Molecular Design and Functional Characterization Portfolio of Flavivirus Therapeutics

by

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ABSTRACT

Flavivirus infections are emerging as significant threats to human health around the globe. Among them West Nile(WNV) and Dengue Virus (DV) are the most prevalent in causing human disease with WNV outbreaks occurring in all areas around the world and DV epidemics in more than 100 countries. WNV is a neurotropic virus capable of causing meningitis and encephalitis in humans. Currently, there are no therapeutic treatments or vaccines available. The expanding epidemic of WNV demands studies that develop efficacious therapeutics and vaccines and produce them rapidly and inexpensively. In response, our lab developed a plant-derived monoclonal antibody (mAb) (pHu-E16) against DIII (WNV antigen) that is able to neutralize and prevent mice from lethal infection. However, this drug has a short window of efficacy due to pHu-E16's inability to cross the Blood Brain Barrier (BBB) and enter the brain. Here, we constructed a bifunctional diabody, which couples the neutralizing activity of E16 and BBB penetrating activity of 8D3 mAb. We also produced a plant-derived E16 scFv-CH₁₋₃ variant with equivalent specific binding as the full pHu-E16 mAb, but only requiring one gene construct for production. Furthermore, a WNV vaccine based on plant-derived DIII was developed showing proper folding and potentially protective immune response in mice. DV causes severe hemorrhaging diseases especially in people exposed to secondary DV infection from a heterotypic strain. It is hypothesized that sub-neutralizing crossreactive antibodies from the first exposure aid the second infection in a process called antibody-dependent enhancement (ADE). ADE depends on the ability of mAb to bind Fc receptors (FcyRs), and has become a major roadblock for developing mAb-based therapeutics against DV. We aim to produce an anti-Dengue mAb (E60) in different

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glycoengineered plant lines that exhibit reduced/differential binding to FcγRs, therefore, reducing or eliminating ADE. We have successfully cloned the molecular constructs of E60, and expressed it in two plant lines with different glycosylation patterns. We demonstrated that both plant-derived E60 mAb glycoforms retained specific recognition and neutralization activity against DV. Overall, our study demonstrates great strives to develop efficacious therapeutics and potent vaccine candidates against Flaviviruses in plant expression systems.

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CHAPTER 1

OVERVIEW OF FLAVIVIRUSES

Flavivirus is one of the genera included in the Flaviviridae family that also includes the genera Hepacivirus and Pestivirus. Further subdivision of the Flavivirus genus is based on cross-neutralizing test results in eight antigenic complexes including Dengue, Japanese encephalitis, Tick-borne encephalitis, Rio Bravo, Tyuleniy, Ntaya, Uganda S, and Modoc antigenic groups (Calisher, 1989). Overall, within *Flavivirus* there are over 70 different viruses, and most noteworthy to human health include yellow fever virus (YFV), Dengue virus (DV), Japanese encephalitis virus (JEV), West Nile virus (WNV) and tick-borne encephalitis virus (TBEV) (Heinz, 2012). These viruses can cause a broad range of disease from mild discomfort to hemorrhagic fevers, flaccid paralysis and even encephalitis (Gould 2008). Other members of this genus are rarely encountered by humans and their reported case numbers are relatively small. Nevertheless, they have the potential to cause severe disease in humans (Heinz, 2012). Most of these viruses are arboviruses with YFV, DV, JEV, and WNV being transmitted by mosquitoes; and TBEV being transmitted by ticks. Humans are considered to be the "dead-end" or incidental host to these viruses, due to humans' inability to maintain high enough viremia titers to reinfect arthropod vectors. However, cases of human to human transmission, by means of blood transfusions and organ transplant have been reported (Nicole, 2012).

Flaviviruses are enveloped icosahedral viruses with a diameter of \approx 500 Å and have a single positive strand RNA genome of 10.7 kb (Kuhn, 2002). The genome contains an open reading frame (ORF) that codes three structural proteins near the N-terminus along with seven non-structural proteins (NS) near the C-terminus. The three

major structural proteins encoded in the genome are the capsid protein (CP), premembrane/membrane protein (preM/M) and envelope protein (E). The CP (100 aa) is a dimer which surrounds positive strand RNA, housing the genome and creating the nucleocapsid core. Little is known about the preM/M protein (166/75 aa) but it is speculated to have a chaperone protein function for E protein, as well as serving as an indicator distinguishing the maturation transition from immature form to the infectious form of the viral particle (preM to M) (Zhang, 2004). The E protein (495 aa) is a dimer with each monomer made up of three domains (domain (D) I, II, and III). It is responsible for the binding of virus to cellular receptors, mediating the entry for virus, and cell membrane fusion (Chamber, 1990). DI carries out a structural rearrangement function in acidic conditions, DII is responsible for virus to cell membrane fusion due to its hydrophobic peptide region, and DIII serves as the binding site for cellular receptors with its C-terminal immunoglobulin (Ig)-like structure. The seven NS protein encoded in the genome are NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. They function mainly on RNA genome replication and viral protein synthesis. Within the seven NS proteins, NS3 and NS5 are the most conserved proteins and they carry out the main functions while the rest of the NS proteins act as activators or support molecules. NS3 has bifunctional activity when coupled with NS2B, providing both protease and possibly helicase activity (Chamber, 1990; Pastorino, 2010). NS5 serves as a viral RNA polymerase with methyltransferase activity (Chamber, 1990; Pastorino, 2010).

Flaviviruses follow a similar viral life cycle as other viruses. The cycle begins with attachment of the virion onto the surface of a host cell. This specific binding induces a receptor-mediated ($\alpha\nu\beta$ 3 integrin and laminin-binding protein) endocytosis, granting

viral entry into the cell (Brinton, 2014). The low pH within the endosomal vesicle triggers conformational changes of the E protein, exposing Domain III. As a result, the viral and cell membranes fuse together (Thompson, 2009), nucleocapsid disassembles, and the RNA genome is released into the cytoplasm of the cell allowing both replication and translation of the genome to occur. Translation of the positive-sense RNA results in a single polyprotein with all 10 viral proteins being synthesized. Further processing incorporates host and viral proteases to cleave polyprotein into the ten mature proteins (Shi, 1996). The NS proteins (specifically NS5) construct a viral replication complex which uses the positive sense genome to generate complementary negative-sense intermediate strands (Chamber, 1990). The intermediate strands act as templates to synthesize the positive sense viral genome. Viral assembly of the viral RNA genome and structural proteins occurs on the surface of the endoplasmic reticulum (ER). The immature virions are transported through the trans-Golgi network (TGN) and pre-M is cleaved by the host protease furin, inducing rearrangement of E protein and activating the infectious form of the viral particle (Pastorino, 2010). After maturation, the virion along with subviral particles (that only contain M and E protein) are exocytosed and ready to infect other cells.

CHAPTER 2

WEST NILE VIRUS

1. Introduction

1.1 General Overview

West Nile virus (WNV) is an arbovirus that belongs to the *Flavivirus* genus of the *Flaviviridae* family. This neurotropic virus falls within the Japanese encephalitis virus antigenic complex; along with Murray Valley encephalitis virus, St Louis encephalitis virus, and Kunjin virus (Calisher, 1988). The virus is enveloped and icosahedral with a single positive stranded RNA genome (10.7 kb). Around the world, two lineages of WNV exist with the first lineage commonly responsible for avian, human, and equine disease. 1.2 Signs and Symptoms

In most cases, WNV infected patients are asymptomatic. Furthermore, 3-14 days after being bitten by an infected mosquito, only 20-30% of patients develop mild and acute symptoms (West Nile Fever) for which generally last 3-6 days (Goodman, 2012). Mild symptoms include a sudden appearance of flu-like symptoms, which may include rhinorrhea, cough, sore throat, malaise, fever, myalgia, nausea, vomiting, anorexia, eye pain, headache, and rash. In rare cases (less than 1%), severe neurological symptoms can arise with a 10% fatality rate (Peterson, 2003, CDC.gov). Severe neurological symptoms include encephalitis and meningitis with more than 50% presenting acute flaccid paralysis or other permanent neurological injury due to neurons inability to regenerate. Susceptibility of developing severe neurological symptoms increases with age (especially among those 60 to 89 years of age) with all ages and genders appearing to be equally susceptible to WNV infection (Hayes, CDC fig). Other than advanced age, people who

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are immunosuppressed or suffer from other predispositions can develop severe neurological symptoms (Petersen, 2003). Predispositions include genetic mutations, such as C—C chemokine receptor type 5 (CCR5) and 2–5 oligoadenylate synthethase (OAS) mutations, or even hypertension, diabetes, and smoking (Sips, 2012; Diamond, 2009a). 1.3. Treatment and Prevention

Currently, there are no approved vaccines or specific antiviral treatments for WNV infections. People that develop symptoms rely on anodynes and supportive treatment until the infection is cleared. Treatment of WNV infection has been of growing importance with considerable research looking into immune γ -globulin, interferon α -2b, and antisense oligomers along with others as potential therapeutic treatments (Diamond, 2009b). Preliminary *in vitro* results of several candidates have shown prophylaxis, however *in vivo* and therapeutic studies have not had the same efficacy (Diamond, 2009b). Aside from the previous candidates, monoclonal antibodies (mAbs) therapies have also been explored as potential therapeutic treatments against viral infections with E16 showing both prophylaxis and therapeutic activity (Both, 2013; Kaufmann, 2006). 1.4. Ecology and Life Cycle

WNV is usually maintained and amplified in enzootic cycles between female mosquito vectors and bird hosts; predominantly, *Culex (Cx)* species of mosquitoes (e.g. *Cx pipiens, Cx tarsalis, Cx salinarius, Cx quinquefasciatus*) and passerine birds, although other species of mosquitoes and birds have been seen to carry the virus (Gea-Banacloche, 2004; Farajollahi, 2011). The female gender of *Culex* mosquito is the primary vector of many viruses, including WNV, due to the higher nutrient requirements needed for the energy demands of reproduction. While feeding on a blood meal they transfer saliva,

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anticoagulants, and other pathogens into the host animal (Tolle, 2009). In most cases the host animals are birds, but in some instances other animals, including humans, can become an incidental/ "dead end" host. Birds are natural reservoirs for WNV with many avian species able to survive infection, become immune, and develop high-titer viremias to transmit to other feeding mosquitoes (Campbell, 2002). WNV infection cycle follows the mosquitoes' activity, which usually starts in the spring where mosquitoes are most active and abundant. The cycle ends early fall when conditions start to become unfavorable and mosquitoes go into diapause.

1.5. Epidemiology

Since the discovery of the virus in the West Nile district of Uganda (1937), major outbreaks have occurred all around the world, except for Antarctica (Kramer, 2008). From 1937 to 1990s, WNV infected people presented mild symptoms, e.g. fevers. Starting from 1990s, the frequency of outbreaks and number of cases presenting severe neurological symptoms, e.g. viral encephalitis, significantly increased. In Romania (1996–1997) an outbreak of WNV caused over 500 clinical cases with 10% of cases ending in fatalities (141). In Israel (2000), 417 cases were reported with 317 of the patients being hospitalized and 35 of them dying (case fatality rate 8.4%) (Weinberger, 2001). Along with these two cases, Algeria (1994), Morocco (1996), Tunisia (1997, 2003), Czech Republic (1997) reported WNV disease (Hayes, 2005).

The first documented occurrence of WNV in the Western hemisphere was in 1999 in New York City (United States (US)), speculated introduction from a single point, spreading throughout the eastern states along with westward migration, reaching as far as North Dakota in 2001 and California in 2002 (Petersen, 2003). Since the introduction of WNV (1999-2012), over 37,000 cases of WNV infection have been reported (1,549 deaths) with 286 people dying in the US in 2012 [Centers for Disease Control and Prevention (CDC)]. Along with rapid expansion in the US, other western hemisphere countries and continents (e.g. Canada, Mexico, Central America, and South America) also reported cases of WNV (Campbell, 2002). In Canada (2001), there were reports of infected birds, horses, and mosquito pools with 462 human cases (10 deaths) (Dauphin, 2004). In Mexico (2002), WNV encephalitis-like symptoms in equine were reported in five different Mexican states from the border of Texas along the Gulf of Mexico to Southern Mexico (Tabasco) (Estrada, 2003).

As previously mentioned, female *Culex* mosquitoes transmit WNV to primarily passerine birds and cycle between each other, with vertebrates an incidental host. For that reason, high frequency of WNV transmission to humans directly correlates to the ecology and feeding behavior of the infected mosquitoes. People at risk of WNV infection include those living near flooded, high vegetation cover, low population density areas which are ideal mosquito habitats (Han, 1999). Rate of infection follows mosquitoes' activity with approximately 85% of human infections occurring in August and September when mosquitoes are most abundant (Peterson, 2004). Susceptibility increases with age, compromised immune systems, or predispositions.

1.6. Pathogenesis

After mosquito inoculation of the WNV through the skin cells, keratinocytes and most importantly Langerhan dendritic cells (LDC), get infected and replicate the virus. Initial recognition of nucleic acid intermediates by pathogen recognition receptors (PRR) (e.g. Toll-like receptors and RIG-like receptors) activates Interferon Regulation Factors (IRF) 3 and 7 for production of type I interferons (IFN) (Diamond, 2003). IFNs work together to "interfere" with viral replication by increasing expression of Protein Kinase R (PKR) and 2'-5' oligoadenylate synthetase (OAS) and to warn nearby cells of viral infection (major function of INF- γ). Binding of PKR to viral dsRNA activates the complex resulting in phosphorylation and inactivation of Eukaryotic Initiation Factor 2 α (eIF2 α), inhibiting translation and leading to apoptosis (Lee, 1994; Szretter, 2011). OAS, which also binds to viral dsRNA for activation, converts ATP to 2'-5'oligoadenylate resulting in binding and activation of RNAse L. RNAse L cleaves both viral and host ssRNA, mRNA, and rRNA inhibiting virus replication and protein expression ending in apoptosis of infected cell (Silverman, 2007). Along with IFN innate response $\gamma\delta$ T cells, NK cells, and macrophages are drawn toward site of infection for specific effector functions.

While INF response is occurring, infected LDC migrate to the nearest draining lymph node, whose primary function is to uptake and process pathogens (viruses) into linear antigens (epitopes) forming antigen presenting complex, better known as Major Histocompatibility Complex 1 (MHCI), and display assembled MHCI to B, T, and other immune cells for adaptive immune response. It is in the lymph node where initial viral amplification occurs, creating a high viremia and allowing easy access into the systemic circulation system, spreading to visceral organs where a second round of amplification occurs (Lim, 2011). During dispersion, naive B-cells are activated by MHCI containing WNV antigen for a primary antibody response (about 4 days into infection), which consists of naive B-cell production of low affinity but high avidity IgM functioning in enhancement of complement activation and immune complex formation (Samuel, 2006).

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6-8 days into the infection (in mice), after CD4 T-cell activation and affinity maturation, higher affinity IgG antibodies are produced along with CD8+ cytolytic T-cell mediated response (Suthar, 2013). If spread of WNV is controlled, symptoms are generally mild and neurodisease does not present itself.

1.7. Neurodisease

At high viremia levels of WNV, production of tumor necrosis factor (TNF), metalloproteinases (Suthar, 2013) and interleukins (Cho, 2012; Welte, 2011) from immune response to periphery infection increases the permeability and chance of WNV crossing the Blood-Brain Barrier (BBB) into the brain. The BBB is made up of an extracellular matrix, endothelial cells, astroglia, neurons, and pericytes with tight junctions making it highly selective to small hydrophobic molecules; blocking access to large polar molecules and certain pathogens (Lawther, 2011). The exact mechanism via which WNV travels through the BBB is still unclear, but several theories have been presented: (1) a relay infection through choroid plexus epithelial cells, neurons, or olfactory bulb; (2) transport through infected immune cells in a "Trojan horse" mechanism; (3) or retrograde transport from infected peripheral neurons through their axons (Kramer, 2007; Welte, 2011; Lim 2011).

After breaching the BBB, infected neurons and other supporting cells contribute to the deterioration of CNS causing the inflammatory neurological disease by apoptosis, cell necrosis, and bystander cytotoxicity (Lim, 2011; Cho, 2012). Apoptosis is considered a normal defense mechanism against tumor cells and virally compromised cells by programmed cell death preventing them from spreading to uninfected cells. Apoptosis can be induced by CD8 T-cells and can take three mechanisms. The first is

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perforin/granzyme cytolysis mechanism, which uses perforin to make pores in infected cells and transport granzyme B into the target cell. Granzyme B, in a series of signal cascades, activates caspase-3 (cysteine-dependent aspartate specific proteases) which cleaves the inhibitory site of caspase-activated DNAse (iCAD to CAD) leading to DNA fragmentation and apoptosis (Reed, 2000). Fas from infected cells and Fas ligand (fasL) from CD8 T-cells bind, activating death domains leading to the caspase-dependent apoptosis cascade (Wallach, 1999). The TRAIL dependent pathway has a similar ending with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) from CD8 T-cells binding to Death receptors (DR5) from infected cells and activating caspase-dependent apoptosis cascade. Other than CD8 T-cells initiating caspase-dependent apoptosis, WNV via NS2B-NS3 can also activate caspase-3 and other non-caspase proteases (Shrestha, 2012). The second mechanism by which WNV affects the CNS is by cell necrosis from extensive budding of WNV progeny losing and compromising membrane integrity. The last mechanism involves other cells (neural and non-neural) releasing cytotoxic factors, including inflammatory cytokines (T-cell chemoattractant Cxcl10, interleukins (ILs), and TNF), near a non-infected neuron resulting in degradation of healthy cells (Cho, 2012). The underlying conclusion is that regulation of inflammatory response needs to be controlled but can be difficult. For example, a minor inflammatory response results in uncontrollable infection, however, a major inflammatory response results in irreversible harm of both infected and uninfected neurons.

1.8. Antibody and Antibody-Based Therapeutics

A full IgG antibody is tetrameric protein with two light (25 kDa) and two heavy chains (LC and HC, respectively) (75 kDa) with each polypeptide held together by

disulfide bonds in the quaternary structure (Wang, 2007). The LC is made up of the light variable (VL) and the light constant (CL) domains. The HC is composed of the heavy variable (VH) and three separate heavy constant domains (CH1-3, respectively) (Harris, 1998). The IgG has two functional regions: the Fab and the Fc region (**Figure 1A**). The Fab region functions in specific antigen recognition and is composed of the LC coupled with VH and CH1 domains. The Fc region (CH2-3) is responsible for activation of many innate cells to perform specific functions and can also determine degree of antibody dependent enhancement (ADE), antibody dependent cell-mediated cytotoxicity (ADCC), and complement dependent cytotoxicity (CDC) involvement (Ying, 2012). Researchers have taken the variable domains and have created a variety of structural antibodies, such as Fab (**Figure 1E**), and single-chain variable fragments (scFv) (**Figure 1C**) (Eleniste, 2013; Re, 1988).



Figure 1: Different Antibody Structures. (A) Full IgG Antibody, (B) tetrameric bifunctional mAb (BsAb), (C) scFv, (D) E16 (scFv-CH1-3)₂, and (E) Fab

1.8.1 E16

Currently, the leading monoclonal antibody (mAb) candidate against WNV is a humanized murine mAb (Hu-E16), which demonstrates neutralizing activity of WNV infection in 90% of mice and hamsters when administered 5 days post inoculation (Morrey, 2006; Dowd, 2011). Hu-E16 recognizes and binds to Domain III (DIII) of the WNV Envelope (E) protein, specifically residues E302–E309 of the N-terminal region, residues E330-E333 (BC), E365-E368 (DE) and E389-E391 (FG) (Nybakken, 2005). As previously mentioned, the E protein is a dimer with each monomer made up of three domains; DI is responsible for conformational arrangement in low pH endosomes, DII provides the fusion between the virus and endosome membranes, and DIII acts as the binding receptor to trigger fusion (Oliphant, 2005). E16 functions in opsonization of WNV, preventing structural rearrangement of the E protein in the acidic environment (Kaufmann, 2006). Consequently, blocking DII fusion and denying the virus access to the cytoplasm of the cell where replication and translation occur. This inhibitory step contains the virus within the endosome ultimately for lysosomal degradation (Thompson, 2009).

1.8.2 8D3



Figure 2: Assembly of two scFv (VL8D3-VHE16 and VLE16-VH8D3) into a diabody.

The Transferrin Receptor (TfR) is highly abundant in capillary endothelium of the BBB and functions in transcytosis of transferrin, an iron carrying glycoprotein in blood plasma. 8D3 mAb, initially a rat IgG2a to the mouse TfR, mimics the specific binding of transferrin to TfR in mice (Kissel et al., 1998). Once 8D3-TfR binding occurs, receptor-mediated endocytosis engulfs the mAb into the cell. Acidic conditions within the endosome dissociate the mAb from TfR binding allowing release of the molecule and transportation across the BBB (Manich, 2013). Recent studies have shown 90% of the conjugated enzyme to 8D3 that entered the brain crossed the BBB into the brain parenchyma (Manich, 2013) with the rest targeting the liver and kidneys (Lee, 2000). Utilization of 8D3 mAb has the potential to carry other specific therapeutics across the BBB for treating neuro-pathogens and neurodisease.

The current challenge with WNV is that there is no known therapeutic that has the capability of crossing the BBB and still be able to retain its therapeutic activity to neutralize the virus. For example, E16 mAb has the neutralizing and therapeutic activity but does not cross the BBB. A recent study by our laboratory described the ability of plants to produce tetrameric bifunctional mAb (BsAb) that are able to recognize two different epitopes or binding sites within the Fab region (He, 2014) (**Figure 1B**). These BsAbs have the potential to cross the BBB and neutralize the virus. On the other hand, the large size of the molecule could decrease the transportation across the BBB membrane, thus decreasing the efficacy of the treatment. In a Dengue study, Brien et al utilized diabody structures to synergistically complement two mAb varying avidities to all four DV serotypes with result showing specific binding of individual mAb with no neutralizing enhancement. A diabody (DiAb) consists of two scFvs containing both VH and VL regions of two different mAbs with a short linker attaching each domain (**Figure 2**). To get around the BBB impediment, we constructed a bifunctional diabody

coupling the E16 mAb WNV neutralizing activity with 8D3 capability to cross the BBB. The molecule was characterized and its bi-specificity was tested for retention of specific binding.

2. Results and Discussion

2.1 Development of a Diabody-Based Therapeutic to WNV

2.1.1 Molecular design

The assembly of a diabody depends on two separately synthesized scFvs, which dimerize to form one molecule with antigen binding sites (Fv) facing away from each other. The first scFv contains the 8D3 variable light (VL) and E16 variable heavy (VH) domain linked together by a short Gly-Ser linker (GGGSGGGG) to connect and prevent intramolecular association. The size of the linker is critical for proper assembly of Fv regions. A Kozac sequence is added to enhance translation initiation at the 5' of the first scFv coding sequence and is followed by a leader sequence for protein secretion by mammalian cells. After the E16 VH coding region, sequence for a kappa LC derived Cterminus pairing domain (FNRGEC) followed by the stop codon is added. The construct is surrounded by a *Hind*III and a *Not*I restriction site (5' and 3', respectively) for ease of cloning (Figure 3A). The second scFv is composed of the complimentary domains, E16 VL and 8D3 VH domain also linked together by a Gly-Ser linker. The second scFv also has a similar molecular arrangement except for a substitution of the LC pairing sequence by an IgG1 hinge-derived pairing domain (VEPKSC) (Figure 3B). A Sac1 restriction site was integrated on the end of the VH sequences of both constructs for exchange of the pairing domains. Both constructs were cloned into both pcDNA3.1/Hygro (+) and pcDNA3.1-zeo (+) vectors for mammalian cell expression.



Figure 3: Schematic of E16-8D3 diabody gene constructs; (A) VL8D3-VHE16-FNRGEC, (B) VLE16-VH8D3-VEPKSC, (C) VLE16-VH8D3-FNRGEC, and (D) VL8D3-VHE16-VEPKSC

The design will seek to improve CNS penetration while maintaining WNV neutralizing activity by reducing the size of the molecule into a diabody format. Theoretically, the small size of the diabody allows for several advantages including ease of production and enhanced ability to pass the BBB. The transferrin mechanism allows for a one way passage through the BBB further supporting entrance into TfR saturated areas. On the other hand, lack of an Fc region makes purification difficult and glycosylation impossible. Also the small size of the molecule could result in rapid clearance from the blood through the kidneys meaning a higher concentration might be needed to have a comparable therapeutic effect as the full antibody.

2.1.2 Molecular Cloning

2.1.2.1 Liquid Culture

The E16-8D3 DiAb constructs genes (VL8D3-GS linker sequence-VHE16 -FNRGEC and VLE16- GS linker sequence-VH8D3-VEPKSC) were synthesized, cloned into pJ201 cloning vector, and transformed into DH10B *Escherichia coli* (*E. coli*) strain by DNA2.0. Both DH10B strains were grown in 3 mL of sterilized Luria- Bertani (LB) medium (1% tryptone, 0.5% yeast extract, and 0.5% NaCl), plus the addition of 100 μ g/ml kanamycin at 37°C in a shaker (300 rpm) for 16 hours.

2.1.2.2 DNA Isolation

After 16 hours, the 3 mL of DH10B culture were centrifuged in a microfuge in 1.5 mL increments for 30 seconds at 12 kG. The supernatant was removed with the pellet resuspended in 50 μ l of TE (10 mM Tris-HCl, 1 mM EDTA, pH 8.0) and vortexed until the pellet is resuspended. 300 μ l of NS (0.1 N NaOH, 0.5% SDS, and sterile water) was added and gently inverted four times to lyse the cells releasing the gene of interest (GOI) containing plasmid. 200 μ l 7.5 M ammonium acetate was immediately added (within a minute after adding NS), mixed and incubated for 5 minutes on ice to neutralize the reaction. After the time had elapsed, the sample was centrifuged (12 kG) at 4 °C for 5 minutes. The resulting supernatant was transferred to clean tube. 330 μ l of isopropanol was added, incubated at room temperature (RT) for 3 minutes, and microfuged (RT) for 10 minutes at 12 kG to precipitate plasmid DNA. The supernatant was removed and the pellet was washed with 70% ethanol. After the wash, the DNA pellet was left to dry until the all of the ethanol evaporated. The DNA was then resuspended in 25 μ l of sterilized

water. The same protocol was used to isolated pcDNA3.1/Hygro (+) and pcDNA3.1-zeo
(+) vectors from DH5α (*E. coli* strain).

2.1.2.3 Restriction Endonuclease Digestion

The isolated plasmid DNA was digested with *Not*I and *Hind*III restriction enzymes (New England Biolab (NEB)). This was prepared by mixing of 2 μ L of 10X buffer 2 (500mM NaCl, 100mM Tris-HCl, 100mM MgCl2, 10mM DTT, pH 7.9@25°C), 13 μ L of the isolated DNA, 2 μ L of Bovine Serum Albumin (10 mg/ml), 1 μ L of RNAse A (10 mg/ml), and 1 μ L of each restriction enzyme into a microfuge tube. The tube was picofuged for 3 seconds and placed in an incubator (37 °C) for 90 minutes.

2.1.2.4 Agarose Gel Electrophoresis of DNA

To separate the digested DNA fragments, they were subjected to agarose gel electrophoresis. 0.32 grams of agarose was melted in 40 mL of 1× TAE buffer (40 mM Tris-HCl, 40 mM acetic acid, 25 mM EDTA pH 8.0) by applying heat (1 minute in a microwave). The agarose was poured into a 7×5 cm agarose gel tray with an eight well comb and set to solidify. After the gel solidified, it was placed on electrophoresis tank and submerged in 1× TAE buffer. 3 μ L of GeneRuler 1 kb Plus DNA Ladder (Thermo Scientific) and each of the 20 μ L digest were pipetted into individual wells. The gel was ran at 80 Volt (constant voltage) for 90 minutes. After the time elapsed, the gel was stained with 0.5% ethidium bromide for 10 minutes and destained with DI water for 20 minutes. After 20 minutes of destaining, the gel was placed in a UV box for analysis and excision of appropriately sized DNA fragments. The DNA was then extracted with Qiagen QIAquick Extraction kit and resuspended in 20 μ L of sterile water.

2.1.2.5 DNA Ligation

The next step requires the ligation of the DNA insert fragment to the vector. After extraction of DNA fragment, an analytical gel (using the same protocol but utilizing a subset of extracted DNA) was ran to estimate the concentration of insert and vector by comparing the intensity of the DNA bands with those of the molecular weight marker (**Figure 4A**). Depending on the amount of DNA recovered the quantities will vary, but an effective ligation recipe consist 1:3 molar ratio of vector to insert, T4 ligation buffer (50 mM Tris-HCl, 10 mM MgCl₂, 1 mM ATP, 10 mM dithiothreitol, pH 7.5 at 25 °C), and 1 unit of T4 DNA ligase. The ligation mixture was mixed and incubated (16°C) overnight.



Figure 4: Analytical agarose gels (A) NotI and HindIII restriction enzyme digestion inserts and vectors. Lane 1: VLE16-VH8D3-FNRGEC; Lane 2: VL8D3-VHE16-VEPKSC insert; Lanes 3 and 4: 232 vector; Lane 5 and 6: 263 vector; Lane 7: Generuler 1kB Plus DNA Ladder (Thermoscientific). (B) NotI and HindIII restriction enzyme digestion of transformants. Lane 1: 458; Lane 2: 459; Lanes 3: 460; Lane 4: 463. (C) PvuI restriction enzyme digestion of transformants. Lane 1-4: transformants from figure 4B, respectively; Lane 5: 467; Lane 6: 468; Lane 7: 469; Lane 8: 470.

2.1.2.6 Electroporation Transformation

The newly ligated DNA was transformed into DH5a by electroporation. First, 2

µL of ligated DNA was mixed with electro-competent cells and incubated on ice for 1

minute. The mixture was transferred to an ice cold 0.2 cm electroporation cuvette, making sure the cells create a circuit between the plates. The cells were pulsed by MicroPulser Electroporator (BioRad) at approximately 2.49 kV with a time constant of 5.5 milliseconds. After the pulse, the cells were immediately transferred into 1 ml of SOC media (2% Tryptone, 0.5% Yeast Extract, 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl₂, 10 mM MgSO₄, 20 mM glucose) in a round bottom (RB) tube. The cells were incubated at 37°C with shaking at 250 rpm for 45 minutes, allowing the cells to recover from the electric shock. After the 45 minutes of incubating, the cells were concentrated by transferring cells to a microfuge tube, centrifuging them at 12 KG for 2.5 minutes and removing 800 μ l of the supernatant. The cell pellet was then resuspended and spread on LB + ampicillin plates (pcDNA3.1/Hygro (+) and pcDNA3.1-zeo (+) vectors carry ampicillin resistance marker gene) and incubated for 24 hours at 37°C.

Colonies were screened for the expected insert and vector size following steps 2.1.2.1-2.1.2.4 (**Figure 4B**). Since the *NotI-Hind*III digest yielded similar size between pcDNA3.1/Hygro (+) and pcDNA3.1-zeo (+), a second restriction enzyme digestion (PvuI) was performed to distinguish the two vectors. pcDNA3.1/Hygro (+) contains two PvuI restriction sites, while pcDNA3.1-zeo (+) only contains one (**Figure 4C**). Analytical gel demonstrates the expected bands for all strains (**Table 1, in Appendix A**). After GOI containing plasmids were identified by gel analysis, the DNA insert in these plasmids was sequence to confirm the identity of the construct and that no mutations had occurred during the cloning process (**Figure 5, in Appendix B**). Our results clearly indicate that we have successfully constructed the intended diabody constructs.

2.1.3 Expression in Mammalian Cell Culture

After confirmation, the DNA was transformed into mammalian cells and screened for expression (performed by Huafang Lai a collaborator in the lab from Arizona State University (ASU)). Mammalian cell-produced E16-8D3 DiAb was examined for its ability to bind DIII antigen. This mammalian cell experiment was aimed to preliminarily test functionality of the diabody design before moving forward in plant expression. Since signal peptide should direct DiAb to be secreted out of mammalian cell, the cells were pelleted and conditional media which should contain DiAb was kept for assessment to DIII binding. We also examine the cell pellets for DiAb.

2.1.4 Diabody Binding Assay

As previously mentioned, the DiAb structure only contains two binding sites (E16 and 8D3) without an Fc region. This makes their characterization more difficult due to lack of secondary detection antibodies that usually bind to the Fc region. The obstacle was overcome by binding the DiAb directly to a high-binding ELISA plate. Thereafter, DIII was incubated in the wells to bind with exposed E16 sites. A rabbit anti-DIII antibody (He, 2014) was used to bind DIII. Subsequently, an HRP-conjugated goat antirabbit antibody was used for detection. Hu-E16 mAb was used as a positive control. While the positive control demonstrated specific DIII binding, no signal was observed from either DiAb contained in the conditional media or the cell pellet. To confirm these results, DIII was conjugated with a fluorochrome and used for detection of E16 binding. Again, no signal was observed.

2.1.5 Discussion of Binding Results

Here, we synthesized a gene construct for E16-8D3 DiAb for the goal of increasing BBB penetration for therapeutic development against WNV neurodisease. Constructs were first produced in mammalian cells to test the binding of the molecule with the future goal to be expressed in plants. Unfortunately, the E16 moiety failed to show any binding to the DIII antigen. We hypothesize the GS linker is not the optimal candidate in size which may lead to improper assembly of the E16 binding site unable to recognize the WNV DIII. Finding the correct linker size would take empirical experimentation, which demands time and resources that are not supported by our current funding. Therefore, we put the DiAb strategy on hold and are pursuing an alternative strategy in the form of Fabs.

2.2 Characterization of Other Anti-WNV Antibody Variants and Antigen

2.2.1 Plant-Produced mAb Therapeutics

There are several culture systems for the production of monoclonal antibodies, including mammalian, bacterial, and insect cell-based systems (Chen, 2011a). More advantageous is the utilization of plant-based expression systems, specifically agrobacterium-mediated vacuum infiltrated transient expression, which offers faster production times and greater scalability for commercial production. Aside from commercial benefits, plants offer greater safety with reduced risk of transmitting human pathogens, perform mammalian-like post-translational modifications (Chen, 2011a; Faye, 2010) and have capability of assembling multimeric proteins (Chen, 2009; Huang, 2010). Several plant produced multimeric proteins include mAbs, virus-like particles (VLPs), and subunit vaccines (Lai, 2012; Negrouk, 2005; Chen, 2009) Historically, people have been afraid that genetically modified organisms (GMOs) would contaminate and decrease biodiversity of naturally occurring species. However, plant transient expression has minimized public concerns over GMOs due to the utilization of non-transgenic plants for production of biologics with transiently transgenic plants being stored within a confined area, eliminating exposure to the environment (Lai, 2012). In the laboratory setting, *Nicotiana benthamiana* (*N. benthamiana*) has been the main species of plants utilized for transient expression due to flexibility for both small scale analytical studies and commercial use, the broad range of expression vectors accessible, high biomass/seed bank yield, and extensive use within the scientific community (He, 2012). Although, tobacco is frequently used, other plants (such as lettuce, potatoes, tomato, etc.) have been used for transient expression (Wrobleski, 2005; Negrouk, 2005; Sohi; 2005).

Plant transient expression involves delivery of a GOI into the host plant's genome for short-term production of the target protein. Delivery of the transgene into plant cells is carried out by *Agrobacterium tumefaciens* (*A. tumefaciens*) in a process called agroinfiltration. The bacterium fills the interstitial space between the mesophyll, delivering GOI containing deconstructed viral vectors into the plant cell (Chen, 2011b; Leuzinger, 2013). Deconstructed viral vectors, such as MagnICON and geminiviral, utilize virus replicative genome without the structural genes necessary for the construction or infectivity of a full live virus, allowing larger transgene inserts to be expressed (Gleba, 2004). MagnICON expression system is based on the tobacco mosaic virus (TMV) and the non-competing potato virus X (PVX) genomes, each consisting of three separately housed components: 5' module (pICH15879 (TMV) and pICH21380 (PVX)) containing the promoter and other genetic elements, 3' module (pICH11599 (TMV) and pICH21595 (PVX)) containing the GOI, and integrase module (pICH14011) for integration of the 5' and 3' modules (Chen, 2013). Utilization of both TMV and PVX vectors depends if target protein contains multimeric subunits.

With all the benefits MagnICON expression offers, the production of mAb requires 5 A. tumefacien strains to be co-infiltrating at once. Entailing higher control parameters for proper expression of both HC and LC, thus increasing the cost to produce these molecules. To overcome this hurdle pE16 scFv-CH₁₋₃ was produced in GnGn transgenic N. Benthamiana (Figure 1D) with the intention of lowering the amount and number of strains of A. tumefaciens being infiltrated into the host plant for better control of anti-WNV therapeutic production. pE16 scFv-CH₁₋₃ was characterized and tested for proper folding and retention of binding site with SDS PAGE/Western Blot and ELISA analysis, respectively. Along with the pE16 scFv-CH₁₋₃, a DIII vaccine was developed in hopes to evoke a specific and sufficiently strong immunological response to provide long term immunity against WNV disease. DIII was also produced in N. benthamiana and characterized utilizing E16 antibody, known to bind to conformational epitopes (Nybakken, 2005), as indication of proper folding. Anti-DIII mouse serum was tested to see if DIII produced E16 like antibodies. Finding a prophylactic and/or therapeutic vaccine candidate for treatment of WNV requires variable attack strategies with a production method that is economically viable for meet the demand. Production of antibody variants as well as WNV DIII proteins in plant expression systems offers a cost effective and scalable option.

2.2.2 Methods, Results, and Discussion

2.2.2.1 Structural Characterization of Plant-Produced E16 scFv-CH₁₋₃

pE16 scFv-CH₁₋₃ was expressed in *N. benthamiana* plants, and purified by protein A chromatography. pE16 scFv-CH₁₋₃ and pE16 mAb (positive control) were ran on a 4-10% SDS PAGE under reducing (5% v/v β -mercaptoethanol) conditions and stained with Coomassie Blue (**Figure 6A**). For Western Blot, pE16 scFv-CH₁₋₃, pE16 mAb, and uninfiltrated GnGn leaf extracts (negative control) were ran on a 4-10% SDS PAGE under reducing (**Figure 6B**) and non-reducing (**Figure 6C**) conditions for 2 hours at 100V. Gels were transferred to PVDF membrane at 80 mA overnight in 4 °C. After transfer, the membrane was blocked with 5% milk in PBST for 2 hours and washed after with PBST. Membrane was probed with 1% milk diluted HRP-conjugated goat anti-human gamma for an hour intended to detect the light and HC, respectively. ECL Western blotting detection reagent (ECL) was added to the membrane and developed on x-ray film. These results demonstrate that pE16 scFv-CH₁₋₃ was expressed in plants with the expected LC and HC components and efficiently assembled into its tetrameric form.



Figure 6: SDS PAGE and Western blot analysis of the pE16 scFv-CH1. (A) Molecular weight marker (lane 1), pE16 mAb (lane 2) and pE16 scFv-CH1 (lane 3) were separated on SDS-PAGE gels under reducing conditions (lanes 1 and 2) and stained with Coomassie Blue. (B and C) uninfiltrated GnGn leaf extracts (lane 1, negative control), pE16 mAb (lane 2), and pE16 scFv-CH1 (lane 3) were separated on SDS-PAGE gels under reducing (B) or non-reducing (C) conditions and transferred onto PVDF membranes. The membranes were incubated with a goat anti-human gamma chain antibody for detection.

2.2.2.2 pE16 scFv-CH₁₋₃ E Protein Binding by ELISA

96-well high-binding ELISA plates were coated with $1 \mu g/mL$ of WNV E protein in 0.1 M Na carbonate buffer and incubated for 4 hours at 37 °C. After the time had elapsed, the plates were washed three times with PBST (PBS with 0.1% Tween-20) and blocked with 5% milk in PBST for an hour at 37°C to reduce non-specific binding. All samples (pE16 scFv-CH₁₋₃ GnGn, pHu-E16 (plant-produced, positive control), mHu-E16 (mammalian cell-produced, positive control), and Hu-IgG Anti-Ebola (negative control)) were diluted in the following concentrations (ng/ml): 2000, 1000, 500, 250, 125, 62.5, 31.25, 15.625 in 1% milk in PBST. Samples were added to appropriate wells and incubated for 2 hours at 37 °C. After a wash step, 50 µL of HRP-conjugated anti-humankappa antibody was added as the detection antibody for 1 hour at 37 °C. The ELISA plates were then thoroughly washed four times with PBST to remove unbound detection antibody
and developed with tetramethylbenzidine (TMB) substrate (KPL Inc). To stop the reaction, 50 μ L of 1 M phosphoric acid was added after 2 minutes and read at 450 nm. ELISA analysis revealed similar binding of pE16 scFv-CH₁₋₃ to WNV E protein as those of pHu-E16 and mHu-E16 (**Figure 7**). This result demonstrates that pE16 scFv-CH₁₋₃ retains the antigen binding specificity of the full pHu-E16 antibody, indicating it is a promising therapeutic candidate against WNV infection.



2.2.2.3 Characterizing Plant-Produced DIII Antigen's Binding to E16 mAb

High-binding ELISA plates were coated with of *E. coli* or plant produced (extracts 1 and 2) DIII (1 μg/mL) in 0.1 M Na carbonate buffer and incubated for 4 hours at 37 °C, separately. E16 mAb was diluted (1% milk) in following concentrations (ng/ml): 2000, 1000, 500, 250, 125, 62.5, 31.25, 15.625 and added in duplicates into wells, followed by incubation for 2 hours at 37 °C. Detection was carried out by HRP-conjugated anti-human-kappa antibody for 1 hour in 37 °C. The plates were developed with TMB substrate and 1M phosphoric acid. The plates were read at 450 nm. Results show plant-produced DIII specifically recognizes E16 mAb. Since E16 has been shown

to only recognize properly assembled DIII antigen (Lai 2010), this result indicates that plant-produced DIII was properly folded in the tertiary structure (**Figure 8**).



Figure 8: Specific binding ELISA of pHu-E16 to plant and E. coli produced DIII. Serial dilutions of pHu-E16 were incubated in sample wells coated with plant and E. coli produced DIII and detected with an HRP-conjugated anti-human kappa antibody. Mean \pm SD of samples from duplicate values.

2.2.2.4 Characterize the Antigenicity of Plant-Produced DIII Antigen by Competitive

ELISA

Plant-produced DIII antigen was examined for its immunogenicity in inducing the production of WNV DIII specific antibodies in mice. 25ug of plant-DIII was injected into groups of mice with PBS as a negative control. Serum samples were collected 12 weeks after the immunization. Two batches of plant-produced DIII were used in the animal study. High-binding ELISA plates were separately coated with *E. coli* or plant produced DIII (batch 1 and 2) (at 1 μ g/mL) and incubated for 4 hours at 37 °C. After blocking and three washes, serum samples from DIII or PBS immunized mice were diluted 1:100 and incubated in the wells for 2 hours at 37 °C. Plates were washed and then incubated with E16 (32.25 ng/mL) for plant-DIII batch 1 and *E. coli* DIII-coated wells, and 62.5 ng/mL for plant DIII-batch 1-coated wells. Detection and analysis were carried out similarly as

ELISAs described above. Inhibition was calculated by the percent difference in OD450 absorption (formula between anti-DIII or preimmune serum samples and anti-PBS serum. Results indicate that antibodies in DIII-immunized serum efficiently compete with pHu-E16 in binding coated DIII antigen, and in turn, inhibit its binding to DIII by ~50% (**Figure 9**). This indicates that plant-produced DIII antigen elicited E16 like antibodies in mice, suggesting this antigen can be used as a potential vaccine candidate.



Figure 9: Competitive ELISA of plant and E. coli produced DIII binding by pHu-E16 and antibodies in anti-DIII serum. Plates coated with respective DIII were pre-incubated with 1:100 dilution of sera and subsequently with pHu-E16. Detection was carried out by anti-human kappa antibody. Mean ± SD represent triplicate samples.

Overall, structural and binding characteristics of pE16 scFv-CH₁₋₃ as well as plant produced DIII were tested with western blot and specific binding ELISAs. Proper assembly into its tertiary structure was confirmed along with specific binding for both pE16 scFv-CH₁₋₃ and DIII, demonstrating plants capacity to produce a great structural array of functional proteins. Furthermore, anti-DIII serums from mice presented competition (over 40% inhibition) against E16 in binding DIII antigen, indicating plant-DIII vaccine was able to generate a specific and potentially protective immune response in mice.

3. Conclusions

WNV is a growing epidemic all around the world with no approved prophylactic or therapeutic vaccines on the market. Great strides have been made to treat and prevent WNV disease especially those that develop into neurological symptoms. E16 mAb is the leading candidate able to prevent death up to 5 days after WNV infection (Morrey, 2006; Dowd, 2011), however lacks the ability to cross the BBB to neutralize CNS bound WNV. The diabody configuration that consists of both E16 and 8D3 scFv moieties was explored to enhance BBB penetration of E16. We successfully developed the molecular constructs of the diabody. However, further work need to be done to optimize the functionality of such design. Our results also demonstrate that the plant-produced E16 scFv-CH₁₋₃ has the specific functionality in recognizing and binding DIII antigen with comparable affinities as pHu-E16 and mHu-E16. Also, the DIII-vaccine candidate was demonstrated to elicit production of E16 like antibodies that has a high likelihood to prevent severe WNV disease. Although, further research is still needed, vast progress has been made for the development of a prophylactic vaccine and an efficacious therapeutic against WNV with innovative strategies and promising results.

CHAPTER 3

DENGUE VIRUS

1. General overview

Dengue virus, also called break-bone fever and the 5-day or 7-day fever, is known as the most encountered *Flavivirus* in the world. Affecting close to a third of the world's population, all four or possibly five (Normile, 2013) distinct enough serotypes (DV 1-4) are capable of causing life-threatening disease.

1.1 Signs and Symptoms

Dengue infection can be asymptomatic or manifest itself in Dengue fever (DF) or Dengue Hemorrhagic Fever (DHF), which involves a rapid onset of capillary leakage leading to Dengue Shock Syndrome (DSS). Severity of DF symptoms usually depends on age of the patient and recurrence of inoculation with a different DV serotype. Younger children and people who have not had a DV infection often encounter the milder symptoms but the disease could still be fatal. Symptoms include high fevers (40 °C), headaches, myalgia, arthralgia, nausea, lymphadenopathy, and rash (Whitehorn, 2011). High fevers result in dehydration and could cause convulsions or other neurological trouble. A severe case of DF presents thrombocytopenia (low platelet counts) and leucopenia (low white blood cell count), which can be observed with hemorrhage complications usually present in the gums, epistaxis (nose), and gastrointestinal tract. Symptoms usually emerge 4-10 days after DV inoculation and last 2-7 days.

DHF typically presents itself in people that are immunocompromised and are exposed to a second infection with a different DV serotype (Guzman, 2003; Effler, 2005). Patients suffering from DHF often present high fevers, severe abdominal pain with persistent/bloody vomit, plasma leakage resulting in high hematocrit concentration (increase of 20%), and hepatomegaly. Although, both DHF and DF share certain symptoms, severity among them differs. Symptoms usually progress together leading to dehydration, fluid accumulation, and eventually circulatory system failure reaching the critical stage (DSS). At that time, temperatures usually decrease (37.5-38 °C) and depending on degree of capillary permeability patient might recover or go into shock. After DSS episode, the patient usually dies within 12-24 hours or recovers with appropriate intravenous fluid replacement therapy. Patients experiencing DSS have a 20% mortality rate in places with insufficient resources or expertise but can be as low as 1% when treatment is applied early (Anne, 2013).

1.2 Treatment and Prevention

Currently, there are no approved vaccines or therapeutic treatments for DV infections; although, there are some promising vaccine candidates in phase 2 of clinical studies. These vaccines aspire to produce immunogenicity against all four DV serotypes (tetravalent), while decreasing DHF/DSS susceptibility to second DV different serotype infection (del Angel, 2013) and being relatively inexpensive to produce due to socioeconomic status of endemic areas. The leading candidate (phase 3 clinical trials) is a Chimeric vaccine (known as ChimeriVax or CYD TDV), which swapped the preM and E genes of yellow fever 17D virus for those of DV 1-4 (Guy, 2011). Other candidates include live attenuated, inactivated, and subunit (protein/DNA/viral-vector) vaccines with decreasing immunogenicity response, respectively (Webster, 2009; Lee 2012). Until approval of a specific and effective vaccine or therapeutic treatment, the recommended treatment regime consists of rest, plenty of water and paracetamol for fever and pain alleviation. Preventative measures involve mosquito control strategies by environmental control (minimizing mosquito breeding areas), biological control (predation), and if necessary chemical control (insecticides) (WHO, 2014).

1.3 Life cycle

Dengue virus is transmitted primarily by Aedes genus mosquitoes with Aedes aegypti (A. aegypti) being the most prominent and other mosquitoes (e.g. Aedes albopictus) less frequent vectors. Aedes aegypti is highly successful in urbanized areas utilizing both man-made and natural sites as breeding areas (Rott, 2010). These mosquitoes are highly resourceful vectors with immature development occurring in manmade containers (e.g. jars, tires, flowerpots, cans) and adult females residing inside houses where they feed exclusively on human blood. For one gonotrophic cycle female mosquitoes require multiple blood meals. Due to this necessity and behavior, A. aegypti is able to transmit DV to multiple human hosts (Mosquitoes, 2009). DV cycles between the vector to humans and other non-human primates with vertical transmission to mosquito progeny. An uninfected A. aegypti can become infected by feeding on a blood meal with high titers of DV; in humans high titers develop 4-7 days post inoculation. This results in replication of the virus in the epithelial cells of the midgut and eventual spread to the salivary glands where it can infect the next blood meal after an extrinsic incubation time of 10-14 days, due to inefficient replication in A. aegypti (Dengue, 2009).

1.4 Epidemiology

The first documented cases of Dengue goes back to the Chin Dynasty (265-420 A.D.) believed to be attributed to flying insects from "poisoned water" (Gubler, 1998). Since then, the virus has been spread to more than 100 countries in the tropical and

subtropical areas of the world (e.g. Southeast Asia, Latin America, the Caribbean, and Mediterranean). Annually, there are ~50 to 100 million reported cases of infection per year with 500,000 of them developing DHF symptoms (Guzman, 2010). The geographical range of the virus is attributed to the spread of the vector, *Aedes* genus mosquitoes, which dispersed from Africa to Asia and later to the rest of the world through increased globalization and global travel (Simmons, 2012). It is thought that rapid development and weak infrastructure in healthcare increases the fitness of *A. aegypti* mosquitoes by providing a breeding sites and dense population of humans to feed on. Although, these mosquitoes are adapted for highly dense urban settings, there has been a movement toward rural areas due to improper vector control.

In Southeast Asia and the Pacific, more than half of the world's population is at risk of DV infections (leading cause of death in children) with several epidemics already occurring in tropical areas (e.g. Indonesia, Thailand, Cambodia) and spreading to deciduous areas (e.g. Bangladesh, India, etc). It is important to mention that all four serotypes are native in this region (DV-1 (1977), DV-2 (1981), DV-4 (1981), and DV-3 (1994)) (Gubler, 1998). In Indonesia (2007) and western pacific countries (2001-2008) 150,000 and approximately 1 million cases were reported, respectively. In both examples, fatality rates were no greater than 1% (WHO, 2009). Outbreaks of Dengue have been documented in African countries but surveillance data is incomplete.

Early eradication campaign of *A. aegypti* (1960-1970s) slowed the dispersion of DV in the Americas. Currently, outbreaks are prominently seen in the tropical regions where mosquito control is not maintained (Guzman, 2002; Kay, 2005). Throughout 2001 to 2007, 30 countries in the Americas reported about 4.3 million cases of dengue

infection with 106,037 developing into DHF (fatality rate 1.2%). Brazil, a highly urbanized country surrounded by rainforest, reported about 64% of the total dengue infections and had the highest fatality rate (WHO, 2009) with 700,000 cases reported per year (Figueiredo, 2012). The Andean countries (19%) reported the highest cases of DHF (61,341) with Central American (13%), Caribbean (3.9%), and North American (<0.1%) reporting lower case numbers (WHO, 2009). Aside from small epidemics occurring in Hawaii, most cases of DV infections in North America are imported from travelers.

The epidemiology studies (Guzman, 2003; Effler, 2005; Halstead, 2007) in Hawaii, Singapore, and Cuba show outbreaks of Dengue in island systems. Within these virgin systems, first exposure (DV-1 in Cuba) generally resulted in the mild disease of DF. After 4 years, a different serotype (DV-2) was introduced and resulted with higher incidences of DHF/DSS, especially previously exposed to DV-1, with long-interval secondary exposures resulting in more severe symptoms. Also, there were higher incidences of DHF/DSS in infants that were never exposed to DV but where the mother had been infected and produced antibodies against the specific DV serotype (Whitehorn, 2011; Kliks, 1988). Conclusions from these results support the theory of ADE and progressive loss of cross neutralizing antibodies with different serotypes of dengue. 1.5 Pathogenesis

Mosquito inoculation of DV eventually infects and replicates in LDC, which transports the DV antigens to the nearest lymph node, presenting to and activating passing innate cells. Innate cells (specifically monocytes and macrophages) travel to the infection site in attempts of killing the virus and any infected cells, but instead get infected by the virus (Ubol, 2010; Murphy, 2011). Throughout the innate immune 35

response infected cells produce interferons and other cytokines to prepare defenses of other cells causing initial DV symptoms. Infected innate cells disseminate the virus throughout the body, while infecting other cells and increasing DV viremia. After activation of adaptive immune system, CD8+ cytolytic T-cells along with B-cell production of IgM and IgG antibodies help kill and neutralize specific DV serotype. Both memory B and CD4+ T-cells recognize and can neutralize to homotypic (same serotype) DV infections for a lifetime and heterotypic (different serotype) DV infections for 3-4 months (Beltramello, 2010; Anne, 2013).

After the short period of protection, secondary heterotypic DV infections have been seen to produce more cases of the severe symptoms (DFH/DSS) in a phenomenon coined ADE (Halstead, 1988). In secondary heterotypic DV infections, antibodies from the first infection are able to recognize and bind to DV but fail to destroy the virus. These sub-neutralizing antibodies facilitate binding to monocytes through the Fc γ regions of the antibodies and Fc γ receptor (Fc γ R) on immune cells, increasing virus uptake and replication, consequently increasing severity of disease (Wan, 2013). Similarly, activation of memory T-cells generates a non-specific inflation of cytotoxic T-cell response incapable of clearing current DV serotype infection. In addition, heighten T-cell activation results in an exaggerated cytokine production, such as IFN γ , TNF α , and IL 2, 6, 8, and 10 (Guzman, 2002), which is suspected of increasing vascular permeability and tissue damage leading to plasma leakage.

1.6 Antibody-Based Therapeutics Against DV: E60



Initially raised against WNV, E60 mAb demonstrated cross reactivity and

Figure 10: Plant and mammalian glycosylation forms for pE60 in transgenic plants. (A) wild type GnGnXF6, (B) GnGn, (C) GnGnF6, (D-F) high mannose forms Man7-9, (G) AA, (H) AAF6.

neutralizing activities against DII fusion loop on the E protein of DV (Oliphant, 2006; Williams, 2013; Brien, 2013). The fusion loop is highly conserved among all DV serotypes (Gromowski, 2008; VanBlargan, 2013). Early work modified E60 from a mouse IgG2a mAb into an E60 chimeric

human IgG1 mAb with a mutation in position 297 (asparagine to glutamine) in Fc γ region (Balsitis, 2010). Administration of E60-chimeric Hu-IgG1 mAb (50 µg) in addition to anti-DV1 serum (to simulate secondary heterotypic DV exposure) 48 hours after initial infection resulted in 80% survival in mice demonstrating therapeutic efficacy (Balsitis, 2010). Similar to E16 mAb, E60 inhibits fusion of the virus to the endosomal membranes after initial binding to receptors for endocytosis (Costin, 2013; Lok 2008). This inhibitory step prevents the virus from gaining access to the translational and replicative machinery of the cell by holding it within the endosome (Thompson, 2009).

The glycosylation patterns and structure of an immunoglobulin molecule have a great impact on its effector function (Arnold, 2007). Specifically, different N-glycosylation patterns to the Fcγ region of CH2 of IgG1 can determine its CDC and ADCC, and ADE activity (Zheng, 2011). Aglycosylated mAb can prevent the binding of

IgG1 to the FcγR, and in turn, eliminating ADE. However, aglycosylated mAb also lost all its CDC activity that may be necessary for its full therapeutic activity. Furthermore, aglycosylation can also cripple the stability of the mAb, thus decreasing the half-life of the molecule (Zheng, 2011; Kayser, 2010). Wild type (WT) and glycoengineered *N. benthamiana* plant lines were used to test the hypotheses that specific glycosylation patterns can reduce or eliminate ADE response; while maintaining the necessary CDC activity for mAb efficacy against DV. Analyzing effects of glycosylation of IgG on ADCC/CDC activity will also provide answers for the basic question of how carbohydrate moieties affect antibody effector functions. Thus, different glycoforms of E60 including WT GnGnXF3, GnGn, GnGnF6, high mannose, AA, AAF6 are being produced in *N. benthamiana* plants (**Figure 10**). Plant-produced E60 was characterized as well as investigated for specific binding (*in vitro* and *in vivo*) to E protein and neutralization activity with the aim of developing an effective of anti-DV therapeutics with enhanced safety.

2. Results and Discussion

2.1 Molecular Design

The humanized E60 VH coding sequence was optimized with tobacco codons and fused with human IgG1 CH1-3 sequence and VL to human kappa CL. Both molecular constructs were preceded with a Kozac and leader sequence to enhance translation and for ER targeting, respectively. In both constructs *Eco*RI and *Bam*HI (5' and 3', respectively) restriction sites bordered the gene for ease of sub-cloning. The longer HC was cloned into 3' TMV vector while the shorter LC was cloned into 3' PVX vector for

MagnICON plant expression due to 3'TMVs has a stronger promoter compared to 3'PVX (**Figure 11**).



Figure 11: Schematic of pE60 gene constructs. (A) pE60 HC-IgG1, and (B) pE60 LC-IgG1.

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2.2 Molecular Cloning

Overlap PCR was utilized to add in the *Eco*RI site, Kozac sequence, start codon, intronless signal peptide to the 5' end, and a *Nhe*I site to the 3' end of both E60 VH (pCI neo-chE60hG1) and E60 VL (pCI neo-chE60Lc). PCR products were cloned into Topo2.1 vector (antibiotic resistant against ampicillin) and transformed into DH5 α (Topo VH and

Topo VL).

Figure 12: Analytical agarose gel of constructed E60 IgG1 cut with EcoRI and BamHI. Lane 1: E60 IgG1 HC in 3' TMV; Lane 2: E60 IgG1 LC in 3' PVX.

The construction of the LC involved a

three way ligation between TOPO VL (*EcoRI*/*NheI*), plant codon optimized human Kappa LC (*NheI*/*Bam*HI) and the 3' PVX vector (*EcoRI*/*Bam*HI). For the HC, the three way ligation was between TOPO VH (*Eco*RI/*Nhe*I); plant optimized human IgG1 CH1-3 region (*NheI/Bam*HI) and the 3' TMV vector (*Eco*RI/*Bam*HI). The only difference in the ligation method is the molar ratio (1:2:2, vector: insert 1: insert 2). Once the constructs were verified through gel analysis (**Figure 12**) and sequence confirmation (**Figure 13, in Appendix C**), the DNA was transformed into *A. tumefaciens* (electroporator settings: 2.20 kV and 5.80 milliseconds) (new strains 485 (E60 HC) and 486 (E60 LC)).

2.3 Plant expression

All MagnICON modules were cultured individually in YENB media (0.75% Bacto yeast extract, 0.8% Nutrient Broth, and pH 7.5) plus appropriate antibiotics in RB tubes at 30 °C in a shaker (300 rpm). Depending on the type of agroinfiltration (syringe or vacuum) and the amount of plants that are going to be infiltrated, volumes will vary with optimal concentrations determined by empirical experimentation (He, 2014). For the following pE60 analysis results, the *A. tumefaciens* concentration used was 0.12 for each construct, totaling a final concentration of 0.60 OD_{600} . Both WT and GnGn six week old plants were infiltrated for p E60 expression. After 4 days post infiltration (dpi), necrosis of the leaf became apparent so samples were gently cut from infiltrated leaf tissue. For small scale estimation of expression levels, samples were weighed to 0.3 gram leaf fresh weight (LFW), placed in microfuge tubes with a scoop of copper beads for plant leaf homogenization, and were immediately stored in -80 °C until usage. For larger scale extraction, leaves were either stored in -80 °C or processed with 30 min of harvest. 2.3.1 Extraction of pE60 from *N. benthamiana* Leaves

Leaf samples were homogenized at 4 °C (to reduce protein degradation) in extraction buffer (100mM Tris-HCl, pH 8.0, 150mM NaCL, 1mM PMSF, tablet protease

inhibitor cocktail) at a 1:1.5 ratio of LFW (g) to buffer (mL). Samples were repeatedly centrifuged at 10 kGs for 15 minutes with supernatant transferred to clean microfuge tubes until extract was clear. Clear extracts were used to initially estimate total protein with Bradford protein assay, characterize pE60 with Western Blot analysis, and binding specificity with E protein binding ELISA. pE60 was purified by ammonium sulfate precipitation and protein A chromatography (by Matthew Dent from ASU). Purified samples were used for yeast binding (performed by Huafang Lai) and neutralization assays (performed by Dr. Michael Diamond lab from Washington University School of Medicine).

2.3.2 Expression Level Quantitation by ELISA

To analyze the total soluble protein we utilized a Bradford protein assay. Regular (non-high binding) ELISA plates were loaded with diluted plant extracts (40x) with 5 μ L going into each well. BSA (positive control) was diluted with PBS (137mM NaCl, 2.7 mM KCl, 10 mM Na₂HPO₄, 1.8 mM KH₂PO₄,) at the following concentrations (μ g/ml): 150, 100, 50, 25, 12.5, 6.25, 3.125, and 0. The Bradford reagent was also diluted (specified by the manufacturer) and 160 μ L was added to each well. The samples were read at 450 and 595 nm with the ratio (595/450) plotted against the known concentrations of BSA (μ g/mL). The crude pE60 ratio was 0.05725 which when calculated suggests the

total protein concentration of pE60 is about 4 mg/mL (Figure 14).



Figure 14: Bradford assay OD595/450 versus BSA concentration. Dilutions of BSA as well as crude pE60 extract (1:40 diluted) was pippetted into plate. Total protein was detected with Bradford's Reagent. Mean ± SD represents duplicate samples.

2.4 Structural and Functional Characterization of Plant-Produced E60.

2.4.1 Proper Assembly of pE60 Analyzed by SDS PAGE and Western Blot

The pE60 samples were ran on a 4-10% SDS PAGE under reducing and nonreducing conditions for 2 hours at 100V. Gels with purified pE60 were stained with Coomassie Blue (**Figure 15A**) and gels loaded with crude pE60 extracts were transferred to PVDF membrane at 80 mA overnight in 4 °C. After transfer, the membranes were blocked with 5% milk in PBST for 2 hours. After blocking, the membranes were washed with PBST and probed with 1% milk diluted HRP-conjugated goat anti-human kappa LC (Southern Biotech) for an hour intended to detect the light chain. ECL reagent was added and developed on x-ray film (**Figure 15B**). Our results indicate that E60 was produced in plants with the expected HC and LC, and they efficiently assemble into the tetrameric structure. In addition, they can be purified to high homogeneity by a two-step processing scheme.



Figure 15: Characterization of pE60 with SDS PAGE (A) and Western blot (B) under reducing (R) and nonreducing (NR) conditions. (A) Molecular weight marker (lane 1), flow through (lane 2), pE60 (lane 3), mE16 (lane 4), mE16 (NR) (lane 5), and pE60 (NR) (lane) were ran on SDS-PAGE gel and stained with Coomassie Blue. (B) pE60 (NR) (lane 1), negative control (lane 2), mE16 (NR) (lane 3), pE60 (R) (lane 4), negative control (lane 5), and mE16 (R) (lane 7) ran on SDS PAGE and transfer to PVDF. The blot was incubated with HRP-conjugated goat anti-human kappa for detection.

2.4.2 Specific Binding to its Antigen Measured by ELISA

To test if pE60 specific binding to its antigen, high binding ELISA plates were coated with 1 μ g/mL of purified WNV E protein in carbonate buffer (100 mM Na₂CO₃, pH 9.6) overnight at 37 °C for 4 hours. The plates were washed three times with PBST and blocked with 5% milk in PBST. Plant extracts were diluted 1:2, 1:4, 1:8, 1:16, 1:32, and 1:64 with 1% milk in PBST. Purified plant E16 ((ng/ml): 2000, 1000, 500, 250, 125, 62.5, and 31.25) was used as a positive control to generate the standard curve and a generic IgG was used as the negative control. All samples were incubated for 2 hours at

37 °C. After washing, the plates were incubated with HRP-conjugated antihuman-kappa LC antibody. The plates were then developed with TMB substrate, stopped with 1 M phosphoric acid, and read at 450 nm. The results show specific binding of pE60 mAb to



Figure 16: Specific binding ELISA of pE60 to WNV E protein. Serial dilutions of pE60 were incubated in sample wells coated with WNV E protein and detected with an HRP-conjugated anti-human kappa antibody.pHu-E16 was used as positive control and a generic human IgG was used as a negative control. Mean ± SD of samples from triplicates values.

WNV E protein. It appeared that the binding affinity of pE60 was lower than that of pHu-E16 mAb (**Figure 16**). However, it is most likely that this discrepancy is due to the different concentration of the two mAbs used in the assay.

2.4.3 Specific Binding to its Antigen Measured by Flow Cytometry

To confirm the ability of pE60 in recognize DV DII in its native conformation, as expressed in DV, recombinant yeast cells expressing DV2 DI-DII were taken from the log phase and incubated in tryptophan free media containing 2% galactose to induce expression of DI-DII. Positive yeast cells were incubated in mE60 (positive control), pE60 (WT and GnGn), stained with Alexa Fluor 467 (Invitrogen), and subject to analysis by BD FACS Calibur flow cytometer. The yeast binding assay demonstrated that pE60 (WT and GnGn) has the same specific binding as mE60 (**Figure 17**).



Figure 17: Binding of E60 mAb to DI-DII displayed on yeast cell surface. Recombinant yeast cells were incubated in (A) PBS, (B) mE60 (positive control), (c) WT pE60, and (D) GnGn pE60. After incubation, yeast cells were stained with an Alexa Fluor -467 and analyzed with FACS Calibur flow cytometer.

2.4.4 Neutralization of DV by plant-produced E60

DV2 was initially incubated with a serial dilution of pE60 (WT or GnGn) and mE60 (positive control). Uninfected Vero cells were incubated in each sample, later fixed and permeabilized. Plaques were quantified by focus



Figure 18: Neutralization of DV by pE60 variants. DV was incubated with serial dilutions of mE60 as positive control, pE60 (WT and GnGn) and used to infect Vero cells. Resulting plaques were analyzed by focus reduction assay and Biospot analysis.

reduction assay and biospot analysis. The neutralization assay demonstrated that pE60 (WT and GnGn) as well as mE60 were able to neutralize DV with full neutralization occurring when concentrations were above 1000 ng/mL (**Figure 18**).

3. Conclusions and future directions

Herein, we produced E60 chimeric human IgG1 mAb against all serotypes of DV in two different glycoforms (WT and GnGn) utilizing plant transient expression in *N. benthamiana*. Our results to date show that the feasibility of utilizing plant expression systems to produce great quantities (> 500ug/g FLW) of different glycoforms of pE60. In addition, both glycoforms of pE60 were able to assemble efficiently and demonstrated specific binding to the fusion loop on DII and while retaining neutralization activity seen in the mammalian cell-produced counterpart. Almost full neutralization of DV2 was achieved at concentration greater than 1000 ng/mL for both pE60 and mE60. These results indicate that plant-produced E60 is a promising candidate for developing efficacious therapeutics against DV. The next step would be to test the different glycoforms for ADCC, CDC, and ADE response in vitro and ultimately in vivo in a mouse model to demonstrate its enhanced safety over the mammalian cell-produced E60.

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APPENDIX A

TABLE 1: DIABODY GENE CONSTRUCTS

Gene Construct	Strain number	Expected Size when cut with NotI/HindIII (Base Pair (bp))
VL8D3-VHE16-FNRGEC (Hygro)	458	881 and 5529
VLE16-VH8D3-VEPKSC (Hygro)	459	878 and 5529
VL8D3-VHE16-FNRGEC (Zeo)	460	881 and 4947
VLE16-VH8D3-VEPKSC (Zeo)	461	878 and 4947
VL8D3-VHE16-VEPKSC (Hygro)	467	881 and 5529
VLE16-VH8D3-FNRGEC (Hygro)	468	878 and 5529
VL8D3-VHE16-VEPKSC (Zeo)	469	881 and 4947
VLE16-VH8D3-FNRGEC (Zeo)	470	878 and 4947
pcDNA3.1/Hygro (+)	232	5529
pcDNA3.1-zeo (+)	263	4947

APPENDIX B FIGURE 5: SEQUENCE COMPARISON OF E16-8D3 DIABODY CONSTRUCTS

A) 458

#458	conf:	Irmation:	all confi	rmed exce	ept #10NA	, but co	onfirmed	by read	ling chr	omatogra	aph.			O antiana d
	(n 1	10	20	30)	40	50		60	70	8	0	- Section 1 98
DART S1	Ľ Č	1)					concercione de la concercione de la concerción de la conc			NENCEE				
458-H reverse 458-F	- (1)												
Consensus	s (1)												Section 2
	(9	9) 99	,110	,12	0	130	140		150	160	,17	70	180	196
DART S1	(1)	CNTNNNCNA	NNGNNNG	TNGNGNN	TACONNO	CNANNTNI	INTATNA	CCACACO	NNTNNG	CTAACTA	GNNNACCC	NCTONTIACI	CONTNATN
458-F	- (1)												
Consensus	s (9	9)												- Section 3
	(19)	7) 197	210)	220	,230	24	40	,250	20	30	270	280	294
DART S1 458-B reverse) (19	1) 7) GAAATT	AATACGACT	CANTATAG	GNAGNNNN	AGCTGG	CTAGCGT	TAAANT	-AAGCTI <mark>T</mark> AAGCTI	GCCACC	ATGGGATG(ATGGGATG(GAGCTGT <mark>A</mark> GAGCTGTN	TCATCCTCT1 TCNTCCTNT1	ECTTGGTAG ECTTGGTAG
458-F	(10	1)				N N N N N	NNNNNN	G <mark>T</mark> TNN <mark>NT</mark> T NT	TAAGCTI	GCCNCC	N <mark>TGGGNN</mark> G	GAGCTGT <mark>A</mark>	TCATCCTCT1	CTTGGTAG
Consensus	5 (15	<i>(</i>)												- Section 4
DADT CA	(29	5) 295 3	00	310 NGCCCCCTC	320	330	CACCTOT	340	350	CTCACA	360	370	380	392
458-R reverse	(29	5) CAACAG	CTACAGGTA	AGGGGCIC	ACAGTAGO	CAGGCTT	GAGGTCT	GACATA	TATATGO	GTGACA	ATGACATC	CACITIGC	CTITCTCTC	CACAGGIGI
458-F Consensus	(6) (29)	7) <mark>CAACAG</mark> 5) CAACAG	CTACAGGTA. CTACAGGTA	AGGGGCTC AGGGGCTC	ACAGTAGO ACAGTAGO	CAGGCTT	GAGGTCT(GAGGTCT(GACATA GGACATA	TATATGO TATATGO	GTGACA	ATGACATC(ATGACATC)	CACTTTGC CACTTTGC	CTTTCTCTCC CTTTCTCTCC	CACAGGTGT CACAGGTGT
	(- Section 5
DART S1	(39)	3) 393 5) <mark>ссас</mark> тс	400 CGACATTCA	410 AATGACTO	420 AGAGCCCI	AGCTTCA	430 CTCTCGG	440	GGAGGAA	450 ATCGTGI	460 ACCATCAC	470 TIGICAGG	480 CGAGCCAGG) 490 Atatiggea
458-R reverse	(39	3) CCANTC	CGACATTCA.	AATGACTO	AGAGCCC	AGCTTCA	CTCTCGG	TTCGCT	GGAGGAA	ATCGTG	ACCATCAC	TIGICAGG	CGAGCCAGG	ATATTGGCA
458-F Consensus	- (16) 5 (39)	3) CCACTC	CGACATICA.	AATGACIC	AGAGCCCI	AGCTTCA	CTCTCGG	CTTCGCT	GGAGGAA	ATCGTG	ACCATCAC	TTGTCAGG	CGAGCCAGG	ATATTGGCA
		. 401	500	510	50	20	520	54		550	560	5	70	Section 6 500
DART S1	(49)	3) ACTGGC	TTGCGTGGT.	ATCAGCAG	AAGCCGGG	GAAAGTC	GCCGCAG	TCCTGA	TCTACGO	CGCCAC	STCGCTTG	CCGATGGT	GIGCCGICC	AGATTCTCC
458-R reverse 458-F	(49	 ACTGGC ACTGGC 	TTGCGTGGT. TTGCGTGGT.	ATCAGCAG ATCAGCAG	AAGCCGGG	GAAAGTC GAAAGTC	GCCGCAG(GCCGCAG	CTCCTGA CTCCTGA	TCTACGG TCTACGG	CGCCAC	GTCGCTTG(GTCGCTTG)	CCGATGGT CCGATGGT	GTGCCGTCC GTGCCGTCC	AGATTCTCC AGATTCTCC
Consensus	(49	 ACTGGC 	TTGCGTGGT.	ATCAGCAG	AAGCCGGG	GAAAGTC	GCCGCAG	CTCCTGA	TCTACGG	GCGCCAC	STCGCTTG	CCGATGGT	GTGCCGTCC	AGATTCTCC
,		590	600	610	61	20	630	64	0	650	660		670	Section 7
DART S1	589) 341) <mark>(</mark>	GGATCACG	GTCCGGTAC	TCAATTCI	CACTGAA	AATCAGO	CGGGTCC	AAGTGGA	GGACAT	CGGAATO	TACTACTO	GCCTGCAA	GCGTATAAC	ACCCCTTG
458-R reverse (589) (361) (GGATCACG GGATCACG	GTCCGGTAC GTCCGGTAC	ICAATTCI ICAATTCI	CACTGAA	AATCAGC AATCAGC	CGGGTCC	AAGTGGA AAGTGGA	GGACAT	CGGAATO	TACTACIO TACTACIO	GCCTGCAA GCCTGCAA	GCGTATAACI GCGTATAACI	ACCCCTTG ACCCCTTG
Consensus (589)	GGATCACG	GTCCGGTAC	ICAATICI	CACTGAA	AATCAGO	CGGGTCC	AAGTGGA	GGACAT	CGGAATO	TACTACTO	GCCTGCAA	GCGTATAAC	ACCCCTTG
/	697)	387	700	71	0	720	730		740	750	. 7	760	770	Section 8
DART S1	439)	GACTTTTG	GAGGGGGCA	CTAAGCTO	GAACTGA	AGGGAGG	AGGATCC	GGGGGAG	GAGGTC	AGGTCCF	ACTGGTC	CAATCOGG	GCAGAGGT	GAAGAAGC
458-R reverse () 458-F ()	687) 459)	GACTTTTG GACTTTTG	GAGGGGGGCA GAGGGGGGCA	CTAAGCTO CTAAGCTO	GAACTGA: GAACTGA:	AGGGAGG AGGGAGG	AGGATCC	GGGGGGAG	GAGGTC GAGGTC	AGGTCCF AGGTCCF	ACTGGTCO	CAATCCGG CAATCCGG	GGCAGAGGT(GGCAGAGGT(GAAGAAGC GAAGAAGC
Consensus (687)	GACTTTTG	GAGGGGGCA	CTAAGCTO	GAACTGA	AGGGAGG	AGGATCC	GGGGGA	GAGGTC	AGGTCCA	ACTGGTCO	CAATCCGG	GGCAGAGGT	GAAGAAGC Section 0
ſ	785)	785 790	800)	810	820	8	30	840	8	350	860	870	882
DART S1	537)	CAGGAGCA	AGCGTGAAA	GIGICAIG	CAAAGCC	AGCGGAT	ACACCTT	CACCGAC	TACTGG	ATCGAAT	GGGTGAG	ACAGGCAC	CCGGACAGG	GCCTGGAG
458-R reverse (458-F ()	785) 557)	CAGGAGCA	AGCGIGAAA	GIGICAIC	CAAAGCC	AGCGGAI AGCGGAT	ACACCII	CACCGAC	TACIGG	ATCGAAI	GGGTGAG	ACAGGCAC	CCGGACAGG(CCGGACAGG)	GCCIGGAG
Consensus (785) 🤇	CAGGAGCA	AGCGTGAAA	GIGICAIG	CAAAGCC	AGCGGAT	ACACCTT	CACCGAC	TACTGG	ATCGAAI	GGGTGAG	ACAGGCAC	CCGGACAGG	Section 10
6	883) 8	383 8	90	900	910	92	0	930	94	0	950	960	970	980
DART S1 (635)	IGGATGGG	AGACATOTT	SIGCGGCA	CTGGGAG	GACCCGG	TACAACG	AAAAGCT	CAAGGC	CCGCGTG	ACCATGA	CGGCCGAC	ACGTCCACC	ICGACCGC
458-F (655)	IGGATGGG	AGACATCII	GIGCGGCA	CTGGGAG	GACCCGG	TACAACG	AAAAGCI	CAAGGC	CCGCGTG	ACCATGA	CGGCCGAC	ACGTCCACC	ICGACCGC
Consensus (883) 3	IGGATGGG	AGACATCTT	SIGCGGCA	CIGGGAG	GACCCGG	TACAACG	AAAAGCI	CAAGGC	CCGCGTG	GACCATGAC	CGGCCGAC	ACGTCCACC:	ICGACCGC
(981)	981	990	1000	1010)	1020	1030		1040	1050	10	60	1078
DART S1 (733)	GTACATGG	AACTCCGCT	CGTTGCGG	TCGGATG	ACACCGO	CGTCTAC	TACTGTO	CCCGCT	CGGCATC	CTACGGC	GATTACGC	AGACTACTG	GGGTCAGG
458-F (753)	GTACATGG	AACTCCGCT	GTTGCGG	TCGGATG	ACACCGC	CGTCTAC	TACTGTO	CCCGCT	CGGCATO	CTACGGC	GATTACGC	ANACTACTG	GGGTCNNN
Consensus (981) (JIACATGG	AACTCCGCT	UGTIGCGG	FICGGATG	ACACCGC	CGTCTAC	TACTGTO	CCCGCT	CGGCATO	CIACGGCO	JAITACGC	AGACTACTG	Section 12
(1	079)	079	1090	1100	,1	110	1120	,11	30	,1140	,115	50	1160	1176
DART S1 (458-B reverse (1)	831) 079)	CACTACC CACTACC	GTTACTGTG. GTTACTGTG.	AGCTCATI AGCTCATI	CAATCGC	GGA <mark>G</mark> AGT GGA <mark>G</mark> AGT	GCTGAGC	GGCCGC- GGCCGC <mark>1</mark>	CGANTC	TAGNNNN	INNNNNNN-			
458-F (851)	ACTACC	GTTACTGTG	AGCTCATI	CAATCGC	GGANANT	GCTGAGC	GGCCGC	CGA TC	TAGAGGG	CCCGTTT	AAACCCGC	TGATCAGCC	ICGACTGN
Consensus (1	019)													

B) 459	
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											Section 1
DADT OF	(1)	1 ,10	20) ,3	0	40	50	60	70	80	98
DART S2 459-R reverse 459-F Consensus	(1) (1) (1) (1)	NNGNTTNNNNN	NNGGGNNNN	NANNNNNN	иссссииис	ACNNNNNGG	NNNNNGTT	TGNNNNAATN	INNNGNANNTI	NNNAAAANN TNGNN I	NNTNCNC
00113611303	(1)	00	110	100	120	140	150	160	170	190	Section 2
DART S2 459-R reverse	(99) (1) (99)	CCCNTNANNNA	ANNGGNCNG	INGNGNGTAC	GNNGGGAGG	 TNTATATNA	GCAGAGNNN	TCTGGCTAAC	TAGAGNNNN	NCTGNTTACTGGCT	TATNGAAA
459-F Consensus	(1) (99)										
	(197)	197	210	,220	230	,240	250	260	270	280	Section 3 294
DART S2 459-R reverse 459-F Consensus	(197) (197) (197)	TTANTACGACT	CACTATAGG	GAGACCCAAG	CTGGCTAGC NNNNNN	GTTTAAACT NNNNGNNNN	AAGCTTGC INNNN <mark>CTTGC</mark> AAGCTTGC	CACCATGGG CACCATGGG CNCCNTGGG CACCATGGG	TGGAGCTGT NGGAGCTGT NGGAGCTGT	ATCATO ATCATO ATCATO CTCTTCTT(ATCATOCTCTTCTT)	GTAGCAA GTAGCAA GTAGCAA GTAGCAA
DADT SO	(295)	295 300	310	,320	,330 CETTCACCT	340	35		0 ,37	70 380	Section 4 392
459-R reverse 459-F	(295)	CAGCTACAGGT. CAGCTACAGGT. CAGCTACAGGT.	AAGGGGCTC/ AAGGGGCTC/	ACAGTAGCAG ACAGTAGCAG	GCTTGAGGT	CTGGACATA CTGGACATA	TATATGGGT	GACAATGACA GACAATGACA	TNCACTTIG	CONTROLOGICACIÓN	GTGTCCA GTGTCCA
Consensus	(295)	000 400	440	400				450	400	470 400	Section 5
DART S2 459-R reverse	(393) (148) (393)	CICCGACATCG CICCGACATCG	410 TGATGACTC TGATGACTC	420 AGTCCCCTGA AGTCCCCTGA	43. CTCCCTTGC. CTCCCTTGC.	GGTGTCCTI GGTGTCCTI	140 GGGTGAACG GGGTGAACG	450 CGCAACCATC CGCAACCATC	4 60 CAACTGCAAAC CAACTGCAAAC	470 480 GCCAGCCAAGATGT GCCAGCCAAGATGT	490 CTCAACCG CTCAACCG
459-F Consensus	(165) (393)	CTCCGACATCG CTCCGACATCG	TGATGACTCI TGATGACTCI	AGTCCCCTGA AGTCCCCTGA	CTCCCTTGC CTCCCTTGC	GGTGTCCTI	GGGTGAACG	CGCAACCATC	AACTGCAAA AACTGCAAA	GCCAGCCAAGATGT(GCCAGCCAAGATGT(CTCAACCG CTCAACCG Section 6
DART S2	(491) (246)	491 500	0 ,51 TATCAGCAG	0 5	20 AGCCTCCAA	530 AGCTGCTGA	540	550 CCAGCACCCG	560 CCATACGGG	570 AGTGCCGGACCGGT	588 ICTCGGGG
459-R reverse 459-F Consensus	(491) (263) (491)	CCGTCGCCTGG CCGTCGCCTGG CCGTCGCCTGG	TATCAGCAG TATCAGCAG TATCAGCAG	AAGCCGGGGCC AAGCCGGGGCC AAGCCGGGGCC	AGCCTCCAA AGCCTCCAA AGCCTCCAA	AGCTGCTGA AGCTGCTGA AGCTGCTGA	TCTCATGGG TCTCATGGG TCTCATGGG	CCAGCACCCG CCAGCACCCG CCAGCACCCG	CCATACGGG CCATACGGG CCATACGGG	AGTGCCGGACCGGT AGTGCCGGACCGGT AGTGCCGGACCGGT	ICTCGGGG ICTCGGGG ICTCGGGG
	(590)	589	600	610	620	630	640	650	660	670	- Section
DART S2 I59-R reverse 459-F Consensus	(344) (589) (361) (589)	TCGGGCAGCGG TCGGGCAGCGG TCGGGCAGCGG TCGGGCAGCGG	AACCGACTT AACCGACTT AACCGACTT AACCGACTT	TACCCTCACI TACCCTCACI TACCCTCACI TACCCTCACI	ATCTCGTCO ATCTCGTCO ATCTCGTCO ATCTCGTCO	SCTCCAGGC SCTCCAGGC SCTCCAGGC SCTCCAGGC	GGAGGACGT GGAGGACGT GGAGGACGT GGAGGACGT	GGCTGTCTAC GGCTGTCTAC GGCTGTCTAC GGCTGTCTAC	TACTGCCAG TACTGCCAG TACTGCCAG	CAGCACTACACCAC CAGCACTACACCAC CAGCACTACACCAC CAGCACTACACCAC	FCCGCTGA FCCGCTGA FCCGCTGA
											LCCCCIGN
	(687)	687	700	,710	,720	730	,740	,750	,760	,770	- Section 78
DART S2 159-R reverse 459-F	(687) (442) (687) (459)	687 TITCGGACAAG TITCGGACAAG TITCGGACAAG	700 GAACCAAAC GAACCAAAC	,710 IGGAAATCAA IGGAAATCAA IGGAAATCAA		730 SATCCGGAG SATCCGGAG	740 GCGGAGGAG GCGGAGGAG GCGGAGGAG	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC) ,770 CGGTGGAGGCCTGG CGGTGGAGGCCTGG CGGTGGAGGCCTGG	- Section 78 FGCAGCCG FGCAGCCG
DART S2 59-R reverse 459-F Consensus	(687) (442) (687) (459) (687)	687 TITCGGACAAG TITCGGACAAG TITCGGACAAG TITCGGACAAG	,700 GAACCAAAC GAACCAAAC GAACCAAAC GAACCAAAC	710 IGGAAATCAA IGGAAATCAA IGGAAATCAA IGGAAATCAA	720 AGGGGGGGG AGGGGGGGG AGGGGGGGG	730 SATCCGGAG SATCCGGAG SATCCGGAG	.740 GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTGCAACT	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC) 770 CGGTGGAGGCCTGG CGGTGGAGGCCTGG CGGTGGAGGCCTGG	– Section 78 78 FGCAGCCG FGCAGCCG FGCAGCCG FGCAGCCG – Section
DART S2 159-R reverse 459-F Consensus DART S2 159-R reverse	(687) (442) (687) (459) (687) (687) (785) (540) (785)	687 TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG 785 790 GAAACTCACTG GAAACTCACTG	700 GAACCAAAC GAACCAAAC GAACCAAAC GAACCAAAC 800 ACCCTGTCG ACCCTGTCG	710 IGGAAATCAA IGGAAATCAA IGGAAATCAA IGGAAATCAA 810 IGTGIGGCA1 IGTGIGGCA1	,720 AAGGGGGGG AAGGGGGGGG AAGGGGGGGG 820 CCCGGCTTT	,730 GATCCGGAG GATCCGGAG GATCCGGAG 83(ACCTTCTCG ACCTTCTCG	740 GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG AACTACGGG AACTACGGG	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTGCAACT 40 8 ATGCACTGGA	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC 50 & TTAGACAAGG) .770 CGGTGGAGGCCTGG CGGTGGAGGCCTGG CGGTGGAGGCCTGG CGGTGGAGGCCTGG 360 <u>870</u> CTCCCAAGAAGGGA	- Section : 78 TGCAGCCG TGCAGCCG TGCAGCCG TGCAGCCG - Section : 88 TTGGAATG
DART S2 59-R reverse 459-F Consensus DART S2 59-R reverse 459-F Consensus	(687) (442) (687) (459) (687) (687) (785) (540) (785) (557) (785)	687 TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG 785 .790 GAAACTCACTG GAAACTCACTG GAAACTCACTG	700 GAACCAAAC GAACCAAAC GAACCAAAC GAACCAAAC ACCTGTCG ACCCTGTCG ACCCTGTCG	710 IGGAAATCAA IGGAAATCAA IGGAAATCAA IGGAAATCAA 810 IGTGTGGCAA IGTGTGGCAA IGTGTGGCAA IGTGTGGCAA	720 ACCCCCCCC ACCCCCCCCC ACCCCCCCCCC 820 CCCCCCTTT CCCCCCTTT CCCCCCTTT	730 CATCCGGAG SATCCGGAG SATCCGGAG SATCCGGAG 830 830 ACCTTCTCG ACCTTCTCG ACCTTCTCG	740 GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG AACTACGGG AACTACGGG AACTACGGG AACTACGGG	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTGCAACT 40 8 ATGCACTGGA ATGCACTGGA ATGCACTGGA	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC 50 & TTAGACAAGC TTAGACAAGC TTAGACAAGC) 770 CGTGGAGCCTGG CGTGGAGCCTGG CGTGGAGCCTGG CGTGGAGCCTGG CGTGGAGGCCTGG CGTGCAAGAAGGGA CTCCCAAGAAGGGA CTCCCAAGAAGGGA	- Section 3 78 rgcAgcco rgcAgcco rgcAgcco - Section 3 88 rrggAarg rrggAarg rrggAarg
DART S2 59-R reverse 459-F Consensus DART S2 59-R reverse 459-F Consensus	(687) (442) (687) (459) (687) (587) (785) (785) (785) (785) (883)	687 TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG 785 790 GAAACTCACTG GAAACTCACTG GAAACTCACTG GAAACTCACTG	700 GAACCAAAC GAACCAAAC GAACCAAAC BOO ACCCTGTCG ACCCTGTCG ACCCTGTCG ACCCTGTCG 900	710 IGGAAATCAH IGGAAATCAH IGGAAATCAH IGGAAATCAH IGGAAATCAH B10 IGTGTGGCAT IGTGTGGCAT IGTGTGGCAT IGTGTGGCAT 910	720 AACGGGGGG AACGGGGGG AACGGGGGGG AACGGGGGGG AACGGGGGGG CCGGCTTT CCGGCTTT CCGGCTTT CCGGCTTT	730 SATCCGGAG SATCCGGAG SATCCGGAG SATCCGGAG 830 ACCTICTCG ACCTICTCG ACCTICTCG 20	740 GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG AACTACGGG AACTACGGG AACTACGGG AACTACGGG AACTACGGG AACTACGGG AACTACGGG	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTGCAACT 40 8 ATGCACTGGA ATGCACTGGA ATGCACTGGA ATGCACTGGA 940	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC 50 g TTAGACAAG TTAGACAAG TTAGACAAG 950) 770 CGTGGAGCCTGG' CGTGGAGCCTGG' CGTGGAGCCTGG' CGTGGAGCCTGG' 360 870 TTCCCAAGAAGGAA TTCCCAAGAAGGGA TTCCCAAGAAGGGA TTCCCAAGAAGGGA 960 970	- Section 1 78 rgCAGCCG rgCAGCCG - Section 1 88 rrgGAATG rrgGAATG rrgGAATG rrgGAATG - Section 1 9 98
DART S2 59-R reverse 459-F Consensus DART S2 59-R reverse 459-F Consensus DART S2 59-R reverse 459-F 59-R reverse 459-F	(687) (442) (687) (459) (687) (540) (785) (557) (785) (785) (883) (638) (655)	687 ITICGGACAAG ITICGGACAAG ITICGGACAAG 785 790 GAAACTCACTG GAAACTCACTG GAAACTCACTG GAAACTCACTG 883 890 ATCGCCATGAT ATCGCCATGAT	700 GAACCAAAC GAACCAAAC GAACCAAAC GAACCAAAC 800 ACCCTGTCG ACCCTGTCG ACCCTGTCG ACCCTGTCG CTACTACGA CTACTACGA	710 IGGAAATCAP IGGAAATCAP IGGAAATCAP IGGAAATCAP IGGTGIGGCAT IGTGIGGCAT IGTGIGGCAT IGTGIGGCAT IGGCIGGAA IAGCICGAAC	720 AACGGGGGGG AACGGGGGGG AACGGGGGGG AACGGGGGGG CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI CCGGCTTTI	730 CATCCGGAG ATCCGGAG SATCCGGAG SATCCGGAG CCTTCTCG ACCTTCTCG ACCTTCTCG CCTCCCGGACAC	740 GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG AACTACGGG AACTACGGG AACTACGGG AACTACGGG AACTACGGG AACTACGGG TGTCAAGGG TGTCAAGGG	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT 40 8 ATGCACTGGA ATGCACTGGA ATGCACTGGA ATGCACTGGA 940 AAGGTTCACT	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC 50 & ITAGACAAGC ITAGACAAGC ITAGACAAGC 950 ATTTCCCGGC ATTTCCCGGC	770 CGCTGGAGGCCTGG CGCTGGAGGCCTGG CGCTGGAGGCCTGG CGCTGGAGGCCTGG 360 870 TTCCCAAGAAGGGA TTCCCAAGAAGGGA TTCCCAAGAAGGGA TTCCCAAGAAGGGA GGO 970 GACCAACTCAAAGAA GACCAACTCAAAGAA GCAACTCAAAGAA	- Section 1 FGCAGCCG FGCAGCCG FGCAGCCG FGCAGCCG FGCAGCCG FGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGAATG FTGGATCT AGGCTCT FACGCTCT
DART S2 59-Rreverse 459-F Consensus DART S2 59-R reverse 459-F Consensus DART S2 59-Rreverse 459-F Consensus	(687) (442) (687) (459) (687) (540) (540) (540) (557) (785) (557) (785) (883) (638) (883) (655) (883)	687 TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG 785 790 GAAACTCACTG GAAACTCACTG GAAACTCACTG GAAACTCACTG 883 890 ATCGCCATGAT ATCGCCATGAT ATCGCCATGAT	700 GAACCAAAC GAACCAAAC GAACCAAAC GAACCAAAC B00 ACCCTGTCG ACCCTGTCG ACCCTGTCG ACCCTGTCG CTACTACGA CTACTACGA CTACTACGA	710 TGGAAATCAN TGGAAATCAN TGGAAATCAN TGGAAATCAN TGGAGAATCAN TGTGTGGCAT TGTGTGGCAT TGTGTGGCAT STGTGGACAT STGCTCGAAC TAGCTCGAAC	720 AACGGGGGG AACGGGGGGG 820 CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI CCGGCTTI	730 SATCCGGAG SATCCGGAG SATCCGGAG SATCCGGAG ACCTTCTCG ACCTTCTCG ACCTTCTCG CCCGGACAC CCCGGACAC CCCGGACAC	740 GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG ACTACGGG AACTACGGG AACTACGGG AACTACGGG AACTACGGG TGTCAAGGG TGTCAAGGG TGTCAAGGG	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTCAACTGGA ATGCACTGGA ATGCACTGGA ATGCACTGGA AAGGTTCACT AAGGTTCACT AAGGTTCACT	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC 50 & TTAGACAAG TTAGACAAG TTAGACAAG 950 ATTTCCCGG ATTTCCCGG ATTTCCCGG	770 CGTEGAGCCTEG CGTEGAGCCTEG CGTEGAGCCTEG CGTEGAGCCTEG CGTEGAGCCTEG CGTEGAGCCTEG CGTEGAGCCTEG CGTEGAGCACTEG CGTCCAAGAAGGAA CTCCCAAGAAGGAA CTCCCAAGAAGGAA CTCCCAAGAAGGAA 960 97(CAACTCAAGAAAGAA CAACTCAAGAAGAA CAACTCAAGAAA CAACTCAAGAA CAACTCAAGAA	- Section 7 7 7 7 7 7 7 6 7 6 7 8 7 7 7 7 8 7 7 7 8 7 7 7 8 8 7 7 7 8 8 7 7 7 8 7 7 8 7 7 8 7 7 8 7 7 8 7 7 8 7 7 8 7 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 8 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 8 8 7 8 9 8 8 8 7 8 8 8 8
DART S2 59-R reverse 459-F Consensus DART S2 59-R reverse 459-F Consensus DART S2 DART S2 59-R reverse 459-F Consensus DART S2 59-R reverse	(687) (442) (687) (459) (540) (785) (557) (785) (638) (638) (638) (683) (655) (883) (655) (883) (655) (883)	687 ITICGGACAAG ITICGGACAAG ITICGGACAAG TTICGGACAAG 785 790 GAAACTCACTG GAAACTCACTG GAAACTCACTG GAAACTCACTG 883 890 ATCGCCATGAT ATCGCCATGAT ATCGCCATGAT ATCGCCATGAT GCTTGACATGA	700 GAACCAAAC GAACCAAAC GAACCAAAC BACCAAAC BACCAAAC BOO ACCCTGICG ACCCTGICG ACCCTGICG CTACTACGA CTACTACGA CTACTACGA CTACTACGA CTACTACGA	710 TGGAAATCAA TGGAAATCAA TGGAAATCAA TGGAAATCAA B10 TGTGTGGCAA TGTGTGGCAA TGTGTGGCAA TGTGTGGCAA 10 TAGCTCGAAG TAGCTCGAAG TAGCTCGAAG 10 TAGCTCGAAG 10 TAGCTCGAAG	720 ACCCCCCC ACCCCCCCC ACCCCCCCCCCCCCCCCC	730 SATCCGGAG SATCCGGAG SATCCGGAG 830 ACCTITICG ACCTITICG ACCTITICG CCCGGACAC CCCGGACAC CCCGGACAC CCCGGACAC CCCGGACAC CCCGGACAC CCCGGACAC CCCGGACAC	740 GCGGAGGAG GCGGAGGAG GCGGAGGAG GCGGAGGAG ACTACGGG ACTACGGG ACTACGGG ACTACGGG ACTACGGG IGTCAAGGG IGTCAAGGG IGTCAAGGG IGTCAAGGG 1030 GCGCCGTCC	,750 AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTGCAACT 40 8 ATGCACTGGA ATGCACTGGA ATGCACTGGA ATGCACTGGA AAGGTTCACT AAGGTTCACT AAGGTTCACT 1040 CAACCTCCCA	760 CGTCGAGTC CGTCGAGTC CGTCGAGTC CGTCGAGTC 50 & TTAGACAAG TTAGACAAG TTAGACAAG 950 ATTTCCCGG ATTTCCCGG ATTTCCCGG ATTTCCCGG 1050 TTAGGTGGT TTACGTGGT	770 CGCTGGAGGCCTGG CGCTGGAGGCCTGG CGCTGGAGGCCTGG CGCTGGAGGCCTGG 360 870 TTCCCAAGAAGGGA TTCCCAAGAAGGGA TTCCCAAGAAGGGA TTCCCAAGAAGGGA TTCCCAAGAAGGGA GGO 970 GACAACTCAAAGGA GACACTCAAAGAA SACAACTCAAAGAA 1060 GATTGTGGGGCC	- Section 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
DART S2 459-F reverse 459-F Consensus DART S2 459-F consensus DART S2 459-F reverse 459-F Consensus DART S2 59-R reverse 459-F Consensus	(687) (442) (687) (459) (687) (785) (540) (557) (785) (557) (785) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) (638) 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DART S2 459-R reverse 459-F Consensus DART S2 459-F Consensus DART S2 459-F reverse 459-F Consensus DART S2 459-R reverse 459-F Consensus	(687) (442) (687) (785) (540) (785) (557) (785) (883) (638) (883) (658) (883) (981) (736) (981) (753) (981)	687 TTTCGGACAAG TTTCGGACAAG TTTCGGACAAG 785 .790 GAAACTCACTG GAAACTCACTG GAAACTCACTG GAAACTCACTG GAAACTCACTG B83 890 ATCGCCATGAT ATCGCCATGAT ATCGCCATGAT ATCGCCATGAT ATCGCCATGAT Q81 990 CCTTGACATGA CCTTGACATGA CCTTGACATGA CCTTGACATGA	700 GAACCAAAC GAACCAAAC GAACCAAAC 800 ACCCTGTCG ACCCTGTCG ACCCTGTCG 900 CTACTACGA CTACTACGA CTACTACGA 0 _1(1 ATAGCCTGA ATAGCCTGA ATAGCCTGA	710 IGGAAATCAN IGGAAATCAN IGGAAATCAN IGGAAATCAN B10 IGTGTGGCAN IGTGTGGCAN IGTGTGGCAN IGTGTGGCAN IAGCTCGAAC IAGCTCGAAC IAGCTCGAAC IAGCTCGAAC IAGCTCGAAC IAGCTCGAAC IAGCTCGAAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC IAGCTCGAC 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CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGACAC CCGCGCACAC CCGCGCACAC CCGCGCACAC CCGCGCACAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCAC CCGCGCGCAC CCGCGCAC CCGCGCC CCGCGCAC CCGCGCAC CCGCGCC CCGCGCAC CCGCGC CCGCGCC CCGCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCC CCGCCC CCGCC CCGCC CCGCCC	740 GCGCAGGAG GCGCAGGAG GCGCAGGAG GCGCAGGAG ACTACGGG ACTACGGG ACTACGGG ACTACGGG ACTACGGG ACTACGGG ACTACGGG IGTCAAGGG IGTCAAGGG IGTCAAGGG IGTCAAGGG GCGCCGTCC GCGCCGTCC GCGCCGTCC III30	750 AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTGCAACT AAGTCACTGGA ATCCACTGGA ATCCACTGGA ATCCACTGGA ATGCACTGGA AAGGTCACT AAGGTCACT 1040 CAACCTCCCA CAACCTCCCA ,1140	760 CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC CGTCGAGTCC TTAGACAAG TTAGACAAG TTAGACAAG ATTTCCCGG ATTTCCCGG ATTTCCCGG 1050 TTACGTGGTC TTACGTGGTC TTACGTGGTC 1150) 770 CGCTGGAGGCCTGG' CGGTGGAGGCCTGG' CGGTGGAGGCCTGG' CGGTGGAGGCCTGG' SGGTGGAGGCCTGG' CGGTGGAGGCCTGG' SGGTGGAGGCCTGG' CGGTGGAGGCCTGG' SGGTGGAGGCCTGG' CGGTGGAGGCCTGG' SGGTGGAGGCCTGG' CGGTGGAGGCCTGG' SGGTGCGAGGAGGA' STCCCAAGAAGGGA' 960 970' SGCCAACTCAAGGAAGGGA' SACAACTCAAAGGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAAGAA SACAACTCAAGAA SACAACTCAAAGAA SACAACTCAAGAA SACAACTCAAAGAA SACAACTCAAGAA SACAACTCAAAGAA SACAACTCAAGAA SACAACTCAAGAA SACAACTCAAGAAGAA SACAACTCAAGAA SACAACTCAAGAA SACAACTCAAGGCC SACAACTCAAGAAC SACAACTCAAGGCC SACACTCAAGGCC SATGTCTGGGCCC SATGTCTGGGCCC SATGTCTGGGCCC SATGTCTGGGCCC SATGTCTGGGCCC SATGTCTGGGCCC <	- Section 1 77 TGCAGCCC TGCAGCCC TGCAGCCC TGCAGCCC TGCAGCCC TGCAGCCC TGCAGCCC TGCAGCCC TGCAGCC TTGGAATG TTGGAATG TTGGAATG TGGAGCT TACGCTCT TACGCTCT TACGCTCT TACGCTCT AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC AGGTGTC

C)	460
\sim ,	100

											 Section 1
	(1)	1 10	,20) ;	30	40	50 6	i0 70) 80)	98
DART S1	(1)								·		
460-R reverse	- (1)	NNNNNNNTNN	NNNAANNN	NNNNNNNNN	ссииииииии	INNNNNGGNNN	NNNAANNNNNN	וממחממו	INNNGGGNNN	CCCAAGCNGN	TNGCNTGN
460-F	(1)									N N	NNNANIC
Consensus	(1)								нин		Section 2
	(00)	99 1	10	120	120	140	150	160	170	190	106
DADT CI	(99)	99 1	10	120	130	140	150	100	170	100	190
460-B roverse	(00)	CAANNNGNNNNN	NNNNNNAGO	CTCANNNNNI	NNNTNTANTG	CCCCNNNANN	NNTNNCNNNNN	ACCCCANNNI	JNNNN <mark>AAA</mark> NNN	ITTGCAGCCC	CACNN_NC
460-F	(22)	CTGGTGTATCCG	CTTGGCAG	GTCA ACACA	GCTTATACTG	CGGGACAATT	GG <mark>T</mark> CA <mark>C</mark> ATATA	A-CGGCAAGA	GTAT <mark>AAA</mark> TG1	TIGCAGCCC	CACACCTC
Consensus	(99)	С	AGO	GTCA	T TA TG	CGGG A	тс	A CGGCA	AAA	TIGCAGCCC	CAC C
											 Section 3
	(197)	197	210	,220	230	240	250	260	270	280	294
DART S1	(1)							-AAGCTTGCC	CCATGGGAT	GAGCTGTAT	CATCCTCT
460-R reverse	(196)	CTTGNCAGGATG	GGNNCCNTO	CCAACGTNN	CTGCCNTGTG	GCAGCTGCTA	GCGTTTAAACT	TAAGCTTGCCI	CCANGGGAT	GAGCTGTNT	CNTCCTCT
460-F	(119)	CTTGGCAGGATG	GGAACCATC	CCAACGTTC	CIGCCIIGIG	GCAGCTGCTA	GCGTTTAAACT	TAAGCTTGCC	CCATGGGAT	GAGCTGTAT	CATCCTCT
Consensus	(197)	CIIG CAGGAIG	GG CC IC	CCARCGI	CIGCC IGIG	GCAGCIGCIA	GCGITIAAACI	TAAGCIIGCCA	ACCAIGGGAIG	GAGCIGIAI	Section 4
		005 000	010	000	000	0.40	050	000	070	000	- Section 4
DADTO	(295)	295 300	310	320	330	340	350	360	370	380	392
DART S1	(38)	TCTTGGTAGCAA	CAGCIACAC	SGIAAGGGGG	CICACAGIAG	CAGGCIIGAG	SICIGGACAIA	TATATGGGIG	CANIGACAI	CACIFICCO	TTTCTCTC
400-h levelse 460-F	(234)	TCTTGGTAGCAA	CAGCTACAC	GGTAAGGGG	CTCACAGIAG	CAGGCTTGAG	GTCTGGACATA	TATATGGGTG	CAATGACAT	CACTITICC	TTTCTCTC
Consensus	(295)	TCTTGGTAGCAA	CAGCTACAG	GGTAAGGGG	CTCACAGTAG	CAGGCTTGAG	GTCTGGACATA	TATATGGGTG	CAATGACAT	CACTTTGCC	TTTCTCTC
	()										 Section 5
	(393)	393 .400	410	.420	. 43	0 .440	.450	460	.470	.480	490
DART S1	(136)	CACAGGTGTCCA	CTCCGACAI	TTCAAATGA	CTCAGAGCCC	AGCTTCACTC	ICGGCTTCGCT	GGAGGAAATC	TGACCATCA	TTGTCAGGC	GAGCCAGG
460-R reverse	(392)	CACAGGTGTCCA	CTCCGACAI	TTCAAATGA	CTCAGAGCCC	AGCTTCACTN	ICGGCTTCGCT	GGAGGAAATC	GIGACCATCA	TTGTCAGGC	GAGCCAGG
460-F	(315)	CACAGGTGTCCA	CTCCGACAI	TTCAAATGA	CTCAGAGCCC	AGCTTCACTC	ICGGCTTCGCT	GGAGGAAATC	GIGACCATCA	TTGTCAGGC	GAGCCAGG
Consensus	(393)	CACAGGTGTCCA	CTCCGACAI	TTCAAATGA	CTCAGAGCCC	AGCTTCACTC	ICGGCTICGCI	GGAGGAAATC	GTGACCATCA	CTIGICAGGC	GAGCCAGG
											_ Section 6
	(491)	491 500	,51	10	520	530	540 5	50 56	50 ₅₇	0	588
DART S1	(234)	ATATTGGCAACT	GGCTTGCG	IGGTATCAG	CAGAAGCCGG	GAAAGTCGCC	GCAGCTCCTGA	TCTACGGCGC	ACGTCGCTT	CCGATGGTG	TGCCGTCC
460-R reverse	(490)	ATATTGGCAACT	GGCTTGCG	TGGTATCAG	CAGAAGCCGG	GAAAGTCGCC	GCAGCTCCTGA	TOTACGGCGCG	CACGTCGCTTC	CCGATGGTG	TECCETCC
460-F	(413)	MIMIIGGCARCI	GGCIIGCG	IGGIAICAG	CAGAAGCCGG	GARAGICGCC	SCAGUICUIGA	I CIACGGCGC	ACGICGCIIC	SCCGAIGGIG	16006100
Conconcue	(491)	ATATTGGCAACT	GGCTTGCGI	TGGTATCAG	CAGAAGCCGG	GAAAGTCGCC	GCAGCTCCTGA	TCTACGGCGCG	CACGTCGCTT	CCGATGGTG	TGCCGTCC
Consensus	(491)	ATATTGGCAACT	GGCTTGCG	IGGTATCAG	CAGAAGCCGG	GAAAGTCGCC	GCAGCTCCTGA	TCTACGGCGCG	CACGTCGCTT	CCGATGGTG	TGCCGTCC - Section 7
Consensus	(491)	589 60	GGCTTGCG	610	620	630	640	650	660	670	TGCCGTCC - Section 7 686
DART S1	(491) (589) (332)	589 60 AGATTCTCCGGA	GGCTTGCG1	610 GGTATCAG	620	630	640	650 GAGGACATCGG	660	670	TGCCGTCC - Section 7 686 GCGTATAA
DART S1 460-R reverse	(491) (589) (332) (588)	ATATTGGCAACT 589 60 AGATTCTCCGGAT AGATTCTCCGGAT	GGCTTGCG1 00 ICACGGTCC ICACGGTCC	GGTATCAG 610 GGTACTCAA GGTACTCAA	620 620 ATTCTCACTG	630 630 AAAATCAGCCC	640 GGTCCAAGTG	650 GAGGACATCGG	660 AATCTACTAC	670 TGCCTGCAA	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA
DART S1 460-R reverse 460-F	(491) (589) (332) (588) (511)	ATATTGGCAACT 589 60 AGATTCTCCGGAT AGATTCTCCGGAT	GGCTTGCG1	610 GGTACTCAP	620 ATTOTCACTG ATTOTCACTG ATTOTCACTG	630 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC	640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG	660 AATCTACTAC AATCTACTAC AATCTACTAC	670 TGCCTGCAA TGCCTGCAA	- Section 7 686 GCGTATAA GCGTATAA GCGTATAA
DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589)	ATATTGGCAACT 589 60 AGATTCTCCGGAT AGATTCTCCGGAT AGATTCTCCGGAT	GGCTTGCG DO ICACGGTCC ICACGGTCC ICACGGTCC ICACGGTCC	GGTATCAG GGTACTCAA GGTACTCAA GGTACTCAA GGTACTCAA	620 620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG	630 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC	640 640 667CCAAGTG 667CCAAGTG 667CCAAGTG 667CCAAGTG	650 GAGGACATOGO GAGGACATOGO GAGGACATOGO GAGGACATOGO	660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC	670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA	- Section 7 - Section 7 686 GCGTATAA GCGTATAA GCGTATAA Section 9
Consensus DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589)	ATATTGGCAACT 589 60 AGATTCTCCGGAT AGATTCTCCGGAT AGATTCTCCGGAT AGATTCTCCCGAT 697	GGCTTGCG1	610 GGTACTCAA GGTACTCAA GGTACTCAA GGTACTCAA GGTACTCAA	620 620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG	GAAAGTCGCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC	GCAGCTCCTGA 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG	660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC	670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA	- Section 7 686 GCGTATAA GCGTATAA GCGTATAA GCGTATAA - Section 8
DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589) (687) (490)	ATATTGGCAACT 589 60 AGATTCTCCGGAT AGATTCTCCGGAT AGATTCTCCGGAT 687	GGCTTGCG1	610 GGTACTCAA GGTACTCAA GGTACTCAA GGTACTCAA CGGTACTCAA ,710	620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG	GARAGTOGOO 630 ARAATCAGCOO ARAATCAGCOO ARAATCAGCOO ARAATCAGCOO 730 CARCOOCCOCCA	640 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG	650 GAGGACATCGO GAGGACATCGO GAGGACATCGO GAGGACATCGO 750	2405105011 660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC 760	CCGATGGTG 670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA 770	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA GCGTATAA - Section 8 784
DART S1 460-R reverse 460-F Consensus DART S1 460-B reverse	(491) (589) (332) (588) (511) (589) (687) (430) (686)	ATATTGGCAACT 589 66 AGATTCTCCGGAT AGATTCTCCGGAT AGATTCTCCGGAT 687 CACCCCTTGGACC CACCCCTTGGACC	GGCTTGCG1 00 ICACGGTCC ICACGGTCC ICACGGTCC ICACGGTCC 700 ITTTGGAGG	610 GGTACTCAP GGTACTCAP GGTACTCAP GGTACTCAP ,710 GGGCACTAP	CAGAAGCCGG 620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG 720 AGCTGGAACT	GAAAGTCGCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC 730 GAAGGAAGGA	GCAGCTCCTGA 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG 740 GGATCCGGGGG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG	CACGTCGCTTC 660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC TCCAACTGGT TCCAACTGGT	CCGATGGTG 670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA 770 CCAATCCGG	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA - Section 8 784 GGCAGAGG GGCAGAGG
Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F	(491) (589) (588) (511) (589) (687) (430) (686) (609)	ATATTGGCAACT 589 60 AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA 687 CACCCCTTGGAC CACCCCTTGGAC	GGCTTGCG1 CACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC 700 TTTTGGAGG TTTTGGAGG	GGTATCAG 610 CGTACTCAF CGTACTCAF CGTACTCAF CGTACTCAF 710 CGGCACTAF CGGCACTAF CGGCACTAF	CAGAAGCCGG 620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG 720 AGCTGGAACT AGCTGGAACT	GAAAGTCGCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC 730 GAAGGGAGGA GAAGGGAGGA	GCAGCTCCTGA 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG 740 GGATCCGGGGG GGATCCGGGGG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG AGGAGGTCAGG	ACGTCGCTT 660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC 760 TCCAACTGGT TCCAACTGGT	CCGATGGTG 670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA 770 CCAATCCGG CCAATCCGG	ETGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA - Section 8 784 GGCAGAGG GGCAGAGG GGCAGAGG
Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-R Consensus	(491) (589) (588) (588) (589) (687) (430) (686) (609) (687)	ATATTGCAACT 589 60 AGATTCTCCGAA AGATTCTCCGAA AGATTCTCCGAA G87 CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC	GGCTTGCG DO TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC 700 TTTTGGAGG TTTTGGAGG TTTTGGAGG TTTTGGAGG	IGGTATCAG 610 CGTACTCAP CGTACTCAP CGGTACTCAP CGGTACTCAP 710 CGGCACTAP CGGCACTAP CGGCACTAP	620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ACTCGAACT AGCTGGAACT AGCTGGAACT	GAAAGTCGCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC 730 GAAGGAGGAGGA GAAGGAGGAGGAC GAAGGAGGAGGAC	GCAGCTCCTGA 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG 740 GGATCCGGGGG GGATCCGGGGG GGATCCGGGGG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG	660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC TCCAACTGGT TCCAACTGGT TCCAACTGGT	670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA 770 CCAATCCGG CCAATCCGG CCAATCCGG	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA SCGTATAA - Section 8 784 GGCAGAGG GGCAGAGG GGCAGAGG
DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589) (687) (430) (686) (609) (687)	ATATTGCAACT 589 60 AGATTCTCCGAA AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA G87 CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC	GGCTTGCG1 DO TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC 700 TTTTGGAGG TTTTGGAGG TTTTGGAGG	GGTATCAG 610 GGTACTCAP GGTACTCAP GGTACTCAP GGTACTCAP 710 GGGCACTAP GGGCACTAP	620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ACTGGAACT AGCTGGAACT	GAAAGTCGCCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC 730 GAAGGGAGGAC GAAGGGAGGAC GAAGGGAGGAC	GCAGCTCCTGA 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG 740 GGATCCGGGGG GGATCCGGGGG GGATCCGGGGG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG	ACGTCGCTT(660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC TCCAACTGGT TCCAACTGGT TCCAACTGGT	670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA CCAATCCGG CCAATCCGG CCAATCCGG	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA GCGTATAA - Section 8 784 GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG - Section 9
Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589) (687) (430) (686) (609) (687) (687)	ATATTGCCAACT 589 60 AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA G87 CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC 785 790	GGCTTGCG 00 TCACGGTCC TCACGGTCC TCACGGTCC 700 TTTTGGAGG TTTTGGAGG TTTTGGAGG 800	IGGTATCAG 610 CGTACTCAP CGTACTCAP CGTACTCAP CGTACTCAP 710 CGGCACTAP CGGCACTAP CGGCACTAP CGGCACTAP 800	620 TTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ACTCGAACT ACTCGAACT ACTCGAACT ACTCGAACT ACTCGAACT ACTCGAACT ACTCGAACT ACTCGAACT ACTCGAACT	GAAAGTCGCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC 730 GAAGGGAGGAG GAAGGAGGAGGA GAAGGAGGAGGA GAAGGAGGAGGA B30	640 GGICCAAGTG GGICCAAGTG GGICCAAGTG GGICCAAGTG GGICCAAGTG GGICCGAGGG GAICCGGGGG GAICCGGGGG GAICCGGGGG B40	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG	ACGTCGCTT 660 IATCTACTAC IATCTACTAC AATCTACTAC AATCTACTAC 760 TCCAACTGGT TCCAACTGGT TCCAACTGGT TCCAACTGGT 1CCAACTGGT 860	670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG 870	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA GCGTATAA - Section 8 784 GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG GGCAGAGG Section 9 882
Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589) (687) (687) (686) (609) (687) (687) (785) (528)	ATATTGGCAACT 589 60 AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA 687 CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC 785 790 TGAAGAAGCCAG	GGCTTGCGT CACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC TTTGGAGG TTTTGGAGG TTTTGGAGG TTTTGGAGG 800 GAGCAAGCG	610 GGTACTCAR GGTACTCAR GGTACTCAR GGTACTCAR CGGTACTCAR 710 GGGCACTAR GGGCACTAR GGGCACTAR GGGCACTAR GGGCACTAR GGGCACTAR	620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG AGCTGGAACT AGCTGGAACT AGCTGGAACT 820 TCATGCAAAG	GAAAGTCACCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC GAAGGAGGAG GAAGGAGGAGGA GAAGGAGGAGGA GAAGGAGGAGGA B30 CCAGCGGATAC	640 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCGGGG GGATCCGGGGG GGATCCGGGGG 840 CACCITCACGG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG 850 ACTACTGGATC	CACGTCGCTT 660 CAATCTACTAC CAATCTACTAC CAATCTACTAC CAATCTACTAC CAATCTACTAC 760 TCCAACTGGT TCCAACTGGT TCCAACTGGT TCCAACTGGT TCCAACTGGT S60 GAATCGGTGA	670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG S70 GACAGGCAC	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA CGTATAA - Section 8 784 GGCAGAGG GGCAGAGG GGCAGAAG GGCAGAGG - Section 9 882 CCGGACAG
Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589) (687) (687) (686) (609) (687) (687) (528) (785) (528) (784)	ATATTGGCAACT 589 60 AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA AGATCCTCGGAC CACCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC CACCCCTGGAC TGAAGAAGCCAG IGAAGAAGCCAGC	GGCTTGCG1 00 TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC 700 TTTTGGAGG TTTTGGAGG TTTTGGAGG 800 GAGCAAGCG GAGCAAGCG	GGTATCAG 610 GGTACTCAP GGTACTCAP GGTACTCAP GGTACTCAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACT	620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG A	6330 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC 730 CAACGGAGGAC GAACGGAGGAC GAACGGAGGAC 830 CCACCGGATAA CCACCGGATAA	GCAGCTCCTGA 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG 740 GGATCCGGGGG GGATCCGGGGG GGATCCGGGGG GGATCCGGGGG GACCTCACGG CACCTTCACCG	650 GAGGACATOG GAGGACATOG GAGGACATOG GAGGACATOG AGGAGTACAG AGGAGTCAG AGGAGTCAG AGGAGTCAG 850 ATACTGGAT	660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC TCCAACTGGT TCCAACTGGT TCCAACTGGT 860 GAATGGTGG	CCGATGGTG 670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG	TGCCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA - Section 8 784 GGCACAGA GGCACAGA GGCACAGA GGCACAGA GGCACAGA CGCACAGA - Section 9 882 CCGGACAG
Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-R reverse 460-R reverse	(491) (589) (332) (588) (511) (589) (687) (430) (686) (687) (687) (687) (785) (528) (784) (707) (795)	ATATTGCCAACT 589 60 AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA 687 CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC 785 790 TGAAGAAGCCAG TGAAGAAGCCAG TGAAGAAGCCAG	GGCTTGCGT CACCGTCC TCACGGTCC TCACGGTCC TCACGGTCC 700 TTTTGGAGG TTTTGGAGG TTTTGGAGG 800 SAGCAAGCG SAGCAAGCG SAGCAAGCG SAGCAAGCG	610 GGTACTCAP GGTACTCAP GGTACTCAP GGTACTCAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCGCACTAP GGGCGCACTAP GGGCGCGCACTAP GGGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGC	620 ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ATTCTCACTG ACCTGGAACT ACCTGGAACT 820 CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG CCATGCAAACG	GAAAGTCGCCC 630 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC 730 GAAGGAGGAC GAAGGAGGAC GAAGGAGGAC GAAGGAGGAC 830 CCACCGGATA' CCACCGGATA'	640 640 GGGICCAAGTG GGGICCAAGTG GGGICCAAGTG GGGICCAAGTG 740 GAICCGGGGG GAICCGGGGG GAICCGGGGG 840 ACCTICACCG ACCTICACCG ACCTICACCG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG 850 ACTACTGGATG ACTACTGGATG	660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC 760 TCCAACTGGT TCCAACTGGT 860 GAATGGTGA GAATGGTGA GAATGGTGA	670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCACGCACCGCAC	TECCGTCC - Section 7 686 GCGTATAA GCGTATAA GCGTATAA GCGTATAA CGGTATAA CGGTATAA GCGTATAA GCGACAGA GGCACAGA GGCACAGA GGCACAGA CCGGACAG CCGGACAG CCGGACAG
Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus	(491) (589) (332) (588) (511) (589) (687) (430) (686) (687) (687) (687) (687) (785) (785) (785) (785)	ATATTGGCAACT 589 60 AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA AGATTCTCCGGA G87 CACCCTTGGAC CACCCCTTGGAC CACCCCTTGGAC 785 TGAAGAAGCCAG TGAAGAAGCCAG TGAAGAAGCCAG	GGCTTGCGT TCACGGTCC TCACGGTCC TCACGGTCC 700 TTTTGCAGG TTTTGCAGG TTTTGCAGG TTTTGCAGG TTTTGCAGG SAGCAAGCG SAGCAAGCG SAGCAAGCG SAGCAAGCG	GGTATCAG 610 GGTACTCAP GGTACTCAP GGTACTCAP 710 GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GGGCACTAP GG	620 httctcactg httctcactg httctcactg httctcactg httctcactg httctcactg httctcactg httctcactg httctcactg httctcactg httctgaact geotggaact geotggaact geotggaact geotggaact geotggaact geotggaact geotggaact httccacaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httctgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httcttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httctttgaag httcttttgaag httcttttgaag httcttttttgaag httcttttttttttttttttttttttttttttttttt	GAAAGCACCC G30 AAAATCAGCCC AAAATCAGCCC AAAATCAGCCC GAAGGAGGACGAC GAAGGAGGACGAC GAAGGAGGACGAC B30 CCAGCGGATAC CCAGCGGATAC	640 640 GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCAAGTG GGTCCGGGG GATCCGGGGG GATCCGGGGG GATCCGGGGG GATCCGGGGG ACCTTCACCG ACCTTCACCG	650 GAGGACATCGG GAGGACATCGG GAGGACATCGG GAGGACATCGG 750 AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG AGGAGGTCAGG 850 ACTACTGGATC ACTACTGGATC	660 AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC AATCTACTAC 760 TCCAACTGGT TCCAACTGGT TCCAACTGGT S60 GAATGGGTGA GAATGGGTGA GAATGGGTGA	CCGATGGTG 670 TGCCTGCAA TGCCTGCAA TGCCTGCAA TGCCTGCAA CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG CCAATCCGG GACAGGCAC GACAGGCAC GACAGGCAC	ISCCGTCC - 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Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus DART S1 460-R reverse 460-F Consensus	(491) (588) (532) (588) (511) (589) (687) (430) (686) (687) (687) (687) (687) (785) (784) (785) (784) (785)	ATATTGGCAACT 589 66 AGATTCTCCGGAT AGATTCTCCGGAT AGATTCTCCGGAT 687 CACCCCTTGGACT CACCCCTGGACCACG TGAAGAAGCCACG GABGAAGCCACG B83 890	GGCTTGCG1 D TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC TCACGGTCC TTTTGGAGG TTTTGGAGG TTTTGGAGG SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC SAGCAAGCC 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800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 GAGCAAGCG 800 800 GAGCAAGCG 800 800 800 800 800 800 800 80	GGTATCAG 610 GGTACTCAM GGTACTCAM GGTACTCAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM GGGCACTAM 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	(1)	1 10	20		30	40	50	60	70	80	98
DART S2	- (i)										
461-R reverse	(1)	CNNNNNNNNNC	NNNN NANI	NNNNNNNT	NCNNNNN	CAGNTNANNN	NNNTNNNNN	NNGGNCN	NTNN TNNNN	INNNNNN <mark>C</mark> N <mark>Z</mark>	NNNNNNNNNNN
461-F	- (1)	NNNNNNNNNNNNNN	NNNN TCC:	TGGTGTAT	CCGCTTGG	CAGGICAACA	CAGCITATAC	TGCG <mark>GGACA</mark>	TIGGICACAI	ATAACGG <mark>C</mark> A	GACGTATAAAT
Consensus	(1)		N1 N1 N1 N1	1		CAGIA		66 6 1		C 1	Section 2
	(00)	00 110		120	120	140	150	160	170	190	3ection 2
DADT SO	(99)			120	,130	,140	,150	,100	,170	100	ACCTTCCCACC
461-B reverse	(95)	NTTNNNNNCCCCC	CNCNCNNI	NNNNNNNN	CNNNNNGG	GANCNNNN <mark>C</mark> N	NNNNNN <mark>C</mark> NNN	CCNTNNNGC	GNNNNTAGNO	TINAAACTI	AGCTTGCNNCC
461-F	(99)	G <mark>TT</mark> TGCAGC <mark>CCC</mark> AC	ACCTCCT:	TGGCAGGA	TGGGAA	CCAT <mark>C</mark> C	AACGTT <mark>C</mark> CTG	CCTTGTGGC	AGCTGC <mark>TAG</mark> CC	GTTTAAACTT <mark>2</mark>	AAGCTTGC <mark>CA</mark> CC
Consensus	(99)	TT CCC C	сс			С	С	CC T GC	AG TAG G	GTT AAACTTA	AAGCTTGCCACC
											—— Section 3
	(197)	197 2	210	220	,230	240	,250	260	270	280	294
DART S2	(13)	ATGGGATGGAGCTG	TATCATC	CICIICII	GGTAGCAA	CAGCTAC <mark>A</mark> GG	TAAGGGGCTC	ACAGTAGCA	GCTTGAGGTC	TGGACATAT?	ATATGGGTGACA
461-R reverse	(193)	ATCCCATCCACCTC	TATCATC	NINTINII	GGTAGCAA	CAGCTACNGG	TAAGGGGGCTC	ACAGTAGON	GCTTGAGGTC	TGGACATATA	ATATGGGTGACA
Consensus	(197)	ATGGGATGGAGCTG	TATCATC	CICITCII	GGTAGCAA	CAGCTACAGG	TAAGGGGGCTC	ACAGTAGCA	GCTTGAGGTC	TGGACATATA	ATATGGGTGACA
	(,										— Section 4
	(295)	295 300	310	.320	330) 34	0 35	0 36	30 37	0 38	30 392
DART S2	(111)	ATGAC <mark>A</mark> TCCACTTI	GCCTTTC	TCTCCACA	GGTGTCCA	CTCCGACATO	GIGAIGACIC	AGTCCCCTG	ACTOCCTIGO	GIGICCIIG	GGTGAACGCGCA
461-R reverse	(291)	ATGAC <mark>N</mark> TCCACTTI	NCCTTTC:	TCTCCACA	GGTGTCCA	CTCCGACATC	GIGAIGACIC	AGTCCCCTG	ACTCCC <mark>N</mark> TGCG	GIGICCIIG	GGTGAACGCGCA
461-F	(289)	ATGACATCCACTTI	GCCTTTC	TCTCCACA	GGTGTCCA	CTCCGACATC	GIGATGACIC	AGTCCCCTG	ACTCCC TIGCO	GIGICCIIG	GTGAACGCGCA
Consensus	(295)	AIGACAICCACIII	GCCTTIC	ICICCACA	GGIGICCA	CICCGACAIC	GIGAIGACIC	AGICCCCIGA	ACTCCCTTGC0	GIGICCIIG	Section 5
	(000)	393 400	410	42	0 /	430	440	450	460	470	480 490
DART S2	(209)	ACCATCAACTGCAA	AGCCAGO	CAAGATGT	CTCAACCG	CONTRACTS	GTATCAGCAG	AAGCOGGGC	AGCCTCCAAA	GCTGCTGAT	TCATGGGCCAG
461-R reverse	(389)	ACCATCAACTGCAA	AGCCAGC	CAAGATGT	CTCAACCG	CCGTCGCCTG	GTATCAGCAG	AAGCCGGGCC	CAGCCTCCAAA	GCTGCTGAT	CTCATGGGCCAG
461-F	(387)	ACCATCAACTGCAA	AGCCAGC	CAAGATGT	CTCAACCG	CCGTCGCCTG	GTATCAGCAG	AAGCCGGGC	CAGCCTCCAAA	GCTGCTGAT	CTCATGGGCCAG
Consensus	(393)	ACCATCAACTGCAA	AGCCAGC	CAAGATGT	CTCAACCG	CCGTCGCCTG	GTATCAGCAG	AAGCCGGGCC	CAGCCTCCAAA	GCTGCTGATO	CICATGGGCCAG
		101 500	540		500	500	5.40	550	500	570	Section 6
DADT CO	(491)	491 500	510		520	530	540	550	560	570	588
JART 52	(307)	CACCOGCCATACGG	GAGIGCO	GGACCGGI	TOTOGGGG	TCGGGCAGCG	GAACCGACII	TACCOTCAC	TATCTCGTCGC	TCCAGGCGG	AGGACGIGGCIG
461-F	(485)	CACCCGCCATACGG	GAGTGCC	GGACCGGT	TCTCGGGG	TCGGGCAGCG	GAACCGACTT	TACCCTCACT	TATCTCGTCGC	TCCAGGCGG	AGGACGTGGCTG
Consensus	(491)	CACCCGCCATACGG	GAGTGCC	GGACCGGT	TCTCGGGG	TCGGGCAGCG	GAACCGACTT	TACCCTCACT	TATCTCGTCGC	TCCAGGCGG	AGGACGTGGCTG
											Section 7
											Gection 7
5 4 5 T 4 4	(589)	589 600)	610	620	630	640	650	660	670	686
DART S2	(589) (405)	589 600 TCTACTACTGCCA) GCAGCACT	610 ACACCACI	620 CCGCTGAC	630	640	650 TGGAAATCA	660	670	686 GGAGGAGAAGTG
DART S2 461-R reverse	(589) (405) (585)	589 600 TCTACTACTGCCAC TCTACTACTGCCAC) GCAGCACT GCAGCACT	610 ACACCACT ACACCACT	620 CCGCTGAC CCGCTGAC	630 TTTCGGACAA TTTCGGACAA	640 GGAACCAAAC GGAACCAAAC	650 TGGAAATCA TGGAAATCA	660 AAGGGGGGGGG AAGGGGGGGGGG	670 ATCCGGAGGC ATCCGGAGGC	686 GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG
DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (583)	589 600 TCTACTACTGCCAC TCTACTACTGCCAC TCTACTACTGCCAC TCTACTACTGCCAC) SCAGCACT SCAGCACT SCAGCACT SCAGCACT	610 ACACCACT ACACCACT ACACCACT ACACCACT	620 CCGCTGAC CCGCTGAC CCGCTGAC	630 TTTCGGACAA TTTCGGACAA TTTCGGACAA TTTCGGACAA	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC	650 TGGAAATCA TGGAAATCA TGGAAATCA	660 AAGGGGGGGG AAGGGGGGGGG AAGGGGGGGGG	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC	686 GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG
DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (583) (589)	589 600 TCTACTACTGCCAC TCTACTACTGCCAC TCTACTACTGCCAC TCTACTACTGCCAC) SCAGCACT SCAGCACT SCAGCACT SCAGCACT	610 ACACCACT ACACCACT ACACCACT ACACCACT	620 CCGCTGAC CCGCTGAC CCGCTGAC	630 TTTCGGACAF TTTCGGACAF TTTCGGACAF	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA	660 AAGGGGGGGG AAGGGGGGGG AAGGGGGGGGG	670 ATCCGGAGGC ATCCGGAGGC ATCCGGANGC ATCCGGAGGC	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG ——————————
DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (589) (589)	589 600 TCTACTACTGCCA TCTACTGCCA TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA 687 7) scagcact scagcact scagcact scagcact 700	610 ACACCACT ACACCACT ACACCACT ACACCACT ,710	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCTGAC	630 TTTCGGACAN TTTCGGACAN TTTCGGACAN TTTCGGACAN 730	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGAACCAAAC	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA 750	660 AAGGGGGGGG AAGGGGGGGG AAGGGGGGGGG 760	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC	686 GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG ——————————
DART S2 461-R reverse 461-F Consensus DART S2	(589) (405) (585) (583) (589) (589) (687) (503)	589 600 TCTACTACTGCCA(TCTACTACTGCCA(TCTACTACTGCCA(TCTACTACTGCCA(G87 7 CAACTCGTCGAGTC 7) GCAGCACT GCAGCACT GCAGCACT 700 CCGGTGGA	610 ACACCACT ACACCACT ACACCACT ACACCACT ,710 GGCCTGGT	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCTGAC 720 CGCAGCCGG	630 TTTCGGACAN TTTCGGACAN TTTCGGACAN TTTCGGACAN 730 GAAACTCAC1	640 СССАРАССАРАС СССАРАССАРАС СССАРАССАРАС	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA 750 TGTGTGGCA	660 AAGGGGGGGG AAGGGGGGGG AAGGGGGGGGG 760 TCCGGCTTTA	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC .770 CCTTCTCGAA	686 GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG — Section 8 784 CTACGGGATGCA
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse	(589) (405) (585) (583) (589) (589) (687) (503) (683)	589 600 TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA CTACTACTGCCA 687 7 CAACTCGTCCAGTC) SCAGCACT SCAGCACT SCAGCACT SCAGCACT 700 CCGGTGGA	610 ACACCACT ACACCACT ACACCACT ACACCACT ,710 GGCCTGGT GGCCTGGT	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCTGAC CCGCTGAC 720 CGCAGCCGG	630 TITCGGACAN TITCGGACAN TITCGGACAN TITCGGACAN 730 GAAACTCACI GAAACTCACI	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGAACCAAAC 740 GACCCTGTCG GACCCTGTCG	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA 750 TGTGTGGCA	660 AAGGGGGGGG AAGGGGGGGG AAGGGGGGGG 760 TCCGGCTTTA TCCGGCTTTA	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC ,770 CCTTCTCGAA	686 GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-R reverse	(589) (405) (585) (583) (589) (589) (687) (683) (683) (681)	589 600 TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA CTACTACTGCCA 687 7 CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT) SCAGCACT SCAGCACT SCAGCACT 700 CCGGTGGA CCGGTGGA	610 ACACCACT ACACCACT ACACCACT ACACCACT ,710 GGCCTGGT GGCCTGGT GGCCTGGT	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCTGAC CCGCTGAC CGCAGCCGG CGCAGCCGG	630 TITCGGACAN TITCGGACAN TITCGGACAN TITCGGACAN 730 GAAACTCACI GAAACTCACI GAAACTCACI	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGAACCAAAC 740 GACCCTGTCG GACCCTGTCG	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA 750 TGTGTGGCA TGTGTGGCA	660 AAGGGGGGGG AAGGGGGGGG AAGGGGGGGG 760 ICCGGCTTTA ICCGGCTTTA	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC 	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAGAGTG Section 8 784 CTACGGGATGCA CTACGGGATGCA
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (589) (589) (583) (503) (683) (681) (687)	589 600 TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT) SCAGCACT SCAGCACT SCAGCACT SCAGCACT 700 CCGGTGGA CCGGTGGA CCGGTGGA	610 ACACCACT ACACCACT ACACCACT ACACCACT 710 GGCCTGGT GGCCTGGT GGCCTGGT	620 CCCCCTGAC CCCCCTGAC CCCCCTGAC CCCCCTGAC CCCCCCGCTGAC CCCCCCCGC CCCCCCCGC CCCCCCGC CCCCCCGG CCCCCC	630 TTTCGGACAA TTTCGGACAA TTTCGGACAA TTTCGGACAA 730 GAAACTCACT GAAACTCACT GAAACTCACT	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC 740 GACCCTGTCG GACCCTGTCG GACCCTGTCG GACCCTGTCG	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA 750 TGGTGTGGCA TGTGTGGCA TGTGTGGCA	660 AAGGGGGGGG AAGGGGGGGG AAGGGGGGGGG 760 TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC 770 CCTTCTCGAA CCTTCTCGAA CCTTCTCGAA	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGGAAGTG Section 8 784 CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA Section 9
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (583) (589) (687) (683) (687)	589 600 TCTACTACTGCCA ICTACTACTGCCA ICTACTACTGCCA CAACTCGCCAGT CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT) SCAGCACT SCAGCACT SCAGCACT SCAGCACT COCGTGGA CCGGTGGA CCGGTGGA CCGGTGGA	610 ACACCACT ACACCACT ACACCACT ACACCACT ,710 GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT	620 CCCCCTGAC CCCCCTGAC CCCCCTGAC CCCCCTGAC CCCCCCGAC CCCCCCGAC CCCCCCGC CCCCCCGC CCCCCCGC CCCCCCGC CCCCCC	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGAACCAAAAC 740 GACCCTGTCG GACCCTGTCG GACCCTGTCG	650 TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA 750 TIGTGTGGCA TIGTGTGGCA TIGTGTGGCA	660 AAGGGGGGGG AAGGGGGGGG AAGGGGGGGGG 760 TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC 770 CCTTCTCGAA CCTTCTCGAA CCTTCTCGAA	Section 7 686 GGACGAGAAGTG GGACGAGAAGTG GGACGAGAAGTG GGACGAGAGAGTG 784 CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CTACGGATGCA CT
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (589) (589) (687) (687) (687) (687) (687)	589 600 TCTACTACTGCCA ICTACTACTGCCA ICTACTACTGCCA ICTACTACTGCCA ICTACTGCCGCA CACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT	CAGCACT SCAGCACT SCAGCACT SCAGCACT 700 CCGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA 800	610 ACACCACT ACACCACT ACACCACT 710 GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT 810	620 CCCCCTGAC CCCCCTGAC CCCCCTGAC CCCCCTGAC CCCCCCGC CCCCCCGC CCCCCCGC CCCCCCGC CCCCCC	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT O 833	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGACCCAAAC 740 GACCCTGTCC GACCCTGTCC GACCCTGTCC GACCTGTCC GACCTGTCC GACCTGTCC 0 844	650 TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGTGTGGCA TIGTGTGGCA TIGTGTGGCA TIGTGTGGCA 0 88	,660 RAGGGGGGGG RAGGGGGGGG RAGGGGGGGGG 760 TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC CTTCTGGAA CCTTCTGGAA CCTTCTGGAA CCTTCTGAA	GGACGAGAAGTG GGACGAGAAGTG GGACGAGAAGTG GGACGAGAAGTG GGACGAGAAGTG CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA Section 9 70 882 CTAAGGGATGCA
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-B reverse	(589) (405) (585) (583) (589) (589) (687) (687) (687) (687) (687) (687) (687)	589 600 ICTACTACTOCCA ICTACTACTOCCA ICTACTACTOCCA ICTACTACTOCCA ICTACTACTOCCA ICTACTOCCCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTOCTOCACT CTGCATTAGACAA ICTGCATTAGACAA	CAGCACT SCAGCACT SCAGCACT SCAGCACT SCAGCACT COGGTGGA CCGGTGGA CCGGTGGA 800 SCTCCCAA	610 ACACCACI ACACCACI ACACCACI ACACCACI ACACCACI GGCCIGGI GGCCIGGI GGCCIGGI GGCCIGGI B10 GAAGGGA-	620 CCCGCTGAC CCCGCTGAC CCCGCTGAC CCCGCTGAC CCCGCCGG CCCGCCGG CCCGCCGG CCCGCCGG CCCGCCG	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP 730 GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC 740 GACCTGTCC GACCTGTCC GACCTGTCC GACCTGTCC GACCTGTCC GACCTGTCC 0 84 ATCTACTACC	650 IIGGAAICA IIGGAAICA IIGGAAICA IIGGAICA IIGGAIGGCA IIGIGIGGCA IIGIGIGGCA 0 88 AIAGCICGA	,660 Arcsccscscs Arcsccscscs Arcsccscs Arcsccscs Arcsccscs Arcsccs Arcsccs Arcsccs Arcsccs Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcsccc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc Arcscc A	670 ATCCGGAGC ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC COTTCTGAA COTTCTGAA COTTCTGAA COTTCTGAA COTTCTGAA COTTCTGAA	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGATGCA Section 9 70 882 GTCAAGGGAA-G GTCAAGGGAA-G
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F	(589) (405) (585) (583) (589) (583) (583) (503) (683) (683) (681) (687) (785) (601) (785) (779)	589 600 TCTACTACTGCCA 1000 TCTACTACTGCCA 1000 TCTACTACTGCCA 1000 687 1000 CARCTCGTCGAGT 1000 CARCTCGTCGAGT 1000 CARCTCGTCGAGT 1000 TCGATTGGCAGT 1000 TCGATTGGCAGT 1000 CTGGATTAGACAA 1000 CTGGATTAGACAA 1000) SCAGCACT SCAGCACT SCAGCACT SCAGCACT CCGGTGGA CCGGTGGA CCGGTGGA 800 SCTCCCAA SCTCCCAA	610 ACACCACI ACACCACI ACACCACI ACACCACI GGCCIGGI GGCCIGGI GGCCIGGI B10 GAAGGGA- GAAGGGA- GAAGGGA-	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCCGCCGC GCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG TGGAATG TTGGAATG	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GAACTCACT GATCGCCATC GATCGCCATC	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGACCTGTCC GACCCTGTCC GACCCTGTCC GACCCTGTCC GACCCTGTCC GACCCTGTCC GACCTGTCC GACCTGTCC 0 84 ATCTACTACCA	650 TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGATGGCA TIGTGTGGCA TIGTGTGGCA TIGTGTGGCA 0 88 ATAGCTCGA ATAGCTCGA	660 AACCGCGCCC AACCGCGCCCC AACCGCCCCCC TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA	670 ATCCGGAGGC ATCCGGAGGC ATCCGGAGGC CTTCTGGAA CCTTCTGGAA CCTTCTGGAA CCTTCTGGAA CCTTCTGGAA	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG Section 8 784 CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA Section 9 70 882 GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (589) (687) (503) (683) (683) (681) (687) (687) (687) (785) (785) (785) (785)	589 600 TCTACTACTGCCA ICTACTACTGCCA ICTACTACTGCCA ICTACTACTGCCA ICTACTCCCGCA CACTCGTCGACT CAACTCGTCGACT CAACTCGTCGACT 785 790 CTGGATTAGACAA CTGGATTAGACAAC CTGGATTAGACAAC	CAGCACT SCAGCACT SCAGCACT SCAGCACT COCGTGGA CCGGTGGA CCGGTGGA CCGGTGGA 800 SCTCCCAA SCTCCCAA SCTCCCAA	610 ACACCACI ACACCACI ACACCACI ACACCACI GGCCIGGI GGCCIGGI GGCCIGGI B10 GAAGGA- GAAGGA- GAAGGA- GAAGGA	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCCGGC CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCG CCAGCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCG CCAGCG CCAGCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCG CCAGCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCG CCAGCG CCAGCG CCAGCCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCCG CCAGCCG CCAGC CCAGC CCAGCCG CCAGCCG CCAGCCG CCAGC CCAGC CCAGCCG CCAGCCG CCAGCCG CCAGC CCAGC CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGC CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCCG CCAGCC	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GATCGCCATG GATCGCCATG GATCGCCATG	640 GGAACCAAAG GGAACCAAAG GGAACCAAAG GGACCTGAAG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG ACTTACTACG ATCTACTACG	650 IIGGAAATCA IIGGAAATCA IIGGAAATCA IIGGAAATCA IIGGAAATCA IIGGGTGGCA IIGTGTGGCA IIGTGTGGCA IIGTGTGGCA IIGTGTGGCA AITAGCTCGA AITAGCTCGA AITAGCTCGA	660 AACCGCGCGCC AACCGCGCGCC AACCGCGCGCCC AACCGCGCCCC TCCGGCTITA TCCGGCTITA TCCGGCTITA TCCGGCTITA ACATGAATTA ACATGAATTA ACATGAATTA	670 ATCCGAGCC ATCCGAGCC ATCCGAGCC TCCGAGCC TCCGAGCC CCTCTCGAA CCTTCTGAA CCTTCTGAA CCTTCTGAA CCTTCTGAA CCTTCTGAA CCTTCTGAA CCTCCGGACACT	CIACGGARAGTG GGACGAGAAGTG GGACGAGAAGTG GGACGAGAAGTG GGACGAGAAGTG GGACGGAGAGTGCA
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (583) (583) (503) (683) (683) (681) (687) (687) (785) (601) (785) (785)	589 600 ICTACTACTOCCA ICTACTACTOCCA ICTACTACTOCCA ICTACTACTOCCA ICTACTACTOCCA ICTACTOCCCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTOCTOCACT CAACTOCTOCACT ICTACTACTOCACT CAACTOCTOCACT ICTACTACTOCACT CTGCATTAGACAA ICTGCATTAGACAA CTGCATTAGACAA ICTGCATTAGACAA) CCAGCACT SCAGCACT SCAGCACT SCAGCACT 700 CCGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA SCTCCCAA SCTCCCAA	610 ACACCACT ACACCACT ACACCACT ACACCACT 710 GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT 810 GAACGGA- GAACGGA- GAACGGA	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCCGAC CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG TGGAATG TTGGAATG TTGGAATG	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP 730 GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GATCGCCATC GATCGCCATC GATCGCCATC	640 GGAACCAAAG GGAACCAAAG GGAACCAAAG GGACCTGTCG GACCCTGTCG GACCCTGTCG GACCCTGTCG GACCCTGTCG GACCCTGTCG GACCCTGTCG GACCTGTCG ATCTACTACG ATCTACTACG ATCTACTACG	650 TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGAAATCACA TIGGATGGCA TIGGATGGCA TIGGATCGA TIAGCTCGA TIAGCTCGA	660 AACCGGGGGG AACCGGGGGGG AACCGGGGGGG AACCGGGGGGG AACCGGGGGGG TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA TCCGGCTTTA CGATGAATTA AGATGAATTA AGATGAATTA	670 ATCCGGAGCC ATCCGGAGCC ATCCGGAGCC TCCGGAGCC TCCGGAGCC CCTCCGAA CCTTCTGAA CCTTCTGAA CCTTCTGAA CCTTCTGAA CCTTCTGAA CCTCCGAACCT CCGGGACACT	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G GTCAAGGGAA-G
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (583) (583) (583) (583) (687) (683) (681) (687) (687) (687) (785) (601) (785) (785) (785) (785)	589 600 TCTACTACTGCCA 100 TCTACTACTGCCA 100 TCTACTACTGCCA 100 687 100 CAACTCGTCGAGT 100 CAACTCGTCGAGT 100 CAACTCGTCGAGT 100 785 790 CTGGATTAGACAAC 100 CTGGATTAGACAAC 100 CTGGATTAGACAAC 100 CTGGATTAGACAAC 100 883 890) GCAGCACT GCAGCACT GCAGCACT GCAGCACT 700 CCGGTGGA CCGGTGGA CCGGTGGA 800 GCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA	610 ACACCACT ACACCACT ,710 GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT B10 GAACGGA GAACGGA GAACGGA GAACGGA GAACGGA	620 CCGCTGAC CCGCTGAC CCGCTGAC CCGCTGAC CCGCCGC CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCGG CCAGCCG CCAGCCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGC CCAGCG CCAGC CCAGCG CCAGCG CCAGCG CCAGC CCAGCG CCAGCG CCAGCG CCAGC CCAGCG CCAGCG CCAGCG CCAGC CCAGCG CCAGCG CCAGCG CCAGC CCAGCG CCAGC CCAGCG CCAGCG CCAGCG CCAGC CCAGCG CCAGC CCAGC CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGCG CCAGC CCAGC CCAGCG CCAGC CCAGC CCAGCG CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC CCAGC C	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP 730 GAAACTCACT GAAACTCACT GAAACTCACT 0 83 GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC	640 GGAACCAAAG GGAACCAAAG GGAACCAAAG GGAACCAAAG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG 0 84 MICTACTACG MICTACTACG 930	650 TIGGAAATCA TIGGAAATCA TIGGAAATCA TIGGATCA TIGGTGGCA TIGTGTGGCA TIGTGTGGCA TIGTGTGGCA TIGTGTGGCA 0 88 ATAGCTCGA ATAGCTCGA ATAGCTCGA 940	660 AACCGCGCCCC AACCGCGCCCCC AACCGCGCCCCCC AACCGCCCCCCCC	670 ATCCGARGC ATCCGARGC ATCCGARGC ATCCGARGC CTTCTCGAR CTTCTCGAR CTTCTCGAR CTTCTCGAR CTTCTCGAR CTTCTCGAR CTTCTCGAR CTTCTCGAR CTTCTCGAR CCCGGACACT CCCGGACACT	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAGAGTG Section 8 784 CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGATGCA GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (589) (583) (687) (503) (687) (687) (687) (687) (687) (687) (687) (687) (687) (785) (697) (785) (697)	589 600 TCTACTACTGCCA 100 TCTACTACTGCCA 100 TCTACTACTGCCA 100 687 100 CAACTCGTCGAGTG 100 CAACTCGTCGAGTG 100 CAACTCGTCGAGTG 100 CAACTCGTCGAGTG 100 CTGGATTAGACAAG 100 CTGGATTAGACAAG 100 CTGGATTAGACAAG 100 CTGGATTAGACAAG 100 SB3 890 GTTCACTATTCCC 100	BCAGCACT SCAGCACT SCAGCACT SCAGCACT SCAGCACT 700 CCGGTGGA CCGGTGGA B00 SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA	610 ACACCACT ACACCACT ACACCACT 710 GGCCTGGT GGCCTGGT GGCCTGGT GGACGGA GAACGGA GAACGGA GAACGGA 91 CTCAAAGA	620 CCCCTGAC CCCGCTGAC CCCCCGAC CCCCCGAC CCCCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC TTGGAATG TTGGAATG TTGGAATG	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT 0 83 GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG	640 GGAACCAAAG GGAACCAAAG GGAACCAAAG GGACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGC GACCTGC GACCTGC GACCTGC GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACG GACG GACG GACG GACG GACCG GACG GACG GACCG GACCG GACCG GACCG GACG GACG GACCG GACCG GACG GACG GACCG GACG GACCG GACCG GACCG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACCG GACG GACG GACG GACG GACG GACG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACCG GACG GACCG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG GACG	650 IIGGAAATCA IIGGAAATCA IIGGAAATCA IIGGAAATCA IIGIGIGGGCA IIGIGIGGCA IIGIGIGGCA IIGIGIGGCA IIGIGIGGCA IIGIGIGCCA ATAGCICGA ATAGCICGA ATAGCICGA ATAGCICGA ATAGCICGA	660 AACCGCGCCCC AACCGCGCCCCC AACCGCCCCCCCCC	670 ATCCGAGCC ATCCGAGCC ATCCGAGCC TCCGAGCC TCCGAGCC CTTCTCGAA CCTTCTCGAA CCTTCTCGAA CCTTCTCGAA CCTTCTCGAA CCTCTCGAA CCTCTCGAA CCTCCGGACACT CCCGGACACT CCCGGACACT	Section 9 70 882 CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCACSGATGCA CTCCCCCCCCA CTCACSGATGCA CTCCCCCCCA CTCCCCCCA CTCCCCCCA CTCCCCCCA CTCCCCCCCA CTCCCCCCA CTCCCCCCA CTCCCCCCA CTCCCCCCCA CTCCCCCCCA CTCCCCCCCA CTCCCCCCCA CTCCCCCCCCA CTCCCCCCCCA CTCCCCCCCCCA CTCCCCCCCCCA CTCCCCCCCCCC
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DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F	(589) (405) (585) (583) (583) (583) (583) (683) (683) (683) (687) (687) (785) (601) (785) (697) (785) (785) (883) (697) (877) (877) (877)	589 600 TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA CTACTACTGCCA 687 7 CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT 785 790 CTGGATTAGACAAC CTGGATTAGACAAC CTGGATTAGACAAC CTGGATTAGACAAC CTGGATTAGACAAC	CCGGCCAA SCAGCACT SCAGCACT SCAGCACT SCAGCACT CCGGTGGA CCGGTGGA SCGCGCGA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA 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GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATC GACG GATCGCCATC GAC GAC GAC GAC GAC GAC GAC GA	640 GGAACCAAAG GGAACCAAAG GGAACCAAAG GGAACCAAAG 740 GACCCIGICG GACCCIGICG GACCCIGICG GACCCIGICG 0 84 AICIACIACG AICIACIACG AICIACIACG 930 IIGAATAGCCI IIGAATAGCCI IIGAATAGCCI	650 ITGGAAATCA ITGGAAATCA ITGGAAATCA ITGGAAATCA ITGGTGGCA ITGGTGGCA 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GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC 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DART S2 461-R reverse 461-F Consensus 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse	(589) (405) (583) (583) (583) (583) (681) (687) (785) (681) (785) (785) (785) (785) (785) (785) (785) (785) (785) (883) (697) (975)	589 600 TCTACTACTGCCA 100 TCTACTACTGCCA 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 <tr td=""></tr>	CGGACCA CGGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA 800 CCCGGTGGA 800 CCCCCAA CCGGTCCAA CCCCCAA CCCCCAA CCCCCAA CCCCCAA CCGGACCA CGGACCAA CGGGACAA	610 ACACCACT ACACCACT ACACCACT 710 GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT GACGCA- GAACGCA- GAACGCA- GAACGCA- 91 CTCAAACA CTCAAACA CTCAAACA CTCAAACA	620 CCCCTGAC CCCCTGAC CCCCTGAC CCCCTGAC CCCCTGAC CCCCCGCGAC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC TTGGAATG TTGGAATG TTGGAATG TTGGAATG TTGGAATG TTGGAATG TTGGAATG TACGCTC IATACGCTC IATACGCTC IATACGCTC CAAGGCGT	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP 730 GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC 920 TACCTTGACF TACCTTGACF TACCTTGACF 1020 GTCAGTTACT	640 GGAACCAAAG GGAACCAAAG GGAACCAAAG GGAACCAAAG GGACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG GACCTGTCG 0 84 %TCTACTACG %TCTACTACG 930 TGAATAGCCT TGAATAGCCT TGAATAGCCT TGAATAGCCT 1GAATAGCCT 1GAATAGCCT 1GAATAGCCT	650 ITGGAAATCA ITGGAAATCA ITGGAAATCA ITGGAAATCA ITGGACGCA ITGTGTGGCA ITGTGTGGCA ITGTGTGGCA ITGTGTGGCA 0 88 ITGTGTGGCA 0 88 ITGTGTGGCA ITGGACGACGA GAGAAGCGA GAGAAGCGA ITGGAACCAA ITGGAACCAA	660 AACCGCGCGCG AACCGCGCGCG AACCGCGCGCGG AACCGCGCGCG	670 ATCCGAGCC ATCCGAAGCC ATCCGGAGCC TCCGGAGCC CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CCTCCTGAA CCCGGACACT CCCGGACACT CCCGGACACT CCCGGACACT CCCGGACACT 960 ATCTACTACTACT ATCTACTACTACT ATCTACTACT ATCTACTACT	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGGAGGAG Section 8 784 CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA Section 9 70 882 GTCAAGGAA-G GTCAAGGAA-G GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG GTCAAGGAAAG CAAGCGTCCCAA GGCCGTCCCAA CGCCGTCCCAA
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DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R reverse 461-R consensus	(589) (405) (583) (583) (583) (583) (687) (687) (687) (785) (785) (785) (785) (883) (697) (887) (887) (883) (697) (975) (975) (975)	589 600 TCTACTACTOCCAN TCTACTACTOCCAN TCTACTACTOCCAN TCTACTACTOCCAN TCTACTACTOCCAN TCTACTACTOCCAN CAACTOCTCCAGTT CAACTOCTCCAGTT CAACTOCTCCAGTO TCGATTAGACAAC 785 790 CTGCATTAGACAAC CTGCATTAGACAAC CTGCATTAGACAAC CTGCATTAGACAAC 883 890 GTTCACTATTTCCC GTTCACTATTTCCC GTTCACTATTTCCC GTTCACTATTTCCC GTCCCCATTAGCTA 981 990 CCTCCCATTAGCTACAGTO CCTCCCATTAGCTACAGTO	CGGACAA CGGACACT CCAGCACT CCAGCACT CCGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA CCGGACAA CGGGACAA CGGGACAA CGGGACAA CGGGACAA	610 ACACCACT ACACCACT ACACCACT ACACCACT ,710 GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT B10 GAAGGGA GAAGGGA GAAGGGA GAAGGGA GAAGGGA GAAGGGA 00 TGTGGGGC TGTGGGGGC TGTGGGGGC	620 CCCCTGAC CCCCTGAC CCCCTGAC CCCCGGAC CCCCCGAC CCCCCGCGAC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CACCCGC CACCCCC LATACGCTC LATACGCTC LATACGCTC LATACGCTC LATACGCTC LATACGCTC LATACGCTC CAACGCTC CCACGCCCCCCCCCCCCCCCCC	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP 730 GAAACTCACT GAAACTCACT GAAACTCACT 0 83 GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GATCGCCATC GCACTTGACP TACCTTGACP TACCTTGACP TACCTTGACP TACCTTGACP TACCTTGACP TACCTTGACP	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGAACCAAAC GACCTGTCC GACCTGTCC GACCTGTCC GACCTGTCC 0 84 ATCTACTACCAC ATCTACTACCAC ATCTACTACCAC JOO IGAATAGCCT IGAATAGCCT IGAATAGCCT IGAATAGCCT IGAATAGCCT IGAATAGCCT IGAATAGCCT IGAATAGCCT	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA TGGATCA TGGTGCGCA TGTGTGCGCA TGTGTGCGCA TGTGTGCGCA TGTGTGCCA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA TGGAACCAA ,1040 TGGAACCAA TGGAACCAA	660 AACCGCGCGCC AACCGCGCGCC AACCGCGCGCCC AACCGCGCGCCC TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTTA TCCGCCTTA SACATGATTA SACATGATTA SACATGATTA SACATGATTA SACATGATTA SACATGATTA SACATGATTA SACATGATTA SACATGATTA SACATGATTA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SACATGATCA SA	670 ATCCGGAGCC ATCCGGAGCC ATCCGGAGCC ATCCGGAGCC CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CCTCTCGAA CCCGGACACT CCCGGACACT CCCGGACACT CCCGGACACT ACCGCGCACACT 1060 ACCGCCCCC ACCGCCCCC ACCGCCCCC ACCGCCCCC	GGACGAGAAGTC GGACGAGAAGTC GGACGAGAAGTG GGACGAGAGAGTG Section 8 784 TACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGATGCA CTACGGATGCA Section 10 970 980 GGCCGTCCCAA GCCCGTCCCAA GCCCGTCCCAA Section 10 NNN Section 12 CGANTCTAGNNA
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus 461-R reverse 461-F Consensus	(589) (405) (583) (583) (583) (583) (583) (583) (503) (681) (681) (681) (681) (681) (681) (687) (785) (687) (779) (785) (883) (697) (883) (981) (795) (975) (981)	589 600 TCTACTACTGCCAX CTACTACTGCCAX TCTACTACTGCCAX CTACTACTGCCAX 687 CARCTCGTCGAGT CACTCGTCGAGT CARCTCGTCGAGT CACTCGTCGAGT 785 790 CTGGATTAGACAAX CTGGATTAGACAAX CTGGATTAGACAAX CTGGATTAGACAAX CTGGATTAGACAAX CTGGATTAGACAAX 083 890 GTTCACTATTTCCC GTTCACTATTTCCC 981 990 CCTCCCATTAGGT CCTCCCATTAGGT 081 990 CCTCCCATTAGGT CCTCCCATTAGGT 1070 100	CGGGCGACACT CCAGCACT CCAGCACT CCGGCTGGA CCGGTGGA CCGGTGGA CCGGTGGA CCGGTGGA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA SCTCCCAA CCGGACAA CCGGACAA CGGGACAA CGGGACAA CGGGACAA	610 ACACCACT ACACCACT ACACCACT 710 GGCCTGGT GGCCTGGT GGCCTGGT 810 GAACGCA- 810 GAACGCA- 91 CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA 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GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAA-G GTCAAGGCAAGGAA-G GTCAAGGCAAGGAA-G GTCAAGGCAAGGAA-G GTCAAGGCAAGGAA-G GTCAAGGCAAGGAA-G GTCAAGGCAAGAAGAAGAAGAAGAAGAAGAAGAAGAAGAAGA
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CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAAGA CTCAAACAAAGA CTCAAACAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAACAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAAGA CTCAAAGAAAGA CTCAAAGA	620 CCCCTGAC CCCCTGAC CCCCTGAC CCCCTGAC CCCCCGAC CCCCCGAC CCCCCGAC CCCCCGAC CCCCCGAC CCCCCGAC CCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCCGAC CCCCCCGAC CCCCCCGAC CCCCCCCGAC CCCCCCCG CCCCCCCG CCCCCCCG CCCCCCCG CCCCCCCC	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP 730 GAAACTCACT GAAACTCACT GAAACTCACT GAAACTCACT GAACTCACT GAACTCACT GAACTCACT GATCGCCATC GATCGCCATC GATCGCCATC 920 TACCTTGACF TACCTTGACF TACCTTGACF TACCTTGACF 1020 GTCACTTACT GTCACTTACT GTCACTTACT GTCACTTACT 1120	640 GGAACCAAAC GGAACCAAAC GGAACCAAAC GGAACCAAAC GACCCIGICG GACCCIGICG GACCCIGICG GACCIGICG GACCIGICG AICTACIACA AICTACIACA AICTACIACA AICTACIACA GIGAATAGCCI IGAATAGCCI IGAATAGCCI ,1030 GIGAGCICAC GIGAGCICAC 1130	650 TGGAAATCA TGGAAATCA TGGAAATCA TGGAAATCA TGGATCA TGGTGTGGCA TGTGTGGCA TGTGTGGCA TGTGTGGCA TGTGTGGCA TGTGTGGCA TGTGTGCCA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA ATAGCTCGA TGGAACCAA TGGAACCAA TGGAACCAA TGGAACCAA TGGAACCAA TGGAACCAA	660 AACGGGGGGG AACGGGGGGGG AACGGGGGGGG AACGGGGGGGG	670 ATCCGGAGCC ATCCGGAGCC ATCCGGAGCC ATCCGGAGCC CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CTTCTCGAA CCTCCGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGACACT GCGGCCCC ,1160	GGACGAGAAGTC GGACGAGAAGTC GGACGAGAAGTC GGACGAGAAGTC Section 8 784 CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA CTACGGGATGCA GTCAAGGGAA GTCAAGGGAAG GTCAAGGGAAG GTCAAGGGAAG GTCAAGGGAAG GCCCGTCCCAA GGCCGTCCCAA GGCCGTCCCAA GGCCGTCCCAA GGCCGTCCCAA MINNNAANAGA Section 12 1176 1176
DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus DART S2 461-R reverse 461-F Consensus	(589) (405) (585) (583) (583) (687) (503) (683) (683) (683) (683) (781) (781) (779) (785) (883) (697) (877) (877) (877) (877) (877) (877) (879) (975) (975) (975) (975) (975) (971) (1079) (880)	589 600 TCTACTACTGCCA TCTACTACTGCCA TCTACTACTGCCA CTACTACTGCCA 687 7 CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT CAACTCGTCGAGT 785 790 CTGGATTAGACAA CTGGATTAGACAA CTGGATTAGACAA CTGGATTAGACAA CTGGATTAGACAA CTGGATTAGACAA CTGGATTAGACAA CTGGATTAGACAA CTGGATTAGACAA 05 700 CTGCATTAGCAA 05 700 CTGCATTAGCAA 05 700 CTGCATTAGCAA 05 700 CTGCATTAGCAA 05 700 CTGCATTAGCAA 05 700 CTGCATTAGCAA 05 700 CTGCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA 05 700 CTCCCATTAGCAA	CGGACAA CGGGTGGA CGGGTGGA CGGGTGGA CGGGTGGA CGGGTGGA CGGGTGGA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCAA SCCCCCCAA SCCCCCCAA SCCCCCCAA SCCCCCCAA SCCCCCCAA SCCCCCCAA SCCCCCCAA SCCCCCCAA SCCCCCCCC	610 ACACCACT ACACCACT ACACCACT ACACCACT GGCCTGGT GGCCTGGT GGCCTGGT GGCCTGGT B100 GAAGGGA GAAGGGA GAAGGGA GAAGGGA (TCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAGA CTCAAAG	620 CCCCTGAC CCCCTGAC CCCCTGAC CCCCGCGAC CCCCCGCGAC CCCCCGCGAC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC CCACCCGC TIGGAATG TIGGAATG TIGGAATG TIGGAATG TIGGAATG TIGGAATG TIGGAATG CACCCCC ACACCCCC ACACCCCC CACCCCCCCACGCCC IIIIO	630 TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP TTTCGGACAP 730 GAAACTCACT GAAACTCACT GAAACTCACT 0 82 GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GATCGCCATG GTCACTTGACF TACCTTGACF TACCTTGACF TACCTTGACF TACCTTGACF TACCTTGACF TACCTTGACF TACCTTGACF TACCTTGACF 1020 GTCACTTACT GTCACTTACT GTCACTTACT 1120 	640 GGAACCAAAG GGAACCAAAG GGAACCAAAG GGAACCAAAG GGAACCAGTG GACCTGTCC GACCTGTCC GACCTGTCC 0 84 ATCTACTACCA ATCTACTACCA 930 ITGAATAGCCT ITGAATAGCCT ITGAATAGCCT ITGAATAGCCT 1030 GTGACCTCAG GTGACCTCAG GTGACCTCAG 1130	650 ITGGAAATCA ITGGAAATCA ITGGAAATCA ITGGAAATCA ITGGACGCA ITGGTGGCA ITGTGTGGCA ITGTGTGGCA ITGTGTGGCA 0 88 ITAGCTCGA ITGTGTGCCA ITGGACCCAA ITAGCTCGA ITGGACCCAA ITGGACCCAA ITGGACCCAA ITGGACCAA ITGGACCAA ITGGACCAA ITGGACCAA ITGGACCAA	660 AACCGCGCCCC AACCGCGCCCCC AACCGCCCCCCCCC	670 ATCCGGAGCC ATCCGGAGCC ATCCGGAGCC CTTCTGGAA CTTCTGGAA CTTCTGGAA CTTCTGGAA CTTCTGGAA CTTCTGGAA CTTCTGGAA CTTCTGGAA CTTCTGAA 30 80 80 80 80 80 80 80 80 80 8	GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG GGAGGAGAAGTG — Section 8 TACGGGATGCA CTACGGGATGCA CTACGGGATGCA — Section 10 970 980 GCCCGTCCCAA GCCAAGGAAAG GTCAAGGAAAG GTCAAGGCAAGAA GCCCGTCCCAA GCCCGTCCCAA GCCCGTCCCAA GCCCGTCCCAA Section 11 1078 Section 11 1078 Section 11 1078 Section 11 1078 Section 11 1078 Section 11 1078 Section 11 1176 NNNNNNANANGC N N Section 11 1176

APPENDIX C FIGURE 13: SEQUENCE COMPARISON OF E16-8D3 DIABODY CONSTRUCTS

A) pE60 IgG1 HV

												section 1
E60 HV-lgG1 DVE60-VH-R rev	(1) (1) (1)	1	,10	20	,30	40	,50	60 <mark>GRATT</mark>	70 Cacaatggga	80 IGGICIIGIAI	CATCOIT	96 ITCIIGG
DVE-6-VH-FF Consensus	(1) (1)	NNNNNN	NNNNNNNN	INNNANNACT	IIIIGIICI	TATTGTTGC	AGGTACCAI	IGGCA <mark>GAATI</mark> GAATI	CACAATGGGA CACAATGGGA	IGGTCITGIAT	CATCOIT:	FETTER FETTER Section 2
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(97) (41) (1) (97) (97)	97 TIGCAAC TIGCAAC TIGCAAC	AGCTACTCC AGCTACTCC AGCTACTCC	12 IGTICATIC IGTICATIC) [1 IGAGGICCA IGAGGICCA IGAGGICCA	30 GGTGCAACA GGTGCAACA GGTGCAACA	140 GTCTGGACC GTCTGGACC GTCTGGACC	150 TGAACTGGT TGAACTGGT	160 GACGCCTGGG GACGCCTGGG	170 DCCTCAGTGAA DCCTCAGTGAA	180 CATATOCI CATATOCI CATATOCI	192 IGCAAGA IGCAAGA IGCAAGA
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(193) (137) (1) (193) (193)	193 сттетор сттетор сттетор	200 ATACACITI ATACACITI	210 CACTGAATA CACTGAATA	220 TACCGTCCA TACCGTCCA TACCGTCCA	230 CTGGGTGAA CTGGGTGAA CTGGGTGAA	240 GCAGAGCCS GCAGAGCCS GCAGAGCCS	250 ATGGAAAGAG ATGGAAAGAG	260 CCTTGAGTGG CCTTGAGTGG	270 ATTGGAGGCAT ATTGGAGGCAT	TAATCOT	288 ACCAGTG ACCAGTG
E60 HV-lgG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(289) (233) (1) (289) (289)	289 GIGGIAC GIGGIAC	300 TAACTACAP TAACTACAP	310 CCAGAGGTT CCAGAGGTT	320 CAGGGGGCAA CAGGGGGCAA CAGGGGGCAA	33 GGCCACATT GGCCACATT GGCCACATT	0 SACTGTAGS GACTGTAGS GACTGTAGS	340 ACAGGTOCTO ACAGGTOCTO	350 CAGCACAGCO CAGCACAGCO CAGCACAGCO	360 37 TACATGGAGCT TACATGGAGCT TACATGGAGCT	70 CCGCAGCO NNNNNCJ CCGCAGCO CCGCAGCO	384 SIGACAT ANNNNNN SIGACAT SIGACAT
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(385) (329) (14) (385) (385)	385 39 CTGAGGA NNTNNNN CTGAGGA CTGAGGA	0 4	CTATTITG	410 TCCACGAAC NNNNCNNNC TCCACGAAC TCCACGAAC	420 CCTCTATGG NNNNNN CCTCTATGG CCTCTATGG	430 CTACCCTTI NNNCCTI CTACCCTTI	440 TIGACITCIC TIGANINN TIGACITCIC	450 GGGCCAAGGC GGGCCAAGGC GGGCCAAGGC	460 ACCACTCTC NNNCCNTNNNN ACCACTCTC A CCACTCTC	470 ACAGICIO NCNNNINO ACAGICIO ACAGICIO	480 CTCAGC NNNANN CTCAGC CTCAGC Section 6
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(481) (423) (104) (479) (481)	481 TAGCACO TAGCNNO TAGCACO TAGCACO	490 AAGGGACCT NNGGGNCCT AAGGGACCT	500 TCTGTITIT TNNNNITIT TCTGTITIT	510 CACTIGCT CNNNNNNN CACTIGCT CCACTIGCT	520 CCIICIICI NNIINIINN CCIICIICI CCIICIICI	530 AAGTCTACI ANNININNI AAGTCTACI AAGTCTACI) 54	0 550 ACTGCTGCTT - CNGCTGCTT ACTGCTGCTT ACTGCTGCTT) 560 CCGITCITIC CCNNININN CCGITCITC CCGITCITC CCGITCITC	STGAAAGJ NNNAANG STGAAAGJ STGAAAGJ	576 ATTACTI ATTACTI ATTACTI
E60 HV-lgG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(577) (519) (198 (575) (577)	577 TOCTGA TNCTNNI TCCTGA	59 CCAGTGAC NCCAGTGAC CCAGTGAC GCCAGTGAC	0 60 CGTTICTIC CGTTI-NNN CGTTICTIC CGTTICTIC	0 AACTCAGG ANNICAGN AACTCAGG AACTCAGG	610 IGCICITAC NN-ICITAC IGCICITAC IGCICITAC	620 ATCIGGIGI AT-NNGNGI ATCIGGIGI	630 IICATACTII IICATACTII IICATACTII	640 CCCAGCIGII CCCAGCIGII CCCAGCIGII	650 CTICAATCITC TICANINITC CTICAATCITC CTICAATCITC	660 AGGACII AGGACII AGGACII AGGACII	672 TACTCACT TACTCA-N TACTCACT TACTCACT
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(673) (615) (289) (671) (673)	673 TTCTTC NNNNTCI TTCTTC TTCTTC	680 ICTICITAC NOTICITAC ICTICITAC ICTICITAC	690 CGTTCCTTC CGTTCNNTN CGTTCCTTC CGTTCCTTC	700 TCAAG-CT TCAAG-CT TCAAG-CT	710 IGGGCACTC NGGGCANTC IGGGCACTC IGGGCACTC	720 agac <mark>c</mark> tacj agacntacj agac <mark>c</mark> tacj agacctacj	730 ATCTGCAATO ATCTGCAATO ATCTGCAATO ATCTGCAATO	TGARTCACAA TGARTCACAA TGARTCACAA TGARTCACAA	.750 ACCCAGCAACA ACCCAGCAACA ACCCAGCAACA ACCCAGCAACA	CCAAGGT CCAAGGT CCAAGGT CCAAGGT	768 TGACAAGA TGACAAGA TGACAAGA TGACAAGA - Section 9
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(769) (710) (385) (766) (769)	769 AAGTTGI AAGTTGI AAGTTGI AAGTTGI	780 AGCCCAAGT AGCCCAAGT ANCCCAAGT AGCCCAAGT	790 CITGIGACAJ CITGIGACAJ CITGIGACAJ CITGIGACAJ	800 GACTCATA GACTCATA GACTCATA GACTCATA) 8 CGTGTCCAC CGTGTCCAC CGTGTCCAC CGTGTCCAC	10 CGTGCCCAC CGTGCCCAC CGTGCCCAC CGTGCCCAC	820 CACCIGAN CACCIGAN CACCIGAN CACCIGAN	830	840 accetcaetet accetcaetet ancetcaetet accetcaetet	850 ICIIGII ICIIGII ICIIGII ICIIGII	864 TCCTCCAA TCCTCCAA TCCTCCAA TCCTCCAA Section 10
E60 HV-lgG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(865) (806) (481) (862) (865)	865 87 AGCCTAL AGCCTAL AGCCTAL AGCCTAL	70 AGGATACCT AGGATACCN NNNATACCT AGGATACCT	880 TGATGATOTO TGATGATOTO TGATGATOTO TGATGATOTO	890 CAGGACTO CAGGACTO CAGGACTO	900 CIGAAGICA CNGAAGICA CIGAAGICA CIGAAGICA	910 CAIGIGIAG CAIGIGIAG NNIGIGIAG CAIGIGIAG	920 TIGTGGAT TIGTGGAT TIGTGGAT	930 TGAGCCATGA TGAGCCATGA TGANCCATGA TGAGCCATGA	940 ACATCCTGAGG ACATCCTGAGG ANANCCTGANN AGATCCTGAGG	950 TGAAGII TGAAGII - GAANII TGAAGII	960 CAACIGGT CAACIGGT CAACIGGT CAACIGGT Section 11
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(961) (902) (577) (957) (957) (961)	961 Atgtgg Atgtgg Ntgnng Atgtgg	970 ATGGTGTGG ATGGTGTGG NNGNNGNNG ATGGTGTGG	980 AAGTGCACAJ AAGTGCACAJ NANTGCNNNJ AAGTGCACAJ	990 TCCCAAGA TCCCAAGA TCCCAAGA TCCCAAGA	1000 CRAAGCCCA CRAAGCCCA NNAAGCCNA CRAAGCCCA) .10 GA-GAGGAJ GA-GAGGAJ NNAN <mark>ANGAJ</mark> GA GAGGAJ	010 ACAGTACAA ACAGTACAA ACAGTACAA ACAGTACAA	1020 .1 DAGCACGTACA AGCACGTACA INN <mark>CACGT</mark> NNN CAGCACGTACA	030 10 GGGTTGTCTCA GGGTTGTCTCA NNTNNNNNCA GGGTTGTCTCA	40 GTICICA GTICICA NINNN-N GTICICA	1056 CIGITCIC CIGITCIC ANNNNNN CIGITCIC Section 12
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(1057) (997) (672) (1050) (1057)	1057 CATCAA CATCAA CNTCAA CATCAA	107 CATTCGTIC CATTCGTIC SATTCGTIC SATTCGTIC	70 10 AATGGCAAAG AATGGCAAAG ANGGNANNNN AATGGCAAAG	80 AGTACAAG AGTACAAG INNNNANN AGTACAAG	1090 Igcaaggtc Igcaaggtc Ngcanggtc Igcaaggtc	1100 TCCAACAAJ TCCAACAAJ TNCAANAAN TCCAACAAJ	1110	,1120 AGCCCCCATTG AGCCCCCATTG INNNN	1130 AGAAGACCATT AGAAGACCATT AGAAGACCATT	1140	1152 CGAAAGGG CGAAAGGG CGAAAGGG
E60 HV-lgG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(1153) (1093) (768) (1113) (1153)	1153 CAACCCC CAACCCC CAACCCC	1160 GTGAACCA GTGAACCA	1170 CAAGTGTACA CAAGTGTACA	1180	1190 CCATCTCGC CCATCTCGC	1200 CATGAACTO CATGAACTO GATGAACTO	121 IACCAAGAAG IACCAAGAAG	0 122 CAGGTCAGCT CAGGTCAGCT	D 1230	GTGAAAG GTGAAAG GTGAAAG	1248 GCTTCTAT GCTTCTAT GCTTCTAT Section 14
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(1249) (1189) (864) (1113) (1249)		1260 CACATAGOT CACATAGOT	1270 STAGAGTGGG STAGAGTGGG	128 AGAGCAAT AGAGCAAT	30 .1: SGGCAACCG SGGCAACCG	290 GAGAACAAC GAGAACAAC GAGAACAAC	1300 TACAAGACI TACAAGACI	,1310 ACACCTCCCG ACACCTCCCG	1320 TTCTCGATTCT TTCTCGATTCT	1330 GACGGCT GACGGCT	
E60 HV-laG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(1345) (1285) (960) (1113) (1345)	1345 [13 CTCTAC; CTCTAC; CTCTAC;	S50 AGCAAGCTC AGCAAGCTC	1360 ACAGTEGACS ACAGTEGACS ACAGTEGACS	1370 AGAGCAGG AGAGCAGG	1380 Iggcaacaa Iggcaacaa	1390 GGGAATGTO GGGAATGTO	1400	1410 TCCGTGATGC TCCGTGATGC	,1420 ATGAGGCTCTT ATGAGGCTCTT	143 CACAATC CACAATC CACAATC	0 1440 ACTACACA ACTACACA ACTACACA
E60 HV-lgG1 DVE60-VH-R rev DVE-6-VH-FF Consensus	(1441) (1381) (1056) (1113) (1441)	1441 Cagaagi Cagaagi Cagaagi	1450	1400 TTGTCTCCCC TTGTCTCCCC TTGTCTCCCCC	1470 GTAAATGAG GTAAATGAG	1480) ,14 tagagtegj	190 (1 Acnngcagn)	1500 IGNT NNN NNN	1519 אאאאאאא		Section 16

B) pE60 IgG1 LC

