CAC AG-3' (FRAG 763) **(SEQ. ID NO: 773)**
5'- A GGG CGG CAT GGC GGG CAC A-3' (FRAG 764) **(SEQ. ID NO: 774)**
5'- A GGG CGG CAT GGC GGG CAC-3' (FRAG 765) **(SEQ. ID NO: 775)**
5'- A GGG CGG CAT GGC GGG CA-3' (FRAG 766) **(SEQ. ID NO: 776)**
5'- A GGG CGG CAT GGC GGG C-3' (FRAG 767) **(SEQ. ID NO: 777)**
5'- A GGG CGG CAT GGC GGG -3' (FRAG 768) **(SEQ. ID NO: 778)**
5'- A GGG CGG CAT GGC GG-3' (FRAG 769) **(SEQ. ID NO: 779)**
5'- A GGG CGG CAT GGC G-3' (FRAG 770) **(SEQ. ID NO: 780)**
5'- A GGG CGG CAT GGC -3' (FRAG 771) **(SEQ. ID NO: 781)**
5'- A GGG CGG CAT GG -3' (FRAG 772) **(SEQ. ID NO: 782)**
5'- A GGG CGG CAT G -3' (FRAG 773) **(SEQ. ID NO: 783)**
5'- A GGG CGG CAT -3' (FRAG 774) **(SEQ. ID NO: 784)**
5'- GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 775) **(SEQ. ID NO: 785)**
5'- GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 776) **(SEQ. ID NO: 786)**
5'- GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 777) **(SEQ. ID NO: 787)**
5'- GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 778) **(SEQ. ID NO: 788)**
5'- GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 779) **(SEQ. ID NO: 789)**
5'- GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 780) **(SEQ. ID NO: 790)**
5'- GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 781) **(SEQ. ID NO: 791)**
5'- GGG CGG CAT GGC GGG CAC AG-3' (FRAG 782) **(SEQ. ID NO: 792)**
5'- GGG CGG CAT GGC GGG CAC A-3' (FRAG 783) **(SEQ. ID NO: 793)**
5'- GGG CGG CAT GGC GGG CAC-3' (FRAG 784) **(SEQ. ID NO: 794)**
5'- GGG CGG CAT GGC GGG CA-3' (FRAG 785) **(SEQ. ID NO: 795)**
5'- GGG CGG CAT GGC GGG C-3' (FRAG 786) **(SEQ. ID NO: 796)**
5'- GGG CGG CAT GGC GGG -3' (FRAG 787) **(SEQ. ID NO: 797)**
5'- GGG CGG CAT GGC GG-3' (FRAG 788) **(SEQ. ID NO: 798)**
5'- GGG CGG CAT GGC G-3' (FRAG 789) **(SEQ. ID NO: 799)**
5'- GGG CGG CAT GGC -3' (FRAG 790) **(SEQ. ID NO: 800)**
5'- GGG CGG CAT GG -3' (FRAG 791) **(SEQ. ID NO: 801)**
5'- GGG CGG CAT G -3' (FRAG 792) **(SEQ. ID NO: 802)**
5'- GG CGG CAT GGC GGG CAC AG G CTG GGC-3' (FRAG 793) **(SEQ. ID NO: 803)**

5'- GG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 794) **(SEQ. ID NO: 804)**
5'- GG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 795) **(SEQ. ID NO: 805)**
5'- GG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 796) **(SEQ. ID NO: 806)**
5'- GG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 797) **(SEQ. ID NO: 807)**
5'- GG CGG CAT GGC GGG CAC AGG C-3' (FRAG 798) **(SEQ. ID NO: 808)**
5'- GG CGG CAT GGC GGG CAC AGG -3' (FRAG 799) **(SEQ. ID NO: 809)**
5'- GG CGG CAT GGC GGG CAC AG-3' (FRAG 800) **(SEQ. ID NO: 810)**
5'- GG CGG CAT GGC GGG CAC A-3' (FRAG 801) **(SEQ. ID NO: 811)**
5'- GG CGG CAT GGC GGG CAC-3' (FRAG 802) **(SEQ. ID NO: 812)**
5'- GG CGG CAT GGC GGG CA-3' (FRAG 803) **(SEQ. ID NO: 813)**
5'- GG CGG CAT GGC GGG C-3' (FRAG 804) **(SEQ. ID NO: 814)**
5'- GG CGG CAT GGC GGG -3' (FRAG 805) **(SEQ. ID NO: 815)**
5'- GG CGG CAT GGC GG-3' (FRAG 806) **(SEQ. ID NO: 816)**
5'- GG CGG CAT GGC G-3' (FRAG 807) **(SEQ. ID NO: 817)**
5'- GG CGG CAT GGC -3' (FRAG 808) **(SEQ. ID NO: 818)**
5'- GG CGG CAT GG -3' (FRAG 809) **(SEQ. ID NO: 819)**
5'- G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 810) **(SEQ. ID NO: 820)**
5'- G CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 811) **(SEQ. ID NO: 821)**
5'- G CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 812) **(SEQ. ID NO: 822)**
5'- G CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 813) **(SEQ. ID NO: 823)**
5'- G CGG CAT GGC GGG CAC AGG CT-3' (FRAG 814) **(SEQ. ID NO: 824)**
5'- G CGG CAT GGC GGG CAC AGG C-3' (FRAG 815) **(SEQ. ID NO: 825)**
5'- G CGG CAT GGC GGG CAC AGG -3' (FRAG 816) **(SEQ. ID NO: 826)**
5'- G CGG CAT GGC GGG CAC AG-3' (FRAG 817) **(SEQ. ID NO: 827)**
5'- G CGG CAT GGC GGG CAC A-3' (FRAG 818) **(SEQ. ID NO: 828)**
5'- G CGG CAT GGC GGG CAC-3' (FRAG 819) **(SEQ. ID NO: 829)**
5'- G CGG CAT GGC GGG CA-3' (FRAG 820) **(SEQ. ID NO: 830)**
5'- G CGG CAT GGC GGG C-3' (FRAG 821) **(SEQ. ID NO: 831)**
5'- G CGG CAT GGC GGG -3' (FRAG 822) **(SEQ. ID NO: 832)**
5'- G CGG CAT GGC GG-3' (FRAG 823) **(SEQ. ID NO: 833)**
5'- G CGG CAT GGC G-3' (FRAG 824) **(SEQ. ID NO: 834)**
5'- G CGG CAT GGC -3' (FRAG 825) **(SEQ. ID NO: 835)**
5'- CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 826) **(SEQ. ID NO: 836)**
5'- CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 827) **(SEQ. ID NO: 837)**
5'- CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 828) **(SEQ. ID NO: 838)**
5'- CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 829) **(SEQ. ID NO: 839)**
5'- CGG CAT GGC GGG CAC AGG CT-3' (FRAG 830) **(SEQ. ID NO: 840)**
5'- CGG CAT GGC GGG CAC AGG C-3' (FRAG 831) **(SEQ. ID NO: 841)**
5'- CGG CAT GGC GGG CAC AGG -3' (FRAG 832) **(SEQ. ID NO: 842)**
5'- CGG CAT GGC GGG CAC AG-3' (FRAG 833) **(SEQ. ID NO: 843)**
5'- CGG CAT GGC GGG CAC A-3' (FRAG 834) **(SEQ. ID NO: 844)**
5'- CGG CAT GGC GGG CAC-3' (FRAG 835) **(SEQ. ID NO: 845)**
5'- CGG CAT GGC GGG CA-3' (FRAG 836) **(SEQ. ID NO: 846)**
5'- CGG CAT GGC GGG C-3' (FRAG 837) **(SEQ. ID NO: 847)**
5'- CGG CAT GGC GGG -3' (FRAG 838) **(SEQ. ID NO: 848)**
5'- CGG CAT GGC GG-3' (FRAG 839) **(SEQ. ID NO: 849)**
5'- CGG CAT GGC G-3' (FRAG 840) **(SEQ. ID NO: 850)**
5'- GG CAT GGC GGG CAC AGG C TG GGC-3' (FRAG 841) **(SEQ. ID NO: 851)**
5'- GG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 842) **(SEQ. ID NO: 852)**
5'- GG CAT GGC GGG CAC AGG CTG G-3' (FRAG 843) **(SEQ. ID NO: 853)**
5'- GG CAT GGC GGG CAC AGG CTG -3' (FRAG 844) **(SEQ. ID NO: 854)**
5'- GG CAT GGC GGG CAC AGG CT-3' (FRAG 845) **(SEQ. ID NO: 855)**
5'- GG CAT GGC GGG CAC AGG C-3' (FRAG 846) **(SEQ. ID NO: 856)**
5'- GG CAT GGC GGG CAC AGG -3' (FRAG 847) **(SEQ. ID NO: 857)**
5'- GG CAT GGC GGG CAC AG-3' (FRAG 848) **(SEQ. ID NO: 858)**
5'- GG CAT GGC GGG CAC A-3' (FRAG 849) **(SEQ. ID NO: 859)**
5'- GG CAT GGC GGG CAC-3' (FRAG 850) **(SEQ. ID NO: 860)**
5'- GG CAT GGC GGG CA-3' (FRAG 851) **(SEQ. ID NO: 861)**
5'- GG CAT GGC GGG C-3' (FRAG 852) **(SEQ. ID NO: 862)**
5'- GG CAT GGC GGG -3' (FRAG 853) **(SEQ. ID NO: 863)**
5'- GG CAT GGC GG-3' (FRAG 854) **(SEQ. ID NO: 864)**
5'- G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 855) **(SEQ. ID NO: 865)**
5'- G CAT GGC GGG CAC AGG CTG GG-3' (FRAG 856) **(SEQ. ID NO: 866)**

5'- G CAT GGC GGG CAC AGG CTG G-3' (FRAG 857) **(SEQ. ID NO: 867)**
5'- G CAT GGC GGG CAC AGG CTG -3' (FRAG 858) **(SEQ. ID NO: 868)**
5'- G CAT GGC GGG CAC AGG CT-3' (FRAG 859) **(SEQ. ID NO: 869)**
5'- G CAT GGC GGG CAC AGG C-3' (FRAG 860) **(SEQ. ID NO: 870)**
5'- G CAT GGC GGG CAC AGG -3' (FRAG 861) **(SEQ. ID NO: 871)**
5'- G CAT GGC GGG CAC AG-3' (FRAG 862) **(SEQ. ID NO: 872)**
5'- G CAT GGC GGG CAC A-3' (FRAG 863) **(SEQ. ID NO: 873)**
5'- G CAT GGC GGG CAC-3' (FRAG 864) **(SEQ. ID NO: 874)**
5'- G CAT GGC GGG CA-3' (FRAG 865) **(SEQ. ID NO: 875)**
5'- G CAT GGC GGG C-3' (FRAG 866) **(SEQ. ID NO: 876)**
5'- G CAT GGC GGG -3' (FRAG 867) **(SEQ. ID NO: 877)**
5'- CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 868) **(SEQ. ID NO: 878)**
5'- CAT GGC GGG CAC AGG CTG GG-3' (FRAG 869) **(SEQ. ID NO: 879)**
5'- CAT GGC GGG CAC AGG CTG G-3' (FRAG 870) **(SEQ. ID NO: 880)**
5'- CAT GGC GGG CAC AGG CTG -3' (FRAG 871) **(SEQ. ID NO: 881)**
5'- CAT GGC GGG CAC AGG CT-3' (FRAG 872) **(SEQ. ID NO: 882)**
5'- CAT GGC GGG CAC AGG C-3' (FRAG 873) **(SEQ. ID NO: 883)**
5'- CAT GGC GGG CAC AGG -3' (FRAG 874) **(SEQ. ID NO: 884)**
5'- CAT GGC GGG CAC AG-3' (FRAG 875) **(SEQ. ID NO: 885)**
5'- CAT GGC GGG CAC A-3' (FRAG 876) **(SEQ. ID NO: 886)**
5'- CAT GGC GGG CAC-3' (FRAG 877) **(SEQ. ID NO: 887)**
5'- CAT GGC GGG CA-3' (FRAG 878) **(SEQ. ID NO: 888)**
5'- CAT GGC GGG C-3' (FRAG 879) **(SEQ. ID NO: 889)**
5'- AT GGC GGG CAC AGG CTG GGC-3' (FRAG 880) **(SEQ. ID NO: 890)**
5'- AT GGC GGG CAC AGG CTG GG-3' (FRAG 881) **(SEQ. ID NO: 891)**
5'- AT GGC GGG CAC AGG CTG G-3' (FRAG 882) **(SEQ. ID NO: 892)**
5'- AT GGC GGG CAC AGG CTG -3' (FRAG 883) **(SEQ. ID NO: 893)**
5'- AT GGC GGG CAC AGG CT-3' (FRAG 884) **(SEQ. ID NO: 894)**
5'- AT GGC GGG CAC AGG C-3' (FRAG 885) **(SEQ. ID NO: 895)**
5'- AT GGC GGG CAC AGG -3' (FRAG 886) **(SEQ. ID NO: 896)**
5'- AT GGC GGG CAC AG-3' (FRAG 887) **(SEQ. ID NO: 897)**
5'- AT GGC GGG CAC A-3' (FRAG 888) **(SEQ. ID NO: 898)**
5'- AT GGC GGG CAC-3' (FRAG 889) **(SEQ. ID NO: 899)**
5'- AT GGC GGG CA-3' (FRAG 890) **(SEQ. ID NO: 900)**
5'- T GGC GGG CAC AGG CTG GGC-3' (FRAG 891) **(SEQ. ID NO: 901)**
5'- T GGC GGG CAC AGG CTG GG-3' (FRAG 892) **(SEQ. ID NO: 902)**
5'- T GGC GGG CAC AGG CTG G-3' (FRAG 893) **(SEQ. ID NO: 903)**
5'- T GGC GGG CAC AGG CTG -3' (FRAG 894) **(SEQ. ID NO: 904)**
5'- T GGC GGG CAC AGG CT-3' (FRAG 895) **(SEQ. ID NO: 905)**
5'- T GGC GGG CAC AGG C-3' (FRAG 896) **(SEQ. ID NO: 906)**
5'- T GGC GGG CAC AGG -3' (FRAG 897) **(SEQ. ID NO: 907)**
5'- T GGC GGG CAC AG-3' (FRAG 898) **(SEQ. ID NO: 908)**
5'- T GGC GGG CAC A-3' (FRAG 899) **(SEQ. ID NO: 909)**
5'- T GGC GGG CAC-3' (FRAG 900) **(SEQ. ID NO: 910)**
5'- GGC GGG CAC AGG CTG GGC-3' (FRAG 901) **(SEQ. ID NO: 911)**
5'- GGC GGG CAC AGG CTG GG-3' (FRAG 902) **(SEQ. ID NO: 912)**
5'- GGC GGG CAC AGG CTG G-3' (FRAG 903) **(SEQ. ID NO: 913)**
5'- GGC GGG CAC AGG CTG -3' (FRAG 904) **(SEQ. ID NO: 914)**
5'- GGC GGG CAC AGG CT-3' (FRAG 905) **(SEQ. ID NO: 915)**
5'- GGC GGG CAC AGG C-3' (FRAG 906) **(SEQ. ID NO: 916)**
5'- GGC GGG CAC AGG -3' (FRAG 907) **(SEQ. ID NO: 917)**
5'- GGC GGG CAC AG-3' (FRAG 908) **(SEQ. ID NO: 918)**
5'- GGC GGG CAC A-3' (FRAG 909) **(SEQ. ID NO: 919)**
5'- GC GGG CAC AGG CTG GGC-3' (FRAG 910) **(SEQ. ID NO: 920)**
5'- GC GGG CAC AGG CTG GG-3' (FRAG 911) **(SEQ. ID NO: 921)**
5'- GC GGG CAC AGG CTG G-3' (FRAG 912) **(SEQ. ID NO: 922)**
5'- GC GGG CAC AGG CTG -3' (FRAG 913) **(SEQ. ID NO: 923)**
5'- GC GGG CAC AGG CT-3' (FRAG 914) **(SEQ. ID NO: 924)**
5'- GC GGG CAC AGG C-3' (FRAG 915) **(SEQ. ID NO: 925)**
5'- GC GGG CAC AGG -3' (FRAG 916) **(SEQ. ID NO: 926)**
5'- GC GGG CAC AG-3' (FRAG 917) **(SEQ. ID NO: 927)**
5'- C GGG CAC AGG CTG GGC-3' (FRAG 918) **(SEQ. ID NO: 928)**

5'- C GGG CAC AGG CTG GG-3' (FRAG 919) **(SEQ. ID NO: 929)**
5'- C GGG CAC AGG CTG G-3' (FRAG 920) **(SEQ. ID NO: 930)**
5'- C GGG CAC AGG CTG -3' (FRAG 921) **(SEQ. ID NO: 931)**
5'- C GGG CAC AGG CT-3' (FRAG 922) **(SEQ. ID NO: 932)**
5'- C GGG CAC AGG C-3' (FRAG 923) **(SEQ. ID NO: 933)**
5'- C GGG CAC AGG -3' (FRAG 924) **(SEQ. ID NO: 934)**
5'- GGG CAC AGG CTG GGC-3' (FRAG 925) **(SEQ. ID NO: 935)**
5'- GGG CAC AGG CTG GG-3' (FRAG 926) **(SEQ. ID NO: 936)**
5'- GGG CAC AGG CTG G-3' (FRAG 927) **(SEQ. ID NO: 937)**
5'- GGG CAC AGG CTG -3' (FRAG 928) **(SEQ. ID NO: 938)**
5'- GGG CAC AGG CT-3' (FRAG 929) **(SEQ. ID NO: 939)**
5'- GGG CAC AGG C-3' (FRAG 930) **(SEQ. ID NO: 940)**
5'- GG CAC AGG CTG GGC-3' (FRAG 931) **(SEQ. ID NO: 941)**
5'- GG CAC AGG CTG GG-3' (FRAG 932) **(SEQ. ID NO: 942)**
5'- GG CAC AGG CTG G-3' (FRAG 933) **(SEQ. ID NO: 943)**
5'- GG CAC AGG CTG -3' (FRAG 934) **(SEQ. ID NO: 944)**
5'- GG CAC AGG CT-3' (FRAG 935) **(SEQ. ID NO: 945)**
5'- G CAC AGG CTG GGC-3' (FRAG 936) **(SEQ. ID NO: 946)**
5'- G CAC AGG CTG GG-3' (FRAG 937) **(SEQ. ID NO: 947)**
5'- G CAC AGG CTG G-3' (FRAG 938) **(SEQ. ID NO: 948)**
5'- G CAC AGG CTG -3' (FRAG 939) **(SEQ. ID NO: 949)**
5'- CAC AGG CTG GGC-3' (FRAG 940) **(SEQ. ID NO: 950)**
5'- CAC AGG CTG GG-3' (FRAG 941) **(SEQ. ID NO: 951)**
5'- CAC AGG CTG G-3' (FRAG 942) **(SEQ. ID NO: 952)**
5'- AC AGG CTG GGC-3' (FRAG 943) **(SEQ. ID NO: 953)**
5'- AC AGG CTG GG-3' (FRAG 944) **(SEQ. ID NO: 954)**
5'- C AGG CTG GGC-3' (FRAG 945) **(SEQ. ID NO: 955)**

In the anti-sense oligonucleotides of the present invention, exemplified by the preceding sequences, adenosine bases may be replaced with an appropriate "spacer" or universal base (e.g., 1-[β-D-2'-deoxyribofuranosyl]-5-nitroindole], or with an adenosine agonist or antagonist that does not stimulate adenosine A_1, A_{2a}, A_{2b} or A_3 receptors or the bradykinin B_2 receptor.

Examples of anti-sense oligo sequences targeted to the adenosine A_{2b} receptors are as follows.

GGC CGG GCC AGC TGG GCC CCG GGC GCC C **(SEQ ID NO: 8)**
GGC CGG GCC AGC TGG GCC CCG G (FRAG 1)
CTC CAG CAG CAT GGC CGG GCC (FRAG 2)
CGC CGT GCC CAC CGC GGC GC (FRAG 3)
GCC CCA CGG CCA CGT CGG CCG C (FRAG 4)

Fragments of SEQ. ID NO: 7 and 8 shown above other than the ones exemplified, which are about 7 to 18 nucleotide long are also encompassed and preferred. Particularly preferred are those where the 3' end is preferentially conserved.

Anti-sense oligos specific to the human adenosine A_{2a} receptor are exemplified below. For gene sequence, see Salvatore, C. A., et al., Genomics (1997). Fragments of the two sequences shown below about 7 to18 nucleotide long are also encompassed and preferred. Particularly preferred are those where the 3' end is preferentially conserved.

GGA GCC CAT GAT GGG CAT GCC (FRAG 1) CCC ACT GCG ATG TCG GCC GCC GCC (FRAG 2) GGC CCT CCC CGC AGC CCT GGG (FRAG 3) CTT CAG CTG TCG TCG GCG CGC C (FRAG 4) **(SEQ. ID NO: 9)**

GGA CCG TGC CCG CTC CCC CGG C (FRAG 1) TGC AGT GTG GAC CGT GCC CGC (FRAG 2) GGG CGT GGC TGC AGT CGG GGC (FRAG 3) GGC CCA CAC TCC TGG CGG GTG GCC G (FRAG 4) GCC GTT GGC CCA CAC TCC TGG CGG G (FRAG 5) **(SEQ. ID NO: 10)**

Chemical analogs of oligonucleotides, e.g., oligonucleotides in which the phosphodiester bonds have been modified, e.g., to the methylphosphonate, the phosphotriester, the phosphorothioate, the phosphorodithioate, or the phosphoramidate, so as to render the oligonucleotide more stable in vivo, are also an aspect of the present invention. The naturally occurring phosphodiester linkages in oligonucleotides are susceptible to degradation by endogenously occurring cellular nucleases, while many analogous linkages are highly resistant to nuclease degradation. See Milligan et al., supra; Cohen, J. S. D., supra. Protection from degradation can be achieved by use of a " 3 ' -end cap" strategy by which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3' end of the oligonucleotide. See Tidd, D. M. and Warenius, H. M., Br. J. Cancer 60, 343-350 (1989) ; Shaw, J.P. et al., Nucleic Acids Res. 19, 747-750 (1991). Phosphoramidates, phosphorothioates, and methylphosphonate linkages all function adequately in this manner. More extensive modification of the phosphodiester backbone has been shown to impart stability and may allow for enhanced affinity and increased cellular permeation of oligonucleotides. See Milligan, et al., supra. Many different chemical strategies have been employed to replace the entire phosphodiester backbone with novel linkages. Id. Backbone analogues include phosphorothioate, methylphosphonate, phosphotriester, thioformacetal, phosphorodithioate, phosphoramidate, formacetal boranophosphate, 3'-thioformacetal, 2'-O-methyl, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite., sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI) or methyleneoxy(methylimino) (MOMI) linkages. Phosphorothioate and methylphosphonate-modified oligonucleotides are particularly preferred due to their availability through automated oligonucleotide synthesis. Id. Anti-sense oligonucleotides containing modifications to the nucleotide base itself, e.g. a C-5 propyne, or C-5 methyl, or to the sugar, e.g. a carbohydrate modification, are also aspects of the present invention. Where appropriate. the anti-sense nucleotide may be administered in the form of their pharmaceutically acceptable salts.

The present anti-sense oligonucleotides may be of any suitable length, preferably about 7 to 60, more preferably about 10 to 36, and still more preferably about 12 to 21, nucleotide long, depending on the particular target being bound and the mode of delivery thereof. Preferably the anti-sense oligonucleotide is directed to an mRNA region containing a junction between intron and exon. Where the anti-sense oligonucleotide is directed to an intron/exon junction, it may either entirely overlie the junction or may be sufficiently close to the junction to inhibit splicing out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g. with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, 10, 5, 3, or 2 nucleotide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon. When administering the anti-sense oligos of the present invention, their sequence may be drawn from a gene or RNA sequence related in origin to the species to which it is administered. When treating humans, human anti-sense may be used if desired.

The agent of the invention is also provided as a pharmaceutical composition comprising an anti-sense oligonucleotide as given above effective to reduce expression of an adenosine and/or bradykinin receptor gene, particularly the adenosine A_1, A_{2a}, A_{2b} and/or A_3 and bradykinin B_2 receptors by passing through a cell membrane and selectively binding to mRNA encoding the receptor mRNA in the cell so as to prevent its translation. Such compositions are provided in suitable formulations, accompanied by a carrier, preferably a pharmaceutically or veterinarily acceptable carrier, e.g. sterile pyrogen-free saline solution. The anti-sense oligonucleotides may be formulated with a hydrophobic carrier capable of passing through a cell membrane (e.g., in a liposome, with the liposomes carried in a pharmaceutically acceptable aqueous carrier). The sequence specific oligonucleotides may also be constructed so as to compose an entity which directly inactivates mRNA, such as a ribozyme. Such oligonucleotides may be administered to a subject in need of the treatment to inhibit the activation of adenosine receptors, such as the adenosine A_1, A_{2b}, A_{2b} and/or A_3 and the bradykinin B_2 receptors. Furthermore, the pharmaceutical formulation may also contain chimeric molecules comprising anti-sense oligonucleotides attached to agents which are known to be internalized and/or taken-up by lysing cells. These oligonucleotide conjugates utilize cellular up-take pathways to increase cellular concentrations of oligonucleotides. Examples of macromolecules used in this manner include transferrin, asialoglycoprotein (bound to oligonucleotides via polylysine) and streptavidin.

In the pharmaceutical formulation the anti-sense oligo may be contained within a lipid particle or vesicle, such as a liposome or microcrystal. The particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the anti-sense oligonucleotide is contained therein. Positively charged lipids, such as N- [1-(2, 3 -dioleoyloxi) propyl] -N, N, N-trimethylammoniumethylsulfate or "DOTAP", are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g., U.S. Patent Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.; 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.; 4,921,757 to Wheatley et al.; etc.

The composition of this invention may be administered to a subject by any means of delivery which will transport the anti-sense nucleotide composition to the lung. The anti-sense oligos of this invention may be administered to the lungs of a patient by any suitable means, but are preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the anti-sense compound, which particles the subject inhales. The respirable particles may be liquid or solid. The particles may optionally contain other therapeutic ingredients.

The anti-sense compound of the present invention is generally delivered in particulate form. The particles should include particles of respirable size, preferably particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, particles ranging from about 0.5 to 10 microns in size are respirable. Particles of non-respirable size which are included in the aerosol tend to deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration, a particle size in the range of 10-500 μm is preferred to ensure retention in the nasal cavity.

Liquid pharmaceutical compositions of active compound for producing an aerosol can be prepared by combining the anti-sense compound with a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds may optionally be included.

Solid particulate compositions containing respirable dry particles of micronized anti-sense compound may be prepared by grinding dry anti-sense compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprised of the anti-sense compound may optionally contain a dispersant which serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which may be blended with the anti-sense

compound in any suitable ratio, e.g. an about 1:1 ratio by weight. Again, other therapeutic compounds may also be included.

The dosage of the anti-sense compound administered will depend upon the disease being treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to a subject, etc. In general, intracellular concentrations of the oligonucleotide of from 0.05 to 50 μM, or more particularly 0.2 to 5 μM, are desirable, however higher or lower concentrations may also be therapeutic. For administration to a subject such as a human, a dosage of about 0.01, 0.1, or 1 mg/Kg up to 50, 100, or 150 mg/Kg or more, is typically employed. Depending on the solubility of the particular formulation of active compound administered, the daily dose may be divided among one or several unit dose administrations. Administration of the anti-sense compounds may be carried out therapeutically (i.e., as a rescue treatment) or prophylactically.

Aerosols of liquid particles comprising the anti-sense compound may be produced by any suitable means, such as with a nebulizer. See, e.g., US Patent No. 4,501,729. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier, the active ingredient comprising about 0.01% to about 40% w/w of the formulation, and higher, preferably up to about 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

Aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the

powder (e.g., a metered dose thereof effective to carry out the treatments described herein) is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150 μl, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. Additionally, other propellants having improved environmental properties as compared to fluor- and chlorofluorocarbon compounds may be employed. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.

The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament may be administered more rapidly.

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereon.

EXAMPLES

In the following examples, μM means micromolar, mL means milliliters, μm means micrometers, mm means millimeters, cm means centimeters, °C means degrees Celsius, μg means micrograms, mg means milligrams, g means grams, kg means kilograms, M means molar, and h or hr means hours.

Example 1: Design and Synthesis of Anti-sense Oliqonucleotides

The design of anti-sense oligonucleotides against the A_1 and A_3 adenosine receptors may require the solution of the complex secondary structure of the target A_1 receptor mRNA,

the target A_{2a} receptor mRNA, the target A_{2b} receptor mRNA and the target A_3 receptor mRNA. After generating this structure, anti-sense nucleotide are designed which target regions of mRNA which might be construed to confer functional activity or stability to the mRNA and which optimally may overlap the initiation codon. Other target sites are readily usable. As a demonstration of specificity of the anti-sense effect, other oligonucleotides not totally complementary to the target mRNA, but containing identical nucleotide compositions on a w/w basis, are included as controls in anti-sense experiments.

Adenosine A_1 receptor mRNA secondary structure was analyzed and used as described above to design a phosphorothioate anti-sense oligonucleotide. The anti-sense oligonucleotide which was synthesized was designated HAdAlAS and had the following sequence:

5' -GAT GGA GGG CGG CAT GGC GGG-3' **(SEQ ID NO:1)**

As a control, a mismatched phosphorothioate anti-sense nucleotide designated HAdAlMM was synthesized with the following sequence:

GTA GGT GGC GGG CAA GGC GGG **(SEQ ID NO:2)**

Each oligonucleotide had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligonucleotide was specific for the human and rabbit adenosine A_1 receptor genes, and that the mismatched control was not a candidate for hybridization with any known gene sequence.

Adenosine A_3 receptor mRNA secondary structure was similarly analyzed and used as described above to design two phosphorothioate anti-sense oligonucleotides. The first anti-sense oligonucleotide (HAdA3AS1) synthesized had the following sequence:

5' -GTT GTT GGG CAT CTT GCC-3' **(SEQ ID NO:3)**

As a control, a mismatched phosphorothioate anti-sense oligonucleotide (HAdA3MM1) was synthesized, having the following sequence:

5' -GTA CTT GCG GAT CTA GGC-3' **(SEQ ID NO:4)**

A second phosphorothioate anti-sense oligonucleotide (HAdA3AS2) was also designed and synthesized, having the following sequence:

5' -GTG GGC CTA GCT CTC GCC-3' **(SEQ ID NO:5)**

Its control oligonucleotide (HAdA3MM2) had the sequence:

5' -GTC GGG GTA CCT GTC GGC-3' **(SEQ ID NO:6)**

Phosphorothioate oligonucleotides were synthesized on an Applied Biosystems Model

396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, MD).

Example 2: In Vitro Effect of Adenosine A_1 Receptor Anti-sense Oligonucleotides

The anti-sense oligonucleotide against the human A_1 receptor (SEQ ID NO:1) described above was tested for efficacy in an in vitro model utilizing lung adenocarcinoma cells HTB-54. HTB-54 lung adenocarcinoma cells were demonstrated to express the A_1 adenosine receptor using standard northern blotting procedures and receptor probes designed and synthesized in the laboratory.

HTB-54 human lung adenocarcinoma cells (10^6/100 mm tissue culture dish) were exposed to 5.0 μM HAdAlAS (SEQ. ID NO:1) or HAdAlMM (SEQ. ID NO:2) for 24 hours, with a fresh change of media and oligonucleotides after 12 hours of incubation. Following 24 hour exposure to the oligonucleotides, cells were harvested and their RNA extracted by standard procedures. A 21-mer probe corresponding to the region of mRNA targeted by the anti-sense (and therefore having the same sequence as the anti-sense, but not phosphorothioated) was synthesized and used to probe northern blots of RNA prepared from HAdAlAS-treated, HAdAlMM-treated and non-treated HTB-54 cells. These blots showed clearly that HAdAlAS (SEQ. ID NO:1) but not HAdAlMM (SEQ. ID NO:2) effectively reduced human adenosine receptor mRNA by >50%. This result showed that HAdAlAS (SEQ. ID NO: 1) is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A_1 receptor, which is involved in asthma.

Example 3: In Vivo Efficacy of A_1 Adenosine Receptor Anti-sense Oligonucleotides

A fortuitous homology between the rabbit and human DNA sequences within the adenosine A_1 gene overlapping the initiation codon permitted the use of the phosphorothioate anti-sense oligonucleotides initially designed for use against the human adenosine A_1 receptor in a rabbit model.

Neonatal New Zealand white Pasteurella-free rabbits were immunized intraperitoneally within 24 hours of birth with 312 antigen units/mL house dustmite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA), mixed with 10% kaolin. Immunizations were repeated weekly for the first month and then biweekly for the next 2 months. At 3-4 months of age, eight sensitized rabbits were anesthetized and relaxed with a

mixture of ketamine hydrochloride (44 mg/kg) and acepromazine maleate (0.4 mg/kg) administered intramuscularly.

The rabbits were then laid supine in a comfortable position on a small molded, padded animal board and intubated with a 4.0-mm intratracheal tube (Mallinkrodt, Inc., Glens Falls, NY). A polyethylene catheter of external diameter 2.4 mm with an attached latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiments. The intratracheal tube was attached to a heated Fleisch pneumotachograph (size 00; DOM Medical, Richmond, VA), and flow was measured using a Validyne differential pressure transducer (Model DP-45161927; Validyne Engineering Corp., Northridge, CA) driven by a Gould carrier amplifier (Model 11-4113; Gould Electronic, Cleveland, OH). The esophageal balloon was attached to one side of the differential pressure transducer, and the outflow of the intratracheal tube was connected to the opposite side of the pressure transducer to allow recording of transpulmonary pressure. Flow was integrated to give a continuous tidal volume, and measurements of total lung resistance (RL) and dynamic compliance (Cdyn) were calculated at isovolumetric and flow zero points, respectively, using an automated respiratory analyzer (Model 6; Buxco, Sharon, CT).

The animals were randomized and pretreatment values for PC50 were obtained on Day 1 for aerosolized adenosine. Anti-sense (HAdAlAS) or mismatched control (HAdAlMM) oligonucleotides were dissolved in sterile physiological saline at a concentration of 5000 μg (5 mg) per 1.0 ml. Animals were subsequently administered the aerosolized anti-sense or mismatch oligonucleotide via the intratracheal tube (approximately 5000 μg in a volume of 1.0 ml), twice daily for two days. Aerosols of either saline, adenosine, or anti-sense or mismatch oligonucleotides were generated by an ultrasonic nebulizer (DeVilbiss, Somerset, PA), producing aerosol droplets 80% of which were smaller than 5 μm in diameter.

In the first arm of the experiment, four randomly selected allergic rabbits were administered anti-sense oligonucleotide and four the mismatched control oligonucleotide. On the morning of the third day, PC50 values (the concentration of aerosolized adenosine in mg/ml required to reduce the dynamic compliance of the bronchial airway 50% from the baseline value) were obtained and compared to PC50 values obtained for these animals prior to exposure to oligonucleotide.

Following a 2 week interval, animals were crossed over, with those previously

administered mismatch control oligonucleotide now administered anti-sense oligonucleotide, and those previously treated with anti-sense oligonucleotide now administered mismatch control oligonucleotide. Treatment methods and measurements were identical to those employed in the first arm of the experiment. It should be noted that in six of the eight animals treated with anti-sense oligonucleotide, adenosine-mediated bronchoconstriction could not be obtained up to the limit of solubility of adenosine, 20 mg/ml. For the purpose of calculation, PC50 values for these animals were set at 20 mg/ml. The values given therefore represent a minimum figure for anti-sense effectiveness. Actual effectiveness was higher. The results of this experiment are illustrated in both Figure 1 and Table 1.

Table 1: Effect of Adenosine A_1 Receptor Anti-sense Oligonucleotide upon PC50 Values in Asthmatic Rabbits

Mismatch Control		A_1 Receptor Anti-sense Oligonucleotide	
Pre-oligonucleotide Administration	**Post-oligonucleotide Administration**	**Pre-oligonucleotide Administration**	**Post-oligonucleotide Administration**
3.56 ± 1.02	5.16 ± 1.03	2.36 ± 0.68	>19.5 ± 0.34**

The results are presented as the mean (N = 8) ± SEM.
The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test.
**Significantly different from all other groups, $p < 0.01$.

In both arms of the experiment, animals receiving the anti-sense oligonucleotide showed an order of magnitude increase in the dose of aerosolized adenosine required to reduce dynamic compliance of the lung by 50%. No effect of the mismatched control oligonucleotide upon PC50 values was observed. No toxicity was observed in any animal receiving either anti-sense or control inhaled oligonucleotide.

These results show clearly that the lung has exceptional potential as a target for anti-sense oligonucleotide-based therapeutic intervention in lung disease. They further show, in a model system which closely resembles human asthma, that downregulation of the adenosine A_1 receptor largely eliminates adenosine-mediated bronchoconstriction in asthmatic airways. Bronchial hyperresponsiveness in the allergic rabbit model of human asthma is an excellent endpoint for anti-sense intervention since the tissues involved in this response lie near to the point of contact with aerosolized oligonucleotides, and the model closely simulates an

important human disease.

Example 4: Specificity of Adenosine A_1 Receptor Anti-sense Oligonucleotide

At the conclusion of the crossover experiment of Example 3, airway smooth muscle from all rabbits was surgically dissected and quantitatively analyzed for adenosine A_1 receptor number. As a control for the specificity of the anti-sense oligonucleotide, adenosine A_2 receptors, which should not have been affected, were also quantified.

Airway smooth muscle tissue was dissected from each rabbit and a membrane fraction prepared according to described methods (J. Kleinstein and H. Glossmann, Naunyn-Schmiedeberg's Arch. Pharmacol. 305, 191-200 (1978), with slight modifications. Crude plasma membrane preparations were stored at 70°C until the time of assay. Protein content was determined by the method of Bradford (M. Bradford, Anal. Biochem. 72, 240-254 (1976)). Frozen plasma membranes were thawed at room temperature and were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. The binding of [^{3}H] DPCPX (A_1 receptor-specific) or [^{3}H] 2- [p- (2-carboxyethyl)-phenethylamino] -5' - (N-ethylcarboxamido) adenosine (CGS-21680; A_2 receptor-specific) was measured as previously described. S. Ali et al., J. Pharmacol. Exp. Ther. 268, Am. J. Physiol 266, L271-277 (1994).

As illustrated in both Figure 2 and Table 2, animals treated with adenosine A_1 anti-sense oligonucleotide in the crossover experiment had a nearly 75% decrease in A_1 receptor number compared to controls, as assayed by specific binding of the A_1-specific antagonist DPCPX. There was no change in adenosine A_2 receptor number, as assayed by specific binding of the A_2 receptor-specific agonist CGS-21680.

Table 2: **Specificity of Action of Adenosine A_1 Receptor Anti-sense Oligonucleotide**

	Mismatch Control Oligonucleotide	A_1 Anti-sense Oligonucleotide
A_1-Specific Binding	1105 ± 48**	293 ± 18
A_2-Specific Binding	302 ± 22	442 ± 171

The results are presented as the mean (N = 8) ± SEM.
The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test.
**Significantly different from Mismatch Control, $p < 0.01$.

The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

Claims

1. A pharmaceutical composition, comprising

an oligonucleotide (oligo) in aerosol form, which is effective for alleviating bronchoconstriction or lung inflammation when administered to a mammal, wherein the oligo is antisense to the initiation codon, the coding region or the 5' and 3' intron-exon junctions of a gene encoding the adenosine A_1 receptor or antisense to an adenosine A_1 receptor mRNA; and

a pharmaceutical carrier.

2. The pharmaceutical composition of claim 1, wherein the oligo comprises at least one mononucleotide linking residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

3. The pharmaceutical composition of claim 2, wherein the all mononucleotide linking residues of the oligo are selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

4. The pharmaceutical composition of claim 1, wherein the oligo is antisense to the initiation codon of a gene encoding an adenosine A_1 receptor or antisense to an adenosine A_1 receptor mRNA.

5. The pharmaceutical composition of claim 1, wherein the oligo is a DNA.

6. The pharmaceutical composition of claim 1, wherein the oligo is an RNA.

7. The pharmaceutical composition of claim 1, wherein the oligo is antisense to the intron-exon junction of an adenosine A_1 receptor gene or antisense to an adenosine A_1 receptor mRNA.

8. The pharmaceutical composition of claim 1, wherein the oligo comprises about 10 to up to about 60 mononucleotides.

9. The pharmaceutical composition of claim 7, wherein the oligo comprises about 18 up to about 21 mononucleotides.

10. The pharmaceutical composition of claim 1, wherein the oligo is antisense to the coding region of a gene encoding the adenosine A_1 receptor or antisense to an adenosine A_1 receptor mRNA.

11. The pharmaceutical composition of claim 1, wherein the oligo is

SEQ. ID NOS: 1 or 7 to 952; or

SEQ. ID NOS: 1 or 7 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

12. The pharmaceutical composition of claim 11, wherein the oligo is selected from

SEQ. ID NOS: 7 to 952; or

SEQ. ID NOS: 7 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

13. The pharmaceutical composition of claim 11, wherein the oligo is selected from SEQ. ID NOS: 1 or 7 to 952.

14. The pharmaceutical composition of claim 13, wherein the oligo is SEQ. ID NO: 7.

15. The pharmaceutical composition of claim 14, wherein the oligo is SEQ. ID NO: 7, wherein all mononucleotide linking residues are phosphorothioate residues.

16. The pharmaceutical composition of claim 11, wherein the oligo is selected from the group consisting of SEQ. ID NOS: 1 or 7 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

17. The pharmaceutical composition of claim 13, wherein the oligo is selected from SEQ. ID NOS: 8 to 952.

18. The pharmaceutical composition of claim 17, wherein the oligo is selected from SEQ. ID NOS: 8 to 952 wherein at least one mononucleotide linking residue is a phosphorothioate residue.

19. The pharmaceutical composition of claim 18, wherein all mononucleotide linking residues are phosphorothioate residues.

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20. The pharmaceutical composition of claim 1, wherein the carrier is selected from the group consisting of solid and liquid carriers.

21. The pharmaceutical composition of claim 1, further comprising an agent selected from the group consisting of antioxidants, flavoring agents, volatile oils, buffering agents, dispersants, surfactants, propellants and preservatives.

22. The pharmaceutical composition of claim 1, wherein the oligo is present in an amount of about 0.1 to about 100 % w/w of the composition.

23. The pharmaceutical composition of claim 22, wherein the oligo is present in an amount of about 0.1 up to about 40% w/w of the composition.

24. The pharmaceutical composition of claim 23, wherein the nucleic acid is present in an amount of about 0.1 up to about 20 % w/w of the composition.

25. The pharmaceutical composition of claim 1, wherein the carrier comprises a hydrophobic carrier.

26. The pharmaceutical composition of claim 25, wherein the carrier comprises lipid particles or vesicles.

27. The pharmaceutical composition of claim 26, wherein the vesicles comprise liposomes and the particles comprise microcrystals.

28. The pharmaceutical composition of claim 26, wherein the vesicles comprise liposomes which comprise the antisense oligo.

29. The pharmaceutical composition of claim 26, wherein the particles comprise a lipid selected from the group consisting of N-(1-(2,3-dioleoxyloxi) propyl)-N,N,N-trimethyl-ammoniummethylsulfate.

30. The pharmaceutical composition of claim 25, comprising liquid or solid respirable particles.

31. The pharmaceutical composition of claim 25, which is an aerosol composition.

32. The pharmaceutical composition of claim 1, comprised in a capsule or cartridge.

33. The pharmaceutical composition of claim 25, comprising solid particles of the oligo.

34. The pharmaceutical composition of claim 25, comprising a suspension or solution of the oligo.

35. The pharmaceutical composition of claim 34, wherein the oligo is suspended or dissolved in a solvent or mixture of solvents.

36. The pharmaceutical composition of claim 35, wherein the solvent is selected from the group consisting of chlorofluorocarbons or chlorofluorocarbons with co-solvents, and the

pharmaceutical composition further comprises an agent selected from the group consisting of surfactants, antioxidants and flavoring agents.

37. The pharmaceutical composition of claim 33, which is comprised within a capsule or cartridge.

38. A method of treating an adenosine A1 receptor mediated respiratory disease or condition associated with bronchoconstriction or lung inflammation, comprising administering directly to the respiration of a mammalian subject in need of such treatment an aerosol of the pharmaceutical composition of claim 1 comprising an amount of the oligo effective for alleviating bronchoconstriction and/or lung inflammation.

39. The method of claim 38, wherein the pharmaceutical composition comprises respirable particles comprising the oligo.

40. The method of claim 38, wherein the disease or condition comprises lung inflammation.

41. The method of claim 38, wherein the disease or condition comprises a respiratory disease or condition associated with bronchoconstriction or lung inflammation.

42. The method of claim 38, wherein the disease or condition comprises asthma.

43. The method of claim 38, wherein the mammalian subject is non-human.

44. The method of claim 38, wherein the mammalian subject is a human.

45. The method of claim 38, wherein the oligo is administered in an amount of about 0.01 to about 115 mg/kg body weight.

46. The method of claim 45, wherein the oligo is administered in an amount of about 1 to about 100 mg/kg body weight.

47. The method of claim 46, wherein the oligo is administered in an amount of about 10 up to about 15 mg/kg body weight.

48. The method of claim 38, being a prophylactic method.

49. The method of claim 38, being a therapeutic method.

50. The method of claim 38, wherein the pharmaceutical composition further comprises an agent selected from the group consisting of antioxidants, flavoring agents, volatile oils, buffering agents, dispersants, surfactants, propellants and preservatives.

51. The method of claim 50, wherein the pharmaceutical composition comprises a surfactant.

52. The method of claim 38, wherein the oligo is antisense to the coding region or the initiation codon of a gene encoding the adenosine A_1 receptor or antisense to an adenosine A1 receptor mRNA, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate,

sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

53. The method of claim 52, wherein all mononucleotide linking residues of the oligo are selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

54. The method of claim 38, wherein the oligo is

SEQ. ID NOS: 1 or 7 to 952; or

SEQ. ID NOS: 1 or 7 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

55. The method of claim 54, wherein the oligo is selected from

SEQ. ID NO: 7 to 952; or

SEQ. ID NO: 7 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

56. The method of claim 55, wherein the oligo is SEQ. ID NOS: 1 or 7 to 952, wherein at least one mononucleotide linking residue is a phosphorothioate residue.

57. The method of claim 54, wherein all mononucleotide linking residues are phosphorothioate residues.

58. The method of claim 56, wherein the oligo is selected from the group consisting of SEQ. ID NOS: 7 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

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59. The method of claim 58, wherein the oligo is selected from the group consisting of SEQ. ID NOS: 8 to 952; wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

60. The pharmaceutical composition of claim 21, comprising a surfactant.

61. An in vivo method of delivering an oligonucleotide (oligo) to a target adenosine A_1 receptor polynucleotide, comprising administering into a mammalian subject's respiration an aerosol of the composition of claim 1, comprising an amount of the adenosine A_1 receptor oligo effective to reach the target A_1 adenosine receptor polynucleotide.

62. The method of claim 61, wherein the aerosol comprises respirable oligo particles.

63. The method of claim 61, wherein the oligo is selected from the group consisting of oligos which are

antisense to an intron-exon junction of an adenosine A_1 receptor gene or antisense to an adenosine A_1 mRNA; and

antisense to an intron-exon junction of an adenosine A_1 receptor gene or antisense to an adenosine A_1 receptor mRNA, wherein the oligo comprises at least one mononucleotide linking residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

64. The method of claim 61, wherein the oligo is delivered to alleviate a disease or condition associated with bronchoconstriction or lung inflammation.

65. The method of claim 64, wherein the disease or condition comprises asthma.

66. The method of claim 61, wherein the mammalian subject is a human.

67. The method of claim 61, wherein the mammalian subject is an non-human mammal.

68. The method of claim 61, wherein the oligo is administered in an amount of about 0.01 to about 115 mg/kg body weight.

69. The method of claim 68, wherein the oligo is administered in an amount of about 1 to about 100 mg/kg body weight.

70. The method of claim 69, wherein the oligo is administered in an amount of about 1 up to about 50 mg/kg body weight.

71. The method of claim 64, being a prophylactic method.

72. The method of claim 64, being a therapeutic method.

73. The method of claim 61, wherein the composition further comprises an agent selected from the group consisting of antioxidants, flavoring agents, volatile oils, buffering agents, dispersants, surfactants, propellants and preservatives.

74. The method of claim 73, wherein the composition comprises a surfactant.

75. The pharmaceutical composition of claim 11, wherein the oligo has at least one phosphorothioate mononucleotide linking residue.

76. The pharmaceutical composition of claim 75, wherein all mononucleotide linking residues are phosphorothioate residues.

77. The method of claim 56, wherein the oligo is selected from SEQ. ID NOS: 7 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

78. The method of claim 77, wherein the oligo is selected from SEQ. ID NOS: 8 to 952, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

79. The method of claim 61, wherein the oligo is selected from oligos which are antisense to the coding region of a gene encoding an A_1 receptor, or antisense to an A_1 adenosine receptor mRNA; or oligos which are antisense to the coding region of a gene encoding an A_1 adenosine receptor, or antisense to an A_1 adenosine receptor mRNA, wherein at least one mononucleotide linking residue is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methyimino), methyleneoxy (methylimino) and phosphoramidate residues.

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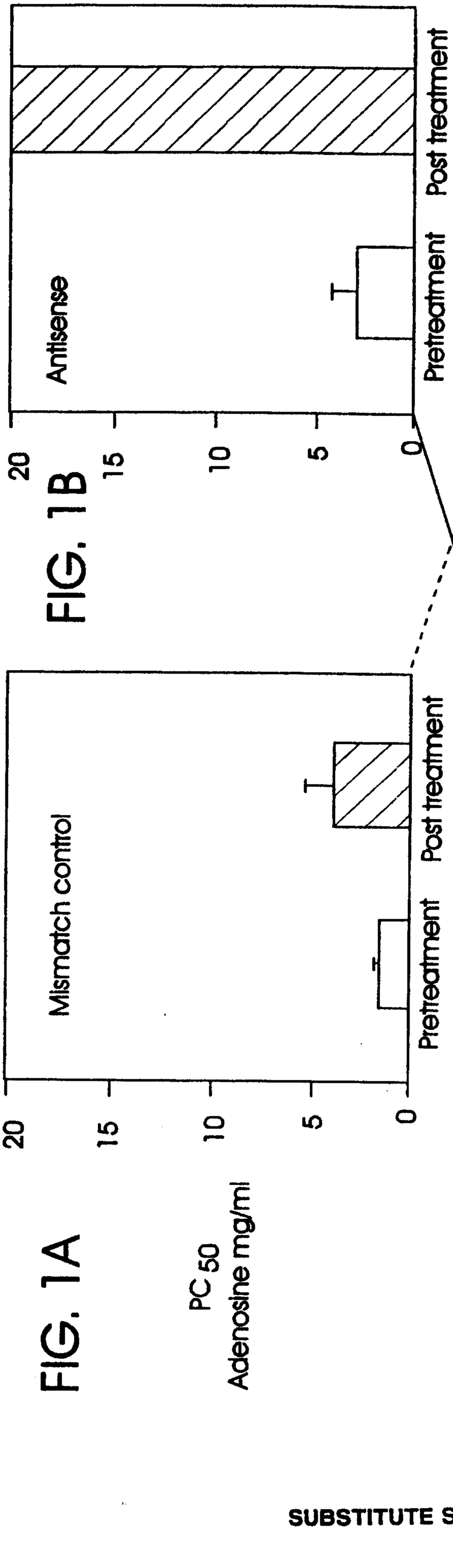


FIG. 1B

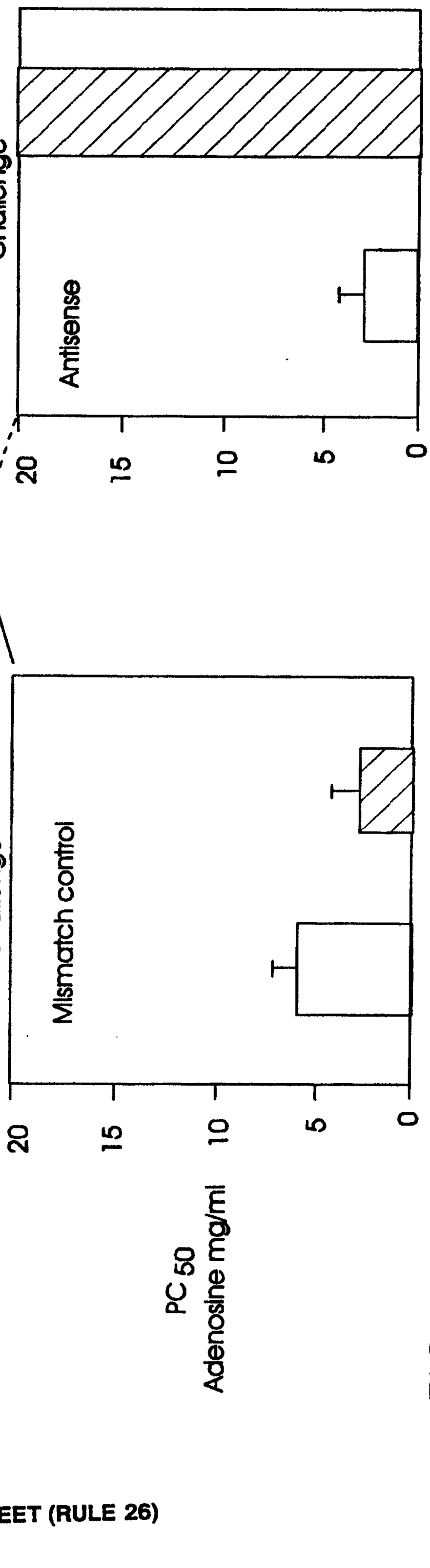


FIG. 1D

FIG. 1A

FIG. 1C

FIG. 2A

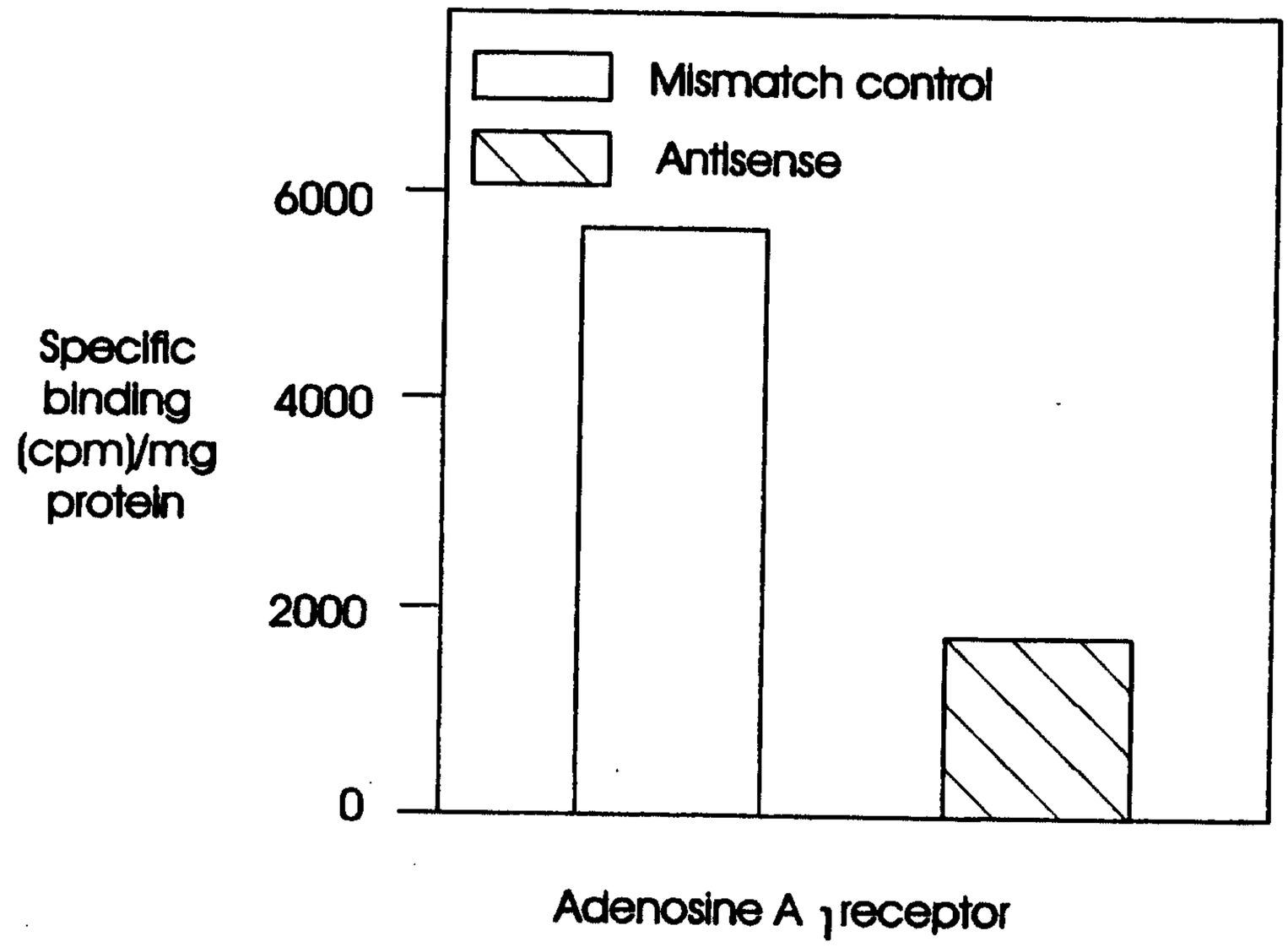
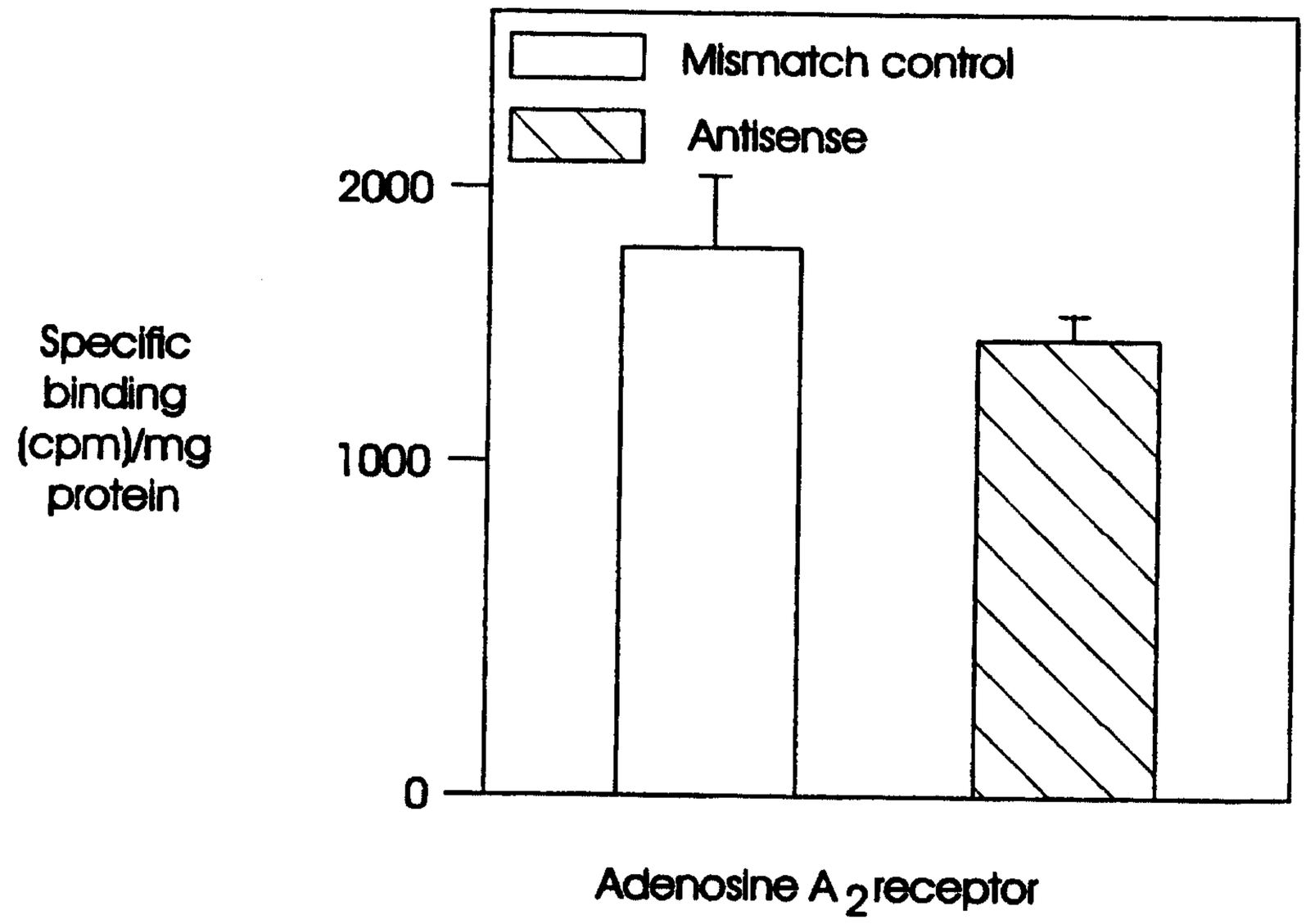

Mismatch control
Antisense
6000
4000
2000
0
Specific binding (cpm)/mg protein
Adenosine A 1 receptor

FIG. 2B


Mismatch control
Antisense
2000
1000
0
Specific binding (cpm)/mg protein
Adenosine A 2 receptor