# TARGETS FOR MAJORITY OF DRUGS: G PROTEIN-COUPLED RECEPTORS – – THEIR STRUCTURE AND INTERACTIONS WITH BIOLIGANDS

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Abstract: G protein-coupled receptors (GPCRs) are the most frequent targets for many drugs. They form the largest superfamily of integral membrane proteins, of which more than 1000 members have the following common features: (i) All GPCRs form 7 hydrophobic  $\alpha$ -helices of length ~38Å (25 amino acids, 7 turns) along a single chain. The consecutive helices alternatively cross the membrane, starting from the extracellular side, so that they form a heptahelical transmembrane domain interwoven with 6 loops, of which the even ones plus the N-terminus create the receptor's extracellular domain while the odd ones plus the C-terminus form its intracellular domain. (ii) All GPCRs are stimulated by diverse extracellular (primary) signals. (iii) Stimulated GPCRs convey the primary signals via their transmembrane and intracellular domains to the cytosolic peripheral heterotrimeric GTP-binding proteins (G proteins), mediating the signal's further transduction to various cellular second messenger systems. A current status of structural studies on GPCRs, consisting of low ~7.5Å resolution experimental structures and supplementary molecular modeling, is outlined. Subsequently, some results of authors' own work on studying essential interactions of the V2 vasopressin renal receptor (V2R) with its agonist [Arg<sup>8</sup>]Vasopressin (AVP) and selected antagonists are presented, as well as their possible impact on the biological signal transduction is discussed. Finally, perspectives for future developments are sketched.

Keywords: G protein-coupled receptor, molecular modeling, GPCR/bioligand interaction, molecular dynamics, membrane

### 1. Biological Signal Transduction via G Protein-Coupled Receptors and G Proteins

A typical career in medicinal chemistry will run across a G protein-coupled receptor (GPCR) as a drug target. GPCRs form the biggest known (~2000 sequences reported to date [1]) superfamily of homological proteins, integral to the membranes in most cells of any vertebrate, where they serve as transducers of a bewildering array of incoming extracellular signals. These signals, after being processed within the receptor and conveyed across the membrane, are picked up by the cytosolic GTP-binding proteins (G proteins) to initiate chains of intracellular

processes virtually controlling all cell activities, see Figure 1. Accordingly, GPCRs, also known as heptahelical transmembrane (7TM), or serpentine receptors, are *de facto* the most frequent drug targets. Ironically, despite their absolutely fundamental physiological roles, little is known about GPCR structure as, being typical integral membrane proteins, they are crystallization-resistant and thus immune against structural elucidation by X-ray.



**Figure 1.** GPCR signal transduction system. The activated receptor catalyses the exchange of GDP for GTP in the  $G_{\alpha\beta\gamma}$  heterotrimer. This triggers the dissociation of the heterotrimer into  $G_{\alpha}$  GTP and  $G_{\beta\gamma}$  which activate effectors: enzymes and/or ion channels. Native  $G_{\beta}$  never separates of helical  $G_{\gamma}$  and has a structure reminiscent of a 7-blade propeller [10] as reflected on the scheme.

Until now, only low-resolution ( $\geq 6$  Å) structures of the light receptor, bovine [2] and frog [3] rhodopsin, are known from the electron diffraction cryo-microscopic measurements. Together with the multi-sequence analysis [4, 5], they have confirmed the structural concensus agreed upon, and schematically shown in Figure 1. Thus, any GPCR consists of a hydrophobic heptahelical transmembrane domain (7TM), interlaced with the 6 alternating extracellular and cytosolic loops (EL1-EL3 and IL1-IL3, respectively), creating with the N-terminus and with the C-terminus the extracellular and intracellular domains, respectively. Accordingly, 7TM is composed of seven transmembrane helices TM1-TM7, aligned one after the other counterclockwise (if viewed from the extracellular space) into a kidney-like shape [1, 6]. The amino acid sequences of respective TM1-TM7 helices, within the most abundant rhodopsin-like GPCR family, are homological to ~20% level, thus supporting a hypothesis on common functionality and structure of their 7TMs. On the contrary, both the extracellular and intracellular domains exhibit no mutual sequence homology, unless among very closely related GPCRs. This diversity is reflected in the enormous wealth of primary signals for GPCRs, ranging from a photon via metal ions, gustatory substances, odorants, biogenic amines, neurotransmitters, to small, medium-size and large peptide/nonpeptide/glycoprotein hormone ligands [1, 6, 7, 8].

Interestingly, this first-messenger diversity merges into a uniform signaltransduction path, embodied within the receptor and at the GPCR/G-protein interface into a putative common mechanism [1, 6-8, 9]. A contribution to the elucidation of the G protein role in this mechanism was appreciated with the Nobel price in physiology and medicine, awarded in 1994 to G.M. Rodbell and A. Gilman. Thus, the G protein is stimulated through the cytosolic domain of a ligand-activated GPCR, see Figures 1 and 2. At this instant, it is a heterotrimer consisting of the  $G_{\alpha}$ 



Figure 2. G protein cycle. The intracellular signal is proportional to the GDP dissotiation rate constant  $k_{des}$  and inversely proportional to the GTP hydrolysis rate constant  $k_{des}$ .

with GDP (guanosine diphosphate) bound,  $G_{\beta}$  and  $G_{\gamma}$  subunits, in short  $G_{\alpha\beta\gamma}$ .GDP. Over 20 isoforms of  $G_{\alpha}$ , 5 isoforms of  $G_{\beta}$  and 11 isoforms of  $G_{\gamma}$  are known [8, 10], yielding > 1100 theoretical  $G_{\alpha\beta\gamma}$  combinations, a figure of an order consistent with the number of various GPCRs.

Since an activated GPCR changes its conformation, the  $G_{\alpha}$  subunit of  $G_{\alpha\beta\gamma}$  receives this as a signal to exchange GDP for omnipresent cellular GTP (guanosine triphosphate). A nascent complex  $G_{\alpha\beta\gamma}$ . GTP first dissociates off the receptor and simultaneously (subsequently?) splits into the funtional  $G_{\alpha}$ . GTP and  $G_{\beta\gamma}$ , see Figure 2, capable of stimulating intracellular efector/second messenger systems. These, depending of primary signal/GPCR/G protein systems, may consist of ion channels and/or various enzymes/second messengers, controlling cellular behavior and function. As the  $G_{\alpha}$ .GTP is simultaneously a slow-acting Mg<sup>2+</sup>-dependent GTPase, it gradually hydrolyses GTP to GDP. Restored  $G_{\alpha}$ .GDP provides a signal for the  $G_{\alpha\beta\gamma}$ .GDP to reassociate, synonymous with the deactivation of the G protein (as both  $G_{\alpha}$ .GTP and  $G_{\beta\gamma}$  dissappear). Thus, the G protein working cycle closes, see Figure 2. A single activation of a GPCR may evoke a few hundred to a few thousand of the G protein cycles; this being a measure of the amplification of a primary signal at this stage.

#### 2. GPCR Structure

Whereas the G protein structures at various stages of the G protein cycle [11, 12, 13, 14, 15, 16, 17], likewise the mechanism of hydrolysis of G. GTP to G. GDP [13, 14], are known, the conformation of GPCRs and our knowledge on what happens at the GPCR/G protein interface are really misty, as the only GPCR structural information available are the low-resolution electron cryo-microscopic images of rhodopsins [2, 3], see above. These images at 6-7Å resolution parallel and 16-17Å resolution perpendicular to the membrane surface are good enough for the reassessment of the match of the specific helices with the three-dimensional low-resolution 7TM image [2, 3, 18]. They are, however, much worse for the prediction of mutual inter-helical arrangements, involving helical rotations, tilts and kinks [4, 19], and they are totally incapable of locating atomic positions. It is only known from the mutagenesis, photoaffinity and spin labeling experiments that some 20 amino acid-long N- and C-terminal G<sub>a</sub> sequences [13] are involved in possible interactions with the IL2, IL3 and possibly C-terminal fragments [7, 8] of GPCRs. Thus, a state-of-the-art molecular modeling is currently the only approach to study the structure of GPCRs and their interactions with bioligands.

Early modeling schemes used the low-resolution structure of bacteriorhodopsin [20], another 7TM — albeit not a GPCR — integral membrane protein, as a template for homology modeling. Interestingly, despite no homology between the transmembrane sequences of bacteriorhodopsin and GPCRs, this modeling resulted in a huge database of GPCR 7TM templates [21]. Using this scheme numerous bioligand-interaction models for various GPCRs have been developed [22]. However, recent comparisons of high-resolution structures of bacteriorhodopsin [23, 24, 25] with low-resolution structures of rhodopsin [2, 3] clearly indicate that the latter, despite a lower resolution, would make a much better generic GPCR 7TM template, as being dissimilar to the former and simultaneously having its 7TM at  $\sim$ 20% homological with other GPCRs. Thus, current molecular modeling of GPCRs consists of rhodopsin-based 7TM templates onto which specific GPCR sentences are threaded.

Multalin version 5.3.3 Copyright I.N.R.A. France 1989, 1991, 1994, 1996 Published research using this software should cite Multiple sequence alignment with hierarchical clustering F. CORPET, 1988, Nucl. Acids Res., 16 💯, 10881-10890 Symbol comparison table: blosum62 Gap weight: 12 Gap length weight: 2 Consensus levels: high=90% low=50% Consensus symbols: ! is anyone of IV \$ is anyone of LM % is anyone of FY # is anyone of NDQEBZ MSF : 659 Check: 0 Name: sp|P02699|OPSD\_BOVIN Len: Check: 4601 659 Weight: 1.19 Name: sp|P25103|NK1R\_HUMAN Len: Check: 7852 659 Weight: 1.10 Name: sp | P21555 | NY1R\_RAT 659 Check: 4036 Weight: Len: 1.10 Name: sp|P41143|OPRD\_HUMAN Len: 659 Check: 3951 Weight: 0.99 Name: sp|P41145|OPRK\_HUMAN Len: 659 Check: 9850 Weight: 0.99

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MGAGVLVLG					sp P08588 B1AR_HUMAN
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PAVGGVPGGA	SAGGAAPSEG	GGSSAGGGGG	FEGPRPDSSA	MTFRDLLSVS	sp P25100 A1AA_HUMAN
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sp	P41145 OPRK_HUMAN	PGPTCAPSAC	LPPNSSAWFP	GWAEPDSNGS	AGSEDAQLEP	AHISPAIPVI
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sp	P07550 B2AR_HUMAN		MGQPGNGS	AFLLAPNRSH	A PDHDV	TQQRDEVWVV
sp	P25100 A1AA_HUMAN	GGGGGVVGAG	SGEDNRSSAG	EPGSAG-AGG	DVNG TAAV	GGLVVSAQGV
sp	P18841 A1AB_MESAU	MNPDLDTG	HNTSAPAQWG	ELKDANFTGP	NQTS SNST	LPQLDVTRAI
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sp	P30518 V2R_HUMAN		MLMASTTS	AVPGHPSLPS	LPSNSSQERP	LDTRDPLLAR
sp	P37288 V1AR_HUMAN	LSAGPDAGPS	GNSSPWWPLA	TGAGNTSREA	EALGEGNGPP	RDVRNEELAK
sp	P47901 V1BR_HUMAN		MDSGPLWDAN	PTPRGTLSAP	NATTPWLG	RDEELAK
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55 NY1R_RAT	LALAYG-AVI	ILGVSCNLAL	IIIILKQKEM	RN VT IL	VNLSFSDLV
43   OPRD_HUMAN	ITALYS-AVC	AVGLL NV	MFGIVRYTKM	KT AT II	FNL L DA-L
45 OPRK_HUMAN	ITAVYS-VVF	VVGLV NS	MFVIIRYTKM	KT··AT I	FNIL LDA-L
28 DADR_HUMAN	LTACFLSLLI	LSTLL	CAAVIRFRHL	RSKVT-VF	ISLVSDLV
88 B1AR_HUMAN	GMGLLMALIV	LLIVACNVIN	IVAIAKTPRL	QT-LT-LL	MSL S D VM
50   B2AR_HUMAN	GMGIVMSLIV	LAIVENV	ITAIAKFERL	QT-VT-XY	TSL C D VM
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21 HH2R_HUMAN	TITVVLAVLI	LITVA NVV	CLAVGLNRRL	RN-LT-NC	VSL, ITD LL
08 5H1A_HUMAN	ITSLLLGTLI	FCAVLENACY	VAAIALERSL	QN-VA-VYL	GSL VID MV
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sp P41143 OPRD_HUMAN	ATSTLEFQSA	KYLMET - OPF	FELLCKAVLS	I YYNMFTS	FTFTMMSVDR
sp P41145 OPRK_HUMAN	VTTTMFQST	VYLMNS-PPF	COVLCKIVIS	INYYNMFTS	FTETMMSVDR
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sp P08588 B1AR_HUMAN	GLLVVFFGAT	IVVWGR- EY	CSFFCELWTS	VID LCVT S	ETI CVIAL <b>DR</b>
sp P07550 B2AR_HUMAN	GLAVVIEFGAA	HILMKM-OTF	ENFWCEFWTS	INCLCVT S	ETICVIAVDR
sp P25100 A1AA_HUMAN	SATVL FSAT	MEVLGF - AF	RAFCDVWAA	VINLCCT S	LSICTISVDR
sp P18841 A1AB_MESAU	SFTVLEFSAT	LEVLGY - VL	<b>CRIFC</b> DIWAA	VINLCCT S	LSCAISIDR
sp P28223 5H2A_HUMAN	GFLVMEVSML	TILYGYRCPL	PSKLCAVWIY	Lovlfst S	MH CAISL <b>DR</b>
sp P25021 HH2R_HUMAN	GLLVLFFSAI	YQLSCK-SF	CKVFCNIYTS	LEVMLCT: S	LN FMISL <mark>DR</mark>
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sp P37288 V1AR_HUMAN	AFFQVLPQMC	WDITYR-FRG	PDWLCRVVKH	L FGMF SA	YM VVMTADR
sp P47901 V1BR_HUMAN	ALFQVLPQLL	WDITYR-FQG	PDLLCRAVKY	L LSMF ST	YM LAMTLDR
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SD PAILAS OPPK HUMAN	TOWCHDUKA	LDFRAPLKEK	TINICIMULS	SSVGISATVL	GGTKVREDVD
SD P21728 DADE HUMAN	WW TSSPERV	FREMERKA	TLUSVANTLS	VIIISFIPVOL	SWHKAKPTSP
SD PO8588 B1AR HIMAN	U. TTSPERV	OSLLUBAR	GLUCTVWAIS	ALVEFLETLM	HWWRA
SD PO7550 B2AR HIMAN	NE TOPEVY	OSLLANNER	VINLAVOTVS	GLTOFL PTOM	HWVRA
SPIPOTSSUBZAR_HUMAN	WUCUDUCT VV	DATMAEDVAA	ATLALLOUVA	I WUSVC - PLI	CWKE
SP P25100 ATAA_HOMAN	WIGWRHSLRI	DTINCOPULT	TALLOUNUE	TWINTG-PLI	CWKE
SPIPI8841 ATAB_MESAU	TGVRISLUI	CDENCOURANT	LALLSVAVLS	VCTOMETOVE	GLOD
SP P28223 SH2A_HOMAN	VOLUNEINH	SKENSKINGE	DUNITANIT2	TUINELETUI	GUQD
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sp P30518 V2R_HUMAN	HR LCREMLA	YRHGSGAHWN	RPULVAMARS	TTTST OTLT	FAQRN
SP P37288 VIAR_HUMAN	NI VCHELKT	LQQ-PARKSK	LMBRAAAWVLS	PVLNILQIPV	FOMIL
sp P47901 VIBR_HUMAN	MLOVCHPLRS	LQQ-PGQSTY	LLMAAPWLLA	AIFSLOVFI	FSLRE
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sp P21555 NY1R_RAT	VSLAAFKD	KYVCFDKFPS	DSHRLSMTTL	LLVLQMFGL	CFIFICEFKI
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SDIP21/28 DADR_HUMAN	SUGNATSLAE	TIDNCD	SSLSKTWAIS	SSVISBIIN	AIMIVISTRI OTMARVISTRI
SPIPU8588 BIAR_HUMAN	ESDEARRCYN	DPKCCD	FVTNKAMAIA	SSVVSBIV	UTHAP VILLEV
sp P0/550 B2AR_HUMAN	THQEAINCYA	NETCCD	FFTNQADAIA	SSIVSBIVE	VIMVEV SRV
sp P25100 A1AA_HUMAN	PVPP	DERFCG	ITEEAGWAVE	SSVCSBYLL	AVIVVMCCRV
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sp P30518 V2R_HUMAN	VEGGSGVTDC	WACFAE	PWGRRTTVTW	IALMVEVALT	LGIAACQVLI
sp P37288 V1AR_HUMAN	VNNVTKARDC	WATFIQ	PWGSRANVTW	MTGGIFVARV	VILGTC GFI
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sp P18841 A1AB_MES.	AU YIVAKRTTKN	LEAGVMKEMS	NS	KELTL	
SD   P28223   5H2A HUM	AN FLTIKSLOKE	ATLCVSDLGT	RA	KLASE	
SD P25021 HH2E HIM	AN FRVARDOAKR	T.N			
		muuunna	DEDUCACDAD	ODVVQUDIQDQ	CODVIDI OUD
SP P08908 SHIA_HOM	AN FRAARFRIKK	TVKKVEKTGA	DTRHGASPAP	QPRKSVNGES	GSRNWRLGVE
sp P21761 TRFR_MOU	SE YGFIARILFL	NPIPSDPKEN			· · · · · · · · · · · · · · · · · · ·
sp P30518 V2R_HUMA	N FREIHASLVP	GPSERPGGRR			
SDIP37288 VIAR HUM	AN CYNTWCNVRG	KT-ASROSKG			
p   D47001   V1 BB HUM	AN CHETCKNIKU	KTONNDVCCC			
SPIP47901 VIBR_HOM	AN CHEICKNERV	KIQAWRVGGG			
sp P30559 OXYR_HUM	AN SFKIWQNLRL	KTAAAAAAEA			
Consens	us				
	351				100
					400
spipuz699 OPSD_BOV	IN				
sp P25103 NK1R_HUM	AN				• • • • • • • • • • •
sp P21555 NY1R_RAT					
SDIP41143 OPED HUM	AN				
ap   DA114E   ODBK HUM	2 M	ARCHAR DE MERSEN DE RECOMPLEMENT			
SPIP41145 OPRK_HOM	AIN				
sp P21/28 DADR_HUM	AN				- HAKNCQTTT
sp P08588 B1AR_HUM	AN		• • • • • • • • • • •	PAPPPGP	PRPAAAAATA
sp P07550 B2AR HUM	AN				-HVONLSOVE
SDIP2510012122 HUM	AN			BIHCRCA	ATGADGAHCM
an D10041 212D				- RINCKGA	AIGADGARGM
SP P18841 AIAB_MES	AU			RIHSKNF	HEDTLSS
sp P28223 5H2A_HUM	AN			SFLPQSS	LS SEKLFQ
sp P25021 HH2R_HUM	AN				
splP0890815H1A HUM	AN SKAGGALCAN	GAVROGDDGA	ALEVIEVHRV	GNSKEHL.PL.P	SFACDTOCAD
cplp21761/mppp Moto	op	0		ONDIGENEL EL	OWNER
Spj221701j1KFK_MOU.	55				- SKMWKNDSI
sp P30518 V2R_HUMA	N			RG	RRTGSPGEGA
sp P37288 V1AR_HUM	AN		• • • • • • • • • • •	AE	QAGVAFQKGF
sp P47901 V1BR HUM	AN			GW	RTWDRPSPST
SDIP30559LOXVE FUM	AN			DF	CANACDCODU
5p115055510MIN_NOR				FL.	GAAAGDGGRV
Consensi	us				
	401				450
SDIP0269910PSD BOV	401 TN	 Δ Ψ ΨΟΥ			450
sp P02699 OPSD_BOV	401 IN	ATTQK	AEKEVTRVI	IMVIAFLICW	450 LPYAGVA
sp P02699 OPSD_BOV sp P25103 NK1R_HUM	401 IN	ATTQK YHEQVS	AEKEVTR VI AKRIVVI VI	IM IAFLI W VV CTFAI W	450 LPYAGVA LP H FFLLP
sp P02699 OPSD_BOV sp P25103 NK1R_HUM sp P21555 NY1R_RAT	401 IN AN	ATTQK YHEQVS SKYRSS	AEKEVTR VI AKR VV VI ETKRINV L	IMVIAFLIOW VV CTFAIOW SIVVAFAVOW	450 LPYAGVA LP H FFLLP LPLT FNTVF
sp P02699 OPSD_BOV sp P25103 NK1R_HUM sp P21555 NY1R_RAT sp P41143 OPRD_HUM	401 IN	ATTQK YHEQVS SKYRSS KEKDR	AEKEVTR VI AKR VVK MI ETKRINV L SLRRITR VL	IMVIAELIOW VVOCTFAIOW SIVAFAVOW VVOGAEVVOW	450 LPYAGVA LP-HFFFLLP LPLTFNTVF AFIHFVIVW
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM.	401 IN AN AN	ATTQK YHEQVS SKYRSS KEKDR REKDR	AEKEVTR VI AKR VVK MI ETKRINV LL SLRRITR VL NLRRITR VL	IMVIAFLIOW VV CTFAIOW SI VAFAVOW VV GAFVVOW VV AVFVVOW	450 LPYAGVA LP-HHFFLLP LPLTFFNTVF APIHEFVIVW TRIHEFILVE
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADB_HUM.	401 IN AN AN AN	ATTQK YHEQVS SKYRSS KEKDR REKDR PESSEKMSEK	AEKEVTR VI AKR VVX JI ETKRINV JL SLRRITR VL NLRRITR VL RETRVLATION	IMVIAELICW VV CTFAIGW SI VAFAVGW VV GAPVVGW VV AVFVVGW VIGVPVCGW	450 LPYAGVA LP H FFLLP LPLT FNTVF APIH FVIVW TPIH FILVE LPHN LNCTL
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P20588 B1AP_HUM.	401 IN AN AN AN GNGKPVECSQ	ATTQK YHEQVS SKYRSS KEKDR REKDR PESSFKMSFK DDSDIVAL	AEKEVTR VI AKR VVK VI ETKRINV L SLRRITR VL NLRRITR VL RET VLTIS	IMVIAFLICW VVCTFAICW SIVAFAVCW VVGAFVVSW VVAVFVVSW VIMGVFVCW	450 LPYAGVA LP HHFFLLP LPLTHFNTVF APIHHFVIVW TPIHHFVIVW TPIHHFVIVE LPSHLNCIL
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P08588 B1AR_HUM.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR	ATTQK YHEQVS SKYRSS KEKDR REKDR PESSFKMSFK RPSRLVAL	AEKEVTROVI AKROVKOVI ETKRINVOL SLRRITROVL NLRRITROVL RETOVLSTPS REQUALSTOG	IMVIAPLICW VVCCTPAICW SIVAPAVCW VVGAPVVCW VMGAPVVCW VMGVPVCW IMGVPTLCW	450 LPYAGVA LP-HIFFLLP LPLT FNTVF APIHIFVIVW TPIHIFILVE LPLNCIL LPLANVVK
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P08588 B1AR_HUM. sp P07550 B2AR_HUM.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS - RLVAL RSS - KF - CL	AEKEVTRVVI AKRIVVIVI ETKRINVIL SLRRITRVVL NLRRITRIVL RETVLTS REQUALTIS KEHGALKTIG	IMVIAPLICW VVOCTFAIGW SIVAFAVGW VVGAFVVGW VMAVFVVGW VMAVFVVGW IMGVFTLGW IMGVFTLGW	450 LP YAGVA LP HH FFLLP LE LT FNTVF AB IHF FNTVF TE IHF FILVE LP LNCIL LP LANVVK LP VNIVH
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P05588 B1AR_HUM. sp P07550 B2AR_HUM. sp P25100 A1AA_HUM.	401 IN AN AN AN AN CNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS - RLVAL RSS - KF-CL SLSVRLLKFS	AEKEVTR VI AKR VV III SLRRITR VL NLRRITR VL NLRRITRIVL RETVL TFS REQUALTIG KEHGALKTIG REKGAAKTA	IMVIAFLIEW VVCFAIGW SIVAFAVGW VVCAFVVGW VVAVFVVGW VIMGVFVCW IMGVFTLGW IMGVFTLGW IVVGVFVLGW	450 LBYAGVA LB-HFFFLP LFLTFFNVF ABIHFFVVW TEHFFILVE LFHALNCIL LFHALNCIL LFHALNVK LFHALNVK LFHALNVK FF25FVLPLG
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P05588 B1AR_HUM. sp P07550 B2AR_HUM. sp P25100 A1AA_HUM. sp P18841 A1AB_MES.	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS	AEKEVTR VI AKRIVVIL ETKRINVIL SLRRITR VL NLRRITRIVL RETIVL TS REQAL TIS KEHALKTG REKAAKTA REKAAATTS	IMVIAFLICW VVCFALCW SIVAFAVCW VVGAFVVSW VIAVFVCW IMCVFVCW IMCVFTLW IMGTFTLW VVGVFVLW VVGVFVLW	450 LP-H-FFLP LLTFNTVF AGIH-FFLVE LP-LNCIL LP-LALNCIL LP-LALNCIL LP-LALNVVK LP-LVNIVH FP-207VLPLG LP-LALPLG
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P05588 B1AR_HUM. sp P07550 B2AR_HUM. sp P25100 A1AA_HUM. sp P18841 A1AB_MES. sp P28223 5H2A_HUM.	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AN RSIHREPGSY AN RSIHREPGSY	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS - RLVAL RSS - KF - CL SLSVRLLKFS SIAVKLFKFS TGRRTMOSIS	AEKEVTR VI AKRIVVII I ETKRINVIL SLRRITR VL NLRRITR VL RET VL TS REQUALTIS KEH ALTIS REK AAKTIS REK AAKTIG NEONACIUS	IMVIAPLICW VVCTFAICW SIVAPAVCW VVGAPVVCW VMAVFVVCW IMGVFVCW IMGVFTLW IVGVFVLW IVGMFILW IVFFLEVMM	450 LP YAGVA LP HH FFLLP LE LT FNTVF AE IH FVIVW TE IH FILVE LP
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P28023   5H2A_HUM. sp   P25021   HH2R_HUM.	401 IN AN AN AN CNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AN RSIHREPGSY AN	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS STAVKLFKFS TGRRTMQSIS HISSWKATT	AEKEVTR VI AKR VV VI I SLRRITR VL NLRRITR VL NLRRITRIVL RETVLTS REO(ALKTIG REK AAKTIG REK AAKTIG NEO(ACXVIG BEH GATVTA	IMUIAFLIEW VVCTFAICW SIVAFAVCW VVCAFVCW VMAVFVVCW IMGVFVCW IMGVFVLW IMGVFVLW IVGVFVLW IVGVFLEW IVFLFVVLW VVCMFILW	450 LP ++ FFLP LP ++ FFLP LFLT FFTVF AF I++ FIVW TE I++ FIVW LP -LANVK LP -LANVK LP -LANVK FP -FVLPLG LP - ALPLG CP - TNIMA
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P05508 B1AR_HUM. sp P07550 B2AR_HUM. sp P25100 A1AA_HUM. sp P18841 A1AB_MES. sp P28223 5H2A_HUM. sp P28028 5H2A_HUM.	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTPRS AU TKAKGHNPRS AN RSIHREPGSY AN	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SLAVKLFKFS TGRRTMQSIS HISSWKAATI	AEKEVTR VI AKR VVN VI ETKRINV VI SLRRITR VI NLRRITR VI RETVL T'S REQUAL T'S KEH AL T'S REK AAKT'A REK AAKT'A REK AAKT'A NEONAC'V'S REH ATVT'A	IMUIAFLIEW SIVAFAVGW VVGAFVVGW VMGAFVVGW IMGVFVCGW IMGVFTLGW IMGVFTLGW VMGVFVLGW IVGGFTLGW IVFFLFVVLW IVFFLFVVLW AVMGAFIIW	450 LBYAGVA LD-HHFFLLP LLTFNTVF AGIHFFILVE LD
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P0550 B2AR_HUM. sp P0550 B2AR_HUM. sp P25100 A1AA_HUM. sp P18841 A1AB_MESS. sp P28223 5H2A_HUM. sp P25021 HH2R_HUM. sp P08908 5H1A_HUM.	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS STAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA	AEKEVTR VI AKRNVVNTI ETKRINVMLL SLRRITRIVL RETIVLTIS REQUALTIG KEH ALTIG REK AARTIG NEQUACIVIG REH ATVTIA RERIATITIG	IMVIAFLICW VVCCTFAICW SIVAFAVCW VVGAFVVCW VIAVFVVCW IMGVFVCW IMGVFTLW IVGCFTLW VVGMFILW IVGFFLLW IVFFLFVVMW AVMGAFIICW	450 LP ++ FFLLP LC LT FNTVF AG H+ FFLVE LP
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P07550 B2AR_HUM. sp P07550 B2AR_HUM. sp P25100 A1AA_HUM. sp P18841 A1AB_MES. sp P28223 5H2A_HUM. sp P25021 HH2R_HUM. sp P25021 HH2R_HUM. sp P21761 TRFR_MOU.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN SE HQNKNLNLNA	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS	AEKEVTR VI AKRVVKI I SLRRITR VL SLRRITR VL SLRRITRIVL RETVLTTS REO(ALKTIG REK AAKTIG REK AAKTIG REK AAKTIG REK AAKTIG REH ATVTIA RESTVITG SRKOVTSLA	IMMIAFLIEW VWCFAFACW SIVAFAVCW VWCAFVCW VMCVFVCW IMGVFVCW IMGVFTLW IVGVFVLW IVGVFVLW IVGVFLFVVMW AVMGAFIICW IMGFFLWW VWILFALIW	450 LP YAGVA LP FFLLP LF FFLLP LF FVLVW TE I FVLVW LP LANUVK LP LANUVK LP LANUVK FP FVLPLG LP ALPLG CP TAFVYR FP TAFVYR FP TAFVYR LP VVALVL M TLVVVN
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P05508 B1AR_HUM. sp P0550 B2AR_HUM. sp P25100 A1AA_HUM. sp P28841 A1AB_MES3 sp P28023 5H2A_HUM. sp P2021 HH2R_HUM. sp P20908 5H1A_HUM. sp P30518 V2R_HUMAI	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SLAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA	AEKEVTR VI AKRNVVNUL SLRRITR VL NLRRITRVL RETVLTTS REQUALTTG KEHGALKTG REKGAAKTG REKGAAKTG REKGAAKTG REKGAAKTG SREVVTG SRKOVTGA AVANTVR TL	IMUIAFLIGW SIVAFAVGW VVGAFVVGW VMGAFVVGW IMGVFVCW IMGVFVCW IMGVFVCW IMGVFVCW IVGVFVLW IVGFFLGVVLW IVFFLFVVMW AVMGAFIIG IMGTFILW VILFALIW VILFALIW	4500 LBYAGVA LB-HFFLLP LBLTHFFLVE LB-TALNCIL LD-SLANVVK LB
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P0550 B2AR_HUM. sp P0550 B2AR_HUM. sp P2510 A1A_HUM. sp P18841 A1AB_MES2 sp P28223 5H2A_HUM. sp P28021 HH2R_HUM. sp P08908 5H1A_HUM. sp P30518 V2R_HUM. sp P30518 V2R_HUM.	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AN RSIHREPGSY AN AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS STAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR	AEKEVTR VI AKRNVVNIL ETKRINVIL SLRRITR VL NLRRITRIVL RETIVLTIS REQUALTIS REQUALTIG REKAAKTIG REKAAKTIG REKAAKTIG REKAAKTIG REKATVTIG SRKOVTCA AVANTVRITL AKIRTVNITF	IMVIAFLICW VVCCTAICW SIVAFAVGW VVGAFVVGW VIAVFVVGW IMGVFVCGW IMGVFTLW IVGCVFVLW VVGFVLW VVGFLFVVW AVMGAFIICW IMGTFILW VVILFALLW VIJVVVLW	450 LP ++ FFLP LC ++ FFLP LC ++ FFLP LC ++ FFLVF LF ++ FVIVW TE ++ FVIVW TE ++ FVIVW LD ++ LNCIL LD ++ LNVV FF ++ VLPLG CP ++ TAFVYR LP ++ FFLP ++ VLPLG CP ++ TAFVY CP ++ TAFVYR LP ++ FFLP ++ VLPLG CP ++ TAFVY CP ++
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P05588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P2500   A1AA_HUM. sp   P2500   A1AA_HUM. sp   P25023   5H2A_HUM. sp   P26908   5H1A_HUM. sp   P2761   TRFR_MOU. sp   P30518   V2R_HUM. sp   P37288   V1AR_HUM.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC AN LLAPC	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS SIAVKLFKFS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVGSIMTED	AEKEVTR VI AKRVVK VI SLRRITR VL NLRRITR VL NLRRITRIVL RETVLT TS REQUALATTG KENAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKATVTA AVATVK TL AKIRTVG TD	IMMIAFLIW VVCFAIW SIVAFAVCW VVGAFVVCW VMGVFVCW IMGVFVLW IMGVFTLW IVGVFVLW IVGVFVLW IVGVFLWW IVGMFILW IVFFLFVVM IMGFFILW VVILFALIW VILFALIW VILFALIW VILVVVVLW	450 LP YAGVA LP FFLLP LF FFLLP LF FVLVW TE I FVLVW TE I FVLVW LP LANVIK LP LANVIK LP LVNIVH FP FVLPLG LP TAFVR FP TAFVR FP TAFVR FP TAFVR LP TAFVR LP TAFVR AB LVVLVA AB LVVLVA AB LVVLVA AB LVVLVA
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P25155   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P08588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P28841   A1AB_MES2 sp   P28223   5H2A_HUM. sp   P28923   5H2A_HUM. sp   P28923   5H2A_HUM. sp   P2761   TRFR_MOV. sp   P30518   V2R_HUM. sp   P37288   V1AR_HUM. sp   P47901   V1BR_HUM.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN QDGRTGHGLR AN RSAKGHTPRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC AN LLATTRGLPS AN AL	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SLAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA VSSVKSISR RVSSINTISR	AEKEVTR VI AKRNVVN I ETKRINV JL SLRRITR VL NLRRITR VL RET VL TFS REQUAL TFG KEHGALKTG REK 4AKTTG REK 4AKTTG REK 4AKTTG REK 4AKTTG SRKOVT A AVANTVR TL AKIRTV TF AKIRTV	IMUIAFLIAW SI VAFAVGW VUGAFVVGW VIGAFVVGW IMGVFVCW IMGVFVCW IMGVFVCW IMGFFLW IVGVFVLW IVGFFLFVVM AVMGAFIIW IMFFLFVVM VIIFALIW VIIFALIW VIIFALIW VIITAYIVGW VIITAYIVGW	450 LBYAGVA LB-H FFLLP LB-LT FFNVF AB-LH FVIVW TE-LH FILVE LD
sp P02699 OPSD_BOV. sp P25103 NK1R_HUM. sp P21555 NY1R_RAT sp P41143 OPRD_HUM. sp P41145 OPRK_HUM. sp P21728 DADR_HUM. sp P07550 B2AR_HUM. sp P07550 B2AR_HUM. sp P25100 A1AA_HUM. sp P28223 5H2A_HUM. sp P28223 SH2A_HUM. sp P28223 SH2A_HUM. sp P2898 SH1A_HUM. sp P2761 TRFR_MOV. sp P30518 V2R_HUM. sp P37288 V1AR_HUM. sp P37288 V1AR_HUM. sp P30559 OXYR_HUM.	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN QDGRTGHGLR AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC AN LLAPC	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPSRLVAL RSSKF-CL SLSVRLLKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR	AEKEVTR VI AKRNVVNIL ETKRINVIL SLRRITR VL NLRRITRIVL RETAVLTS REQALTIS KEHGALATIG REKGALATIG REKGALATIG REKGALTIG REKGALTIG REKGALTIG SRKOVTGA AVATVR TL AKIRTVGTF AKIRTVGTF	IMVIAFLICW VVCTFALCW SIVAPAVCW VVGAFVVCW VIAVFVVCW IMGVFVCCW IMGVFTLW IVGVFVLW VVGFLLW IVGFLLW IVFFLFVVMW AVMGAFIICW IMGTFILW VVILFALIW VICTAVIVCW VICAVIXW VICAVIXW ILAYIACW ILAFIVCW	450 LB-++ FFLP LCLTFFNTVF AGIH-FFLVE LD-ALNCIL LD-ALNCIL LD-ALNCIL LD-ALNVVK LD-ALNVVK LD-ALNVVK LD-ALNVVK LD-ALPLG CD-TNIMA FD-ATAFVYR LD-ALVLVL MO-RTLVVVN AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA AD-ALVQLWA
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P0558   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P2500   A1AA_HUM. sp   P25023   SH2A_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P25011   TRFR_MOU. sp   P30518   V2R_HUM. sp   P37288   V1AR_HUM. sp   P30559   OXYR_HUM.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC AN LLAPC AN ALA 15	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS SIAVKLFKFS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR	AEKEVTR VI AKRVVK VI SLRRITR VL SLRRITR VL SLRRITR VL SLRRITR VL SEQUALATUS REQUALATUS REK AAKTUS REK AAKTUS REK AAKTUS REK AAKTUS REK AAKTUS SRKOVT AKIRTV TF AKIRTV TF AKIRTV TF	IMMIAFLIEW VVCFAFAVCW SIVAFAVCW VVGAFVVCW VMGVFVCW IMGVFVLW IMGVFTLW IVGVFVLW IVGVFVLW IVGVFLFVVM VMGAFILW VFLFVVMW VMGAFILW VILFALIW VILFALIW VILAYIAW ILAYIAW ILAYIAW ILAFIVCW	450 LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAUVA LP
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P05588   B1AR_HUM. sp   P0550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P25100   A1AA_HUM. sp   P2623   5H2A_HUM. sp   P2623   5H2A_HUM. sp   P2698   5H1A_HUM. sp   P2761   TRFR_MOV. sp   P30518   V2R_HUM. sp   P37288   V1AR_HUM. sp   P37288   V1AR_HUM. sp   P37559   OXYR_HUM. Sp   P30559   OXYR_HUM.	401 IN AN AN AN CNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA AN LLAPC AN LLAPC AN LAATTRGLPS AN ALA	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TURCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR	AEKEVTR VI AKRVVVII SLRRITR VL SLRRITR VL NLRRITRIVL RET VL TS REQUALTIG KEHGALKTIG REK AAKTIG NEQUACIVIG REK AAKTIG NEQUACIVIG REH ATVTIG RER TV TIG AKIRTVUTT AKIRTVUTT AKIRTV	IMMIAFLIAW SI VAFAVGW VVGAFVVGW VMGAFVVGW IMGVFVCW IMGVFVCW IMGVFTLW IVGVFVLW IVGMFILW IVGFFLFVVMW AVMGAFIIGW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW VIIFALW	450 LBYAGVA LB-HFFTVF AB-IHFFTVF AB-IHFFILVE LB-IALNCIL LD-IALNCIL LD-IALNVK LB-IVNIVH FB-FVLPLG CB-ITNIMA FB-TAFVYR LD-IAFVYR LD-IAFVYR LD-IAFVYR LD-IAFVYR AB-ILVVVN AB-ILVVVN AB-ILVVWS AB-SVQMWS FF-FVQMWS B-ILV
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P18841   A1AB_MES. sp   P28223   5H2A_HUM. sp   P28021   HH2R_HUM. sp   P28908   5H1A_HUM. sp   P28908   SH1A_HUM. sp   P30518   V2R_HUM. sp   P37288   V1AR_HUM. sp   P37288   V1AR_HUM. sp   P3759   OXYR_HUM. Consensu	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN QDGRTGHGLR AN RSAKGHTPRS AU TKAKGHNPRS AU TKAKGHNPRS AN ASFERKNERN SHREPGSY AN ASFERKNERN SH QUKNLNLNA N AN LLAPC AN LLAPC ALA 451	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSVKLISK	AEKEVTR VI AKR.VVNIL SLRRITR VL NLRRITRIVL RETIVL TS REQAL TIS REQAL TIS REALANTS REKAANTS REKAANTS REKAANTS REKAANTS REHATVTS AKIRTVE TE AKIRTVE TE AKIRTVE TE	IMVIAFLIEW VVCFAVGW VVGAFVVGW VMGAFVVGW IMGVFVCW IMGVFVCW IMGVFVCW IMGVFVLW VGGFVLW VGGFLLW VVGFLFVVM AVMGAFIIG VIGTFLLW VTIFALIW VIJVVVLW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJAVIVW VIJVAVIVW VIJAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVVW VIJVAVIVW VIJVAVIVW VIJVAVIVW VIJVAVIVVW VIJVAVIVVW VIJVAVIVVW VIJVAVIVVVVVVVVVVVVVVVVVVVVVVVVVVVVVVVV	450 LP ++ FFLP LD ++ FFLP LD ++ FFLP LD ++ FFLVE LD ++ FILVE LD +LNCIL LD +LNCIL LD +LNVVK LD ++ VIVH FD +VLPLG CD +- TNIMA FD +- TAFVYR LD +- VALVL LD +- VALVL LD +- VALVL LD +- VALVL LD +- VALVL LD +- VALVL LD +- VALVA AD +- LVQLWA AD +- LVQLWA
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P0558   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P02699   OPSD_BOV.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC AN LLAPTTRGLPS AN ALA IS 451 IN FYIFTHOG	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR	AEKEVTR VI AKRVVVIII SLRRITR VL SLRRITR VL NLRRITRIVL RETVLTTS REOVALTTG KEH AALTTG REK AALTTG REK AALTTG REK AALTTG REH AALTTG SRKOVTA AVATVR TL AKIRTV TF AKIRTV TF AKIRTV TF	IMMIAFLIEW VVCFAFACW SIVAFAVCW VVGAFVVCW VMGVFVCW IMGVFVLW IMGVFVLW IVGVFVLW IVGVFVLW IVGVFLWW VVGAFILW VMGAFILW VMGAFILW VILAYIAW UI LAYIAW ILAYIAW ILAYIAW ILAYIAW	450 LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAUVE LP YAUVE L
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P05588   B1AR_HUM. sp   P0550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P28023   SH2A_HUM. sp   P28098   SH1A_HUM. sp   P20908   SH1A_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OYR_HUM. sp   P30559   OYR_HUM. Sp   P30559   OYR_HUM. Sp   P30559   OYSD_BOVI sp   P02699   OPSD_BOVI sp   P25103   NK1P_HUM.	401 IN AN AN AN AN AN CNGKPVECSQ AN PLANGRAGKR AQ DGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N LLAPC AN LLAPTRGLPS AN ALA IS 451 IN FYIF - THQG M YINDDYY	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS SLAVKLFKFS TGRTMQSIS HISSWKAATI AEAKRKMALA TURCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR SDFGPIFMTI	AEKEVTR VI AKRVVVII SLRRITR VL SLRRITR VL NLRRITREVL RET VL TS REQUALTIG KEHGALTIG REK AAKTIG NEQUACIVIG REK AAKTIG NEQUACIVIG REK AAKTIG NEQUACIVIG REK AAKTIG SRKOVTIA AKIRTVNITF AKIRTVNITF AKIRTVNITF AKIRTVNITF	IMMIAFLIAW SIVAFAVGW VVGAFVVGW VMGAFVVGW VMGVFVCW IMGVFVCW IMGVFTLW IVGVFVLW IVGFLFVVW VGMFILW IVGFLFVVMW IVGFLFVVMW IMGFFILW VILFALIW VILFALIW VILFALIW VILAYIAW IIGFFILW VILAYIAW IIGFVVVVLW VILAYIAW IIGFVVVVLW	450 LBYAGVA LB-HFFTVF AB-IHFFTVF AB-IHFFTVF LB-IHFFILVE LB-IALNCIL LD-IALNCIL LD-IALNVK LD-IALVVK LD-IALPLG CB-ITNIMA FD-FVLPLG LD-IALPLG CB-ITNIMA FD-FVLVVN AB-IQMWS AB-SVQMWS EB-ID-14 S00 KQ-SRNCMVT
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P28223   SH2A_HUM. sp   P28223   SH2A_HUM. sp   P28908   SH1A_HUM. sp   P20518   V2R_HUM. sp   P30518   V2R_HUM. sp   P37288   V1AR_HUM. sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P02699   OPSD_BOV. sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM.	401 IN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN QDGRTGHGLR AN RSAKGHTPRS AU TKAKGHNPRS AU TKAKGHNPRS AN ASFERKNERN SHREPGSY AN ASFERKNERN SH HQNKNLNLNA N AN LLAPC AN LLATTRGLPS AN ALA 451 IN FYIFTHQG NYINPDLYL	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSVKLISK SDFGPIFMTI KKFIQQVYLA	AEKEVTR VI AKRNVVNIL SLRRITR VL NLRRITRIVL RETIVL TS REQUAL TIS KEHGALTTG REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA AKIRTVTA AKIRTVTTA AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF	IMVIAFLIEW VVCFALEW SIVAVFAVCW VVGAFVVCW VIMCVFVCW IMCVFVCW IMCVFVCW IMCVFVCW IMCVFVLW VGVFVLW VVGVFVLW VVGVFVLW VVFLFVVWW AVMGAFIICW VIFLFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VILFALIW VIL	450 LPH FFLP LDH FFLP AB HFFNVF AB HFFVIVW TE HFFILVE LD SLANVVK LD SLANVVK LD SLANVVK LD ALPLG CF TNIMA FP FVLPLG CF TNIMA FP VLPLG CF TNIMA FP VLPLG FF TNIMA FF TNIMA FF TNIMA FF TNIMA FF TNIMA FF TNIMA FF TN
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT	401 IN AN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC ALAATTRGLPS AN ALA IS 451 IN FYIFTHQG AN YINPDLYL DWNHQIIA	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL	AEKEVTR VI AKRVVVIII SLRRITR VL NLRRITRIVL RETVLTVS REOVALTTG KEN AAKTG REK AAKTG REK AAKTG REK AAKTG REK AAKTG REK AAKTG REK AAKTG REK AAKTG REK AAKTG REK AKTG REK	IMMIAFLIEW VVCFAFAVCW VVGAFVVCW VTAVFVVCW IMGVFVLW IMGVFVLW IVGVFVLW IVGVFVLW IVGVFVLW IVGVFIEW VVGMFILW VVGMFILW VVGMFILW VVGMFILW VTLAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW VILAVIAW	450 LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAGVA LP YAUVE LP YAUVE L
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sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P08588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P28841   A1AB_MES. sp   P28223   5H2A_HUM. sp   P2896   SH1A_HUM. sp   P20761   TRFR_MOV. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OXYR_HUM. sp   P30559   OXYR_HUM. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT. sp   P41145   OPRK_HUM.	401 IN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN ASFERKNERN SH HQNKNLNLNA N AN LLAPC AN LLAPC AN LLATTRGLPS AN ALA IS 451 IN FYIFTHQG IN FYIFTHQG IN FYIFTHQG IN FYIFTHQG IN TLVDIDRR IN ALGSTSH.	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS SLAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMAL TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSVKLISK SDFGPIFMTI KKFIQQVYLA TCNHNLLFL DPLVVAALHL STAALSSYYF	AEKEVTR VI AKRNVVN I ETKRINV VL SLRRITR VL NLRRITRIVL RETVL TFS REQUAL TFG KEHGALTTG REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA REKGAATTA	IMMIAFLIAW VVCFALWW SI VAFAVCW VVGAFVVCW VMGAFVCW IMGVFVCW IMGVFVCW IMGVFVCW IVGGFVLW VVGMFILW VVGMFILW VVGMFILW VVGMFILW VTFALWW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW VIJFALW IMMN VNPIFVCCN NNPIFVCLN NNPIFVCLN	450 LP-++ FFLTP LD-++ FFLTP AD-++ FFLTP
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P25021   H4R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OXYR_HUM. sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P2503   NK1R_HUM. sp   P2555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM.	401 IN AN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC AN LLAPC AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRG. BN YINPDLYL DWNHQIIA N LLOP.IDRR AN ALGS.TSH.	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSVKLISK SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL DPLVVAALHL STAALSSYYF FCIDSNTFDV	AEKEVTR VI AKRVVKI I SLRRITR VL SLRRITR VL SLRRITR VL SLRRITR VL SEQUALTTG KEM AALTTG REK AALTTG RE	IMMIAFLIEW VVCFAFAVCW VVGAFVVCW VMGAFVVCW IMGVFVCW IMGVFVLW IMGVFVLW IVGVFVLW IVGVFVLW IVGVFLFVVM VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMGAFILW VMFL MGAFILW MMPVYMMM VMFLYCCLN VMFLYGFLN LNFIYAFLD LNFIYAFLD LNFIYAFLD	450 LP YAGVA LP YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGVA YAGV
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P21728   DADR_HUM. sp   P05588   B1AR_HUM. sp   P2500   A1AA_HUM. sp   P2502   S12A_HUM. sp   P26923   S12A_HUM. sp   P26923   S12A_HUM. sp   P25021   H12R_HUM. sp   P25021   H12R_HUM. sp   P25021   H12R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OYSD_HUM. sp   P30559   OYSD_BOVI sp   P30559   OPSD_BOVI sp   P2555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM.	401 IN AN AN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERNMERN SE HQNKNLNLNA N LLAPC AN LLAPC AN LLATTRGLPS AN ALA IS 451 IN FYIFTHQG AN TLVDIDRR AN TLVDIDRR ALGSTSH- N PFCGSGETQP AN ALGS	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSINTISR SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL DPLVVAALHL STAALSSYYF FCIDSNTFDV PLVDDJ EVE	AEKEVTR VI AKRVVVII SLRRITR VL SLRRITR VL NLRRITREVL RET VL TS REQ ALTTG KEH AALTTG REK AAATTG NEQ ACIVG REK AAATTG NEQ ACIVG REK AAATTG REK AA	IMMIAFLIEW VVCFAFAVCW VVCGAFVVCW VVCGAFVVCW VIMCVFVCW IMGVFVCW IMGVFTLCW IVGCFTLCW IVGCFTLCW VVCFFLFVVMW AVMGAFILCW VVCFFLFVVMW IMGTFILW VVCFFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCFAFU VVCF	450 LBYAGVA LB-HFFVVF AB-LHFFVVF AB-LHFFVVF LB-LALNCIL LD-LALNCIL LD-LALNVK LD-LALNVK LD-LVNVK LD-LVNVK LD-LVVLVL AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN AB-LVVVN B-LFV EN-KRCRRD AD-RKACSTO
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sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P25202   HH2R_HUM. sp   P26223   SH2A_HUM. sp   P262021   HH2R_HUM. sp   P08908   SH1A_HUM. sp   P20502   HH2R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P2550   NK1R_HUM. sp   P21555   NY1R_RAT. sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P08588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM.	401 IN	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSVKLISK SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL DPLVVAALHL STAALSYYF FCIDSNTFDV ELVPDRLFVF NLIRKEVYIL	AEKEVTR VI AKRVVVIII SLRRITR VL SLRRITR VL NLRRITRIVL RETVLTTS REOGALATTG KENGALATTG REKGAATTG REKGAATTG REKGAATTG REKGAATTG RENGACTG RENGACTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGATTG RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT RENGAT	IMMIAFLIEW VVCFAFAVCW VVGAFVVCW VTACFVCW IMGVFVCW IMGVFVLW IMGVFVLW IVGVFVLW IVGFFLWW VGMFILW IVGFFLWW VGMFILW VMGAFILW VMGAFILW VTLAVIAW UILFALIW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW ILAYIAW VILAYIAW ILAYIAW	450 LEYAGVA LE-HFFLP LE-LT-FNTVF AE IHFFILVE LE-LT-FNTVF LE-LT-FNTVF LE-LNTVF LE-LANVK LE-LANVK LE-LANVK LE-LANVK LE-LANVK LE-LANVK AE-SVQWS LE-LVVN AB-LVVN AB-LVVLWA AB-SVQWS LE-LVVN AB-LVVVN AB-LVVLWA AB-SVQWS E-LVVN C-SRNCMVT DR-SRLGKH KN-QRDLQF EN-KRCRQ D-SRKAFST PD-SRKAFST PD-SRKAFST PD-SRKAFST
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P21728   DADR_HUM. sp   P05588   B1AR_HUM. sp   P2500   A1AA_HUM. sp   P25021   H42R_HUM. sp   P25021   H42R_HUM. sp   P25021   H42R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OYSD_HUM. sp   P30559   OYST_HUM. sp   P30559   OYST_HUM. sp   P2503   NK1R_HUM. sp   P2555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DAR_HUM. sp   P21728   DAR_HUM. sp   P21555   NY1R_RAT sp   P41145   OPRK_HUM. sp   P08588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM.	401 IN	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS TGRTMQSIS HISSWKAAIA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSINTISR RVSSINTISR SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL DPLVVAALHL STAALSSYYF FCIDSNTFDV ELVPDRLFVF NLIRKEVYIL SE GVFKV	AEKEVTR VI AKRVVVII SLRRITR VL SLRRITR VL NLRRITREVL RET VL TS REQ ALTTG KEH ALTTG REK AAKTG NEQSACIVG REK AAKTG NEQSACIVG REK AAKTG REK AAKTG REK AKTT AKIRTVTA AKIRTVTTA AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF AKIRTVTTF	IMMIAFLIGW VVCFAFAVGW VVGAFVVGW VVGAFVVGW VIAVFVCW IMGVFVCW IMGVFVCW IMGVFTLW IVGCFVLW VVGMFILW VVGMFILW VVGMFILW VVGAFIIGW VVGAFIIGW VVGAFIIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFIGW VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVGAFU VVVVV VV VV VVGAFU VVVVV VV VV VV VV VV VV VV VV VV VV VV	450 LBYAGVA LB-HFFVVF AB-LHFFVVF AB-LHFFVVF LB-LALNCIL LD-LALNCIL LD-LALNCIL LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LALNCI LD-LAL
<pre>sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P05588   B1AR_HUM. sp   P0550   B2AR_HUM. sp   P0550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P28841   A1AB_MES? sp   P28923   SH2A_HUM. sp   P20518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OYSD_BOV. sp   P30559   OYST_HUM. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM. sp   P25100   A1AA_HUM. sp   P25100   A1AA_HUM. sp   P18841   A1AB_MES?</pre>	401 IN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN ALA AN ALS AN ALS AN ALS AN ALS AN AN AN ALS AN AN AN ALS AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN AN A	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS SLAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSVKLISK SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL DPLVVAALHL STAALSSYYF FCIDSNTFDV ELVPDRLFVF NLIRKEVYIL SE GVFKV PD AVFKV	AEKEVTR VI AKRNVVVII SLRRITR VL NLRRITRIVL RETVLTTS REQUALTIG KEHGALKTIG REK 4AATTA REK 4AATTA REK 4AATTA REK 4AATTA REK 4ATTA AKIRTVTA AKIRTVTA AKIRTVTA AKIRTVTT AKIRTVTT AKIRTVTT AKIRTVTT AKIRTVTT AKIRTVTT AKIRTYTT CHLTAMISTC CIA ASS FNWF WA S FNWF WA S	IMUIAFLIAW VVCFALW SI VAFAVCW VVGAFVVCW VIAVFVVCW IMGVFVCW IMGVFVCW IMGVFVCW IMGVFVCW 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AB-LVV
<pre>sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P25203   SH2A_HUM. sp   P26203   SH2A_HUM. sp   P26203   SH2A_HUM. sp   P26201   HH2R_HUM. sp   P26201   HH2R_HUM. sp   P26201   HH2R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P08588   B1AR_HUM. sp   P0550   B2AR_HUM. sp   P0550   B2AR_HUM. sp   P28223   SH2A_HUM.</pre>	401 IN AN AN AN AN GNGKPVECSQ AN PLANGRAGKR AN QDGRTGHGLR AN RSAKGHTFRS AU TKAKGHNPRS AU TKAKGHNPRS AN RSIHREPGSY AN ASFERKNERN SE HQNKNLNLNA N AN ASFERKNERN SE HQNKNLNLNA N AN LLAPC AN LLAPC AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN ALA.TTRGLPS AN SIFPDLYL DWNHQIIA N TLVDIDRR AN ALGS.TSH. N FCGSGETQP AN SLFPQLKP AU SLFPTLKP AU SLFPTLKP	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPSRLVAL RSSKF-CL SLSVRLLKFS SIAVKLFKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSVKLISK SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL DPLVVAALHL STAALSYYF FCIDSNTFDV ELVPDRLFVF NLIRKEVYIL SEGVFKV PDAVFKV EDVIGALLNV	AEKEVTR VI AKRVVKI I ETKRINV 22 SLRRITR V1 NLRRITRIVI RETVLTTS REQUALATTG KENALATTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAATG REKAAKTG REKAAKTG REKAATG REKAATG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAATG REKAATG REKAATG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAAKTG REKAATG REKAAKTG REKAAKTG REKAATG REKAATG REKAATG REKATG REKA REKATG REKAATG REKATG REKA REKATG REKATG REKA REKATG REKATG REKATG REKA REKATG REKATG REKATG REKA REKATG REKATG REKA REKATG REKATG REKATG REKA REKATG REKATG REKA REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG REKATG	IMMIAFLIEW VVCFALWW VVGAFVVCW VVGAFVVCW VMGVFVCW IMGVFVLW IMGVFVLW IVGVFVLW IVGVFVLW IVGVFLWW VVGMFILW VVGMFILW VVGMFILW VVGMFILW VMGAFILW VMGAFILW VILAXIAW VILAXIAW VILAXIAW VILAXIAW VILAXIAW VILAXIAW VILAXIAW VILAXIAW VILAXIAW ILAXIA VMPVYIAW ILAXIA VMPVYIAW ILAXIA VMPIYYAFLD NPIYAFLD NPIYAFLD NPIYAFLD NPIYAFLD NPIYAFL VNPLYPCSS VNPLYYCSS	450 LE YAGVA LE H-FNTVF ALD H-FNTVF ALD H-FNTVF LE LT FNTVF LL LANVK LE LANVK LE LANVK LE LANVK LE LANVK LE LANVK ALD TALPAG CE LANVK LE LANVK ALD TALPAG CE LANVK ALD TALPAG SVQWS E LANVK SVQWS E LANVK SVQ SVQWS E LANVK SVQ SVQWS E LANVK SVQ SVQ SVQ SVQ SVQ SVQ SVQ SVQ
sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P05588   B1AR_HUM. sp   P0550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P2502   A1AA_HUM. sp   P2502   HH2R_HUM. sp   P2502   HH2R_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OYST_HUM. sp   P30559   OYST_HUM. Sp   P2503   NK1R_HUM. sp   P2555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DARA_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DARA_HUM. sp   P21728   DARA_HUM. sp   P21728   DARA_HUM. sp   P21728   DARA_HUM. sp   P21728   DARA_HUM. sp   P21728   DARA_HUM. sp   P25100   A1AA_HUM. sp   P18841   A1AB_MESA sp   P28223   SH2A_HUM.	401 IN	ATTQK YHEQVS SKYRSS KEKDR PESSFKMSFK RPSRLVAL RSS KF-CL SLSVRLLKFS SIAVKLFKFS TGRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA ' HVSA ' HVSA ' HVSA ' HVSA '	AEKEVTR VI AKRVVVII SLRRITR VL SLRRITR VL NLRRITRIVL RET VL TS REQ ALCTIG KEH ALCTIG REK AAKTIG NEQ ACIVIG REK AAKTIG NEQ ACIVIG REK AAKTIG REK AAKTIG REK AAKTIG SRKOVT AKIRTVT AKIRTVT TAKIRTVT TAKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T AKIRTVT T A AKIRTVT T A AKIRTVT T A A A A A A A A A A A A A A A A A	IMMIAFLIEW VVCFALWW VVGAFVVW VVGAFVVW VTAVFVCW IMGVFVCW IMGVFVCW IMGVFLW VGMFILW VVGMFILW VVGMFILW VVGMFILW VVGMFILW VVGAFIIW VVGAFIIW VVGAFIIW VVILFALW VILFALW VILFALW VILFALW VILAXIAWW VILAXIAWW VILAXIAWW VILAXIAWW VILAXIAWW VILAXIAWW VNPIYCCLN VNPIYCCLN VNPIYCCLN VNPIYCCS NPIYCSS VNPLYCSS VNPLYCSS VNPLYCSS	450 LBYAGVA LB-HFFVVF AB IHFFVVF AB IHFFVVF LB-IHFFILVE LD-IALNCIL LP-IALNCIL LP-IALNVK LD-IVNVK LD-IVNVK LD-IVNVK LD-IVNVK LD-IVNVK LD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD-IVNVK AD
<pre>sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P05588   B1AR_HUM. sp   P0550   B2AR_HUM. sp   P0550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P25021   H42R_HUM. sp   P26923   5H2A_HUM. sp   P2761   TRFR_MOV. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30519   V1R_HUM. sp   P30559   OYSD_BOV. sp   P30559   OYSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM. sp   P21728   DADR_HUM. sp   P2500   DADR_HUM. sp   P2500   DADR_HUM. sp   P2500   DATA_HUM. sp   P18841   A1AB_MESA sp   P28223   5H2A_HUM. sp   P25021   HH2R_HUM. sp   P25021   HH2R_HUM. sp   P25021   HH2R_HUM.</pre>	401 IN	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPS RLVAL RSS KF-CL SLSVRLLKFS SLAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA ' VVSA ' VVSA ' VVSA '	AEKEVTR VI AKRNVVVII SLRRITR VL SLRRITR VL NLRRITRIVL RET VL TYS REQUALTIG KEHGALKTG REK 4AATTA REK	IMUIAFLIAW VVCTFILW SIVAFAVCW VVGAFVCW VTAVFVCW VTAVFVCW IMGVFVCW IMGVFVCW IMGVFVCW IMGVFVCW IMGVFVCW IMGVFLWW VGCFILW VGFLFVVMW AVMGAFIIW VFLFALW VVGFALW VTAVFALW VTIAFLAW VTIAFLAW VILAYIAW IILAFIVW VILAYIAW IILAFIVW VFLFXGEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN NPIXCEN	450 LBYAGVA LB-H FFLVE LB-THFFNVF AB IH FFIVE LB-TALNCIL LD-TALNCIL LD-TALNCIL LD-TALNUK LD-TALVIK FB-FVVPLG CD-TNIMA FB-FVVPLG CD-TNIMA FB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVVN AB-TVVV
<pre>sp   P02699   OPSD_BOV. sp   P25103   NK1R_HUM. sp   P21555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P41145   OPRK_HUM. sp   P07580   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P25203   SH2A_HUM. sp   P25203   SH2A_HUM. sp   P26203   SH2A_HUM. sp   P26203   SH2A_HUM. sp   P26201   HH2R_HUM. sp   P08908   SH1A_HUM. sp   P30518   V2R_HUM. sp   P30518   V2R_HUM. sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P30559   OXYR_HUM. Sp   P2555   NY1R_RAT sp   P41143   OPRD_HUM. sp   P21728   DADR_HUM. sp   P08588   B1AR_HUM. sp   P07550   B2AR_HUM. sp   P25100   A1AA_HUM. sp   P2500   A1AA_HUM. sp   P28223   SH2A_HUM. sp   P28021   HH2R_HUM. sp   P28021   HH2R_HUM. sp   P28021   HH2R_HUM. sp   P28021   HH2R_HUM. sp   P08908   SH1A_HUM.</pre>	401 IN	ATTQK YHEQVS SKYRSS REKDR PESSFKMSFK RPSRLVAL RSSKF-CL SLSVRLLKFS SIAVKLFKFS SIAVKLFKFS TGRRTMQSIS HISSWKAATI AEAKRKMALA TNRCFNSTVS HVSA 'VSSVKSISR RVSSINTISR RVSSINTISR RVSSINTISR RVSSVKLISK SDFGPIFMTI KKFIQQVYLA TCNHNLLFLL DPLVVAALHL STAALSYYF FCIDSNTFDV ELVPDRLFVF NLIRKEVYIL SEGVFKV PDAVFKV EDVIGALLNV DAINEVLEAI CHMPTLLGAI	AEKEVTR VI AKRVVKI I SLRRITR VL SLRRITR VL SLRRITR VL SLRRITR VL SLRRITR VL SEQUALSTG KENGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG REKGALSTG	IMMIAFLIEW VVCFAFAVCW VVGAFVVCW VTACFVCW IMGVFVCW IMGVFVLW IMGVFVLW IVGCFVLW IVGFFLWW VJGMFILW IVGFLFVVM VGMFILW VVGAFIIW VTLAVIAW VTLAVIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW ILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW VILAYIAW	450 LE YAGVA LE H-FYIVE LE LT FFNTVF AE IH FVIVW TE IH FILVE LE LANVVK LE LANVVK LE LANVVK LE LANVVK LE LANVVK AE LANVVK AE TAFVR FE TAFVR E TAFVR AE TAFVR AE TAFVR AE TAFVR AE TAFVR E TAFVR E TO AF TAFVR E TO AF TAFVR E TO AF TAFVR E TO AF TAFVR AE T

sp	P30518 V2	R_HUMAN	AWDP EAPL	EGA · PFVL	LMLLASLNSC	TNPWIYASFS	SSVSSE-LRS
sp	P3 / 288   V1	AR_HUMAN	VWDP MSVW	TESENPTITI	TALLESLINSC	CNPWHYMFFS	GHLLQDCVQS
SD	P30559   OX	YR HUMAN	VWDA NAPK	EASAFII	VMLUASLNSC	CNEWIYMLET	GHLEHELVOR
	C	onsensus			lgy ns	NP iY	E E
					TM	7	
			501				550
sp	P02699 OP	SD_BOVIN	TLCCGKNPLG	DDEASTTVSK	TETSQVAPA	VIZUODI DOMT	CONTROL VERDE
sp	P23103   NK	TR RAT	FENECDERSR	DDDVETIANS	TRILQIQGSV	IKVSRLEITI	STVVGAHEEE
sp	P4114310P	RD HUMAN	LCRKPCGRPD	PSSESRPREA	TARERVTACT	PSDGPGGGRA	A
sp	P41145 OP	RK_HUMAN	FCFPLKMRME	RQSTSRVRNT	VQDPAYLRDI	DGMNKPV	
sp	P21728 DA	DR_HUMAN	LLGYRLCPA	TNNAIETVSI	NNNGAAMFSS	HHEPRGSISK	ECNLVYLIPH
sp	P08588 B1	AR_HUMAN	LLCCARRAAR	RRHATHGDRP	RASGCLARPG	PPPSPGAASD	DDDDDVVGAT
sp	P07550 B2	AR_HUMAN	LLCLRRSSLK	AYGNGY	SSNGNTGEQ-	SGYHVEQ	EKENKLLCED
sp	P25100   A1	AA_HUMAN	LLROQCR R	RRRRRPLWRV	YGHHWRASTS	GLRQDCAPSS	GDAPPGAPLA
sp	P18841 A1	AB_MESAU	ILGOQCRSGR	RRRRRRRLGA	CAYTYRPWTR	GGSLERSQSR	KDSLDDSGSC
sp	P28223   5H	2A_HUMAN	I ECODI ANDN	CULTER DENN	1 PALAIKSSQ	LQMGQKKNSK	QDAKT TDNDC
sp	P0890815H	1 A HIMAN	TIKCKECBO	SHRISLKSINA	SQUSKIQSKE	PRQQEERPLK	LÕAMPGIEAL
sp	P21761 TR	FR MOUSE	LCNCKOKPTE	KAANYSVALN	YSVIKESDRF	STELEDITVT	DTYVSTTKVS
sp	P30518 V2	R HUMAN	LLCCARGRTP	PSL-GPODES	CTTASSSLAK	DTSS	
sp	P37288 V1	AR_HUMAN	FPCONMKEK	FNK-EDTDSM	SRRQTFYS	NNRSPT	NSTGMWKDSP
sp	P47901 V1	BR_HUMAN	LACCGGPQPR	MRR-RLSDGS	LSSRHTTLLT	RSSCPATLSL	SLSLTLSGRP
sp	P30559 OX	YR_HUMAN	FLCCSASYLK	GRRLGETSAS	KKSNSSSFVL	SHRSSSQRSC	SQPSTA
	С	onsensus	c				
			F F 1				600
en		SD BOUTN	221				600
sp	P25103 NK	1R HUMAN	PEDGPKATPS	SLDLTSNCSS	RSDSKTMTES	FSFSSMULS	
SD	P21555   NY	1R RAT		000010100000	Robbittitibb	1010000000	
sp	P41143   OP	RD_HUMAN					
sp	P41145 OP	RK_HUMAN					
sp	P21728 DA	DR_HUMAN	AVGSS-EDLK	KEEAAGIARP	LEKLSPALSV	ILDYDTDVSL	EKIQPITQNG
sp	P08588 B1	AR_HUMAN	PPARLLEPWA	GCNGGAAADS	DSSLDEPCRP	GFASESKV	
sp	P07550 B2	AR_HUMAN	LPGT EDFV	GHQGTVPSDN	ID		
sp	P25100   A1	AA_HUMAN	LTALPDPDPE	PPGTPEMQAP	VASRRKPPSA	FREWRLLGPF	RRPTTQLRAK
sp	P18841 A1	AB_MESAU	MSGSQRTLPS	ASPSPGYLGR	GAQPPLELCA	YPEWKSGALL	SLPEPPGRRG
sp	P26223   5H	2R HUMAN	ADOCATOR	ELASKDINSDG	VNERVSCV		
sp	P0890815H	1A HUMAN	AFQGAIDA				
sp	P21761 TR	FR MOUSE	FDDTCLASEN				
sp	P30518 V2	R_HUMAN					
sp	P37288 V1	AR_HUMAN	KSSKSIKFIP	VST			
sp	P47901 V1	BR_HUMAN	RPEESPRDLE	LADGEGTAET	IIF		
sp	P30559 OX	YR_HUMAN					
	C	onsensus					
			601				650
SD	P0269910P	SD_BOVIN					050
sp	P25103 NK	1R_HUMAN					
sp	P21555 NY	1R_RAT					
sp	P41143 OP	RD_HUMAN					
sp	P41145 OP	RK_HUMAN					
sp	P21728 DA	DR_HUMAN	QHPT				
sp	P08588 B1	AR_HUMAN					
sp	P07550 B2	AR_HUMAN					
sp	P188/11 A1	AR MESAN	RIDSCRIFTE	KLLGEBESBC	TE-CDASNCC	CDATTDI ANC	OPCEKENMET
SD	P2822315H	2A HUMAN			12 GDADWGG	CDATIDIANG	AT OL KOMMEL
SD	P25021   HH	2R_HUMAN					
sp	P08908 5H	1A_HUMAN					
sp	P21761 TR	FR_MOUSE					
sp	P30518 V2	R_HUMAN					
sp	P37288 V1	AR_HUMAN					
sp	P47901 V1	BR_HUMAN					
sp	P30229 OX.	YK_HUMAN					
	C	onsensus					

	651
sp P02699 OPSD_BOVIN	
sp P25103 NK1R_HUMAN	
sp P21555 NY1R_RAT	
sp P41143 OPRD_HUMAN	
sp P41145 OPRK_HUMAN	
sp P21728 DADR_HUMAN	
sp P08588 B1AR_HUMAN	
sp P07550 B2AR_HUMAN	
sp P25100 A1AA_HUMAN	YSNLRETDI
sp P18841 A1AB_MESAU	APGHF
sp P28223 5H2A_HUMAN	
sp P25021 HH2R_HUMAN	
sp P08908 5H1A_HUMAN	
sp P21761 TRFR_MOUSE	
sp P30518 V2R_HUMAN	
sp P37288 V1AR_HUMAN	
sp P47901 V1BR_HUMAN	
sp P30559 OXYR_HUMAN	
Consensus	

Figure 3. A typical multiple sequence alignment. 18 various GPCRs were aligned using the Multalin program; see the header in the listing for reference. The SWISS-PROT-encoded sequences decypher into the following human (unless otherwise stated) GPCRs in the descending order: bovine rhodopsin, NK1 receptor, rat neuropeptide Y(1) receptor, opioid  $\delta$  receptor, opioid  $\kappa$  receptor, D(1a) dopamine receptor, adrenergic  $\beta$  1a receptor, adrenergic  $\beta$  2a receptor, adrenergic  $\alpha$ 1a receptor, rabbit adrenergic  $\alpha$ 1b receptor, serotonin 2A receptor, histamine H2 receptor, serotonin 1A receptor, mouse thyroliberin receptor, V2R, V1aR, V1bR and OTR. Invariant residues are black and conservative residues are gray. The trasmembrane helices TM1-TM7 are underlined.

The following three schemes for 7TM building are our favorite:

- (i) The older scheme of Baldwin [4], based on a critical alignment, see Figure 3, of ~200 GPCR sequences. Through an extensive examination of distributions along the putative helices of polar/non-polar and conservative/non-conservative residues, the method enables a rational choice of the helical sequences TM1-TM7 and their unique threading onto a low-resolution structure of rhodopsin. This 7TM model was subsequently refined to the self-consistency of 1.67Å, by the inclusion of all experimentally available distance, positional and orientational constraints typical of bovine rhodopsin [26]. The automated GPCR-modeling server, based on this scheme, is available via Internet [27].
- (ii) The most recent scheme of Baldwin et al [19] using the same rationale as the original one [4] yet for as many as ~500 sequences and therefore enabling refinements such as variable helical lengths, relative TM shifts, and kinks in TM5 and TM6, all features affirmed by recent experimental data. A relevant 7TM template is available from the authors upon request.
- (iii) The *ab initio* model of Mosberg et al [28]. This model also uses multi-sequence alignment for the choice of the 7TM helices, followed by a distance-geometry optimization applied simultaneously to 410 GPCR sequences. First, putative hydrogen bonds between polar/charged residues within the GPCR interior are

singled out. Subsequently, they are used collectively and simultaneously for many overlapping GPCRs as constraints in the iterative distance-geometry procedure, aimed at the optimization of *an averaged* 7TM bundle.

All three methods have in common an extensive use of multi-sequence analysis for making choices of TM1 through TM7. Ones the helices singled out, the methods [(i) and (ii)] probe the TM1-TM7 mutual arrangement either by a rule-based threading them onto the foggy shape of rhodopsin, upon an assumption that the sequence homology legitimates 7TM 3-dimensional structure homology, or [Method (iii)] by a rule-based *ab initio* 7TM arrangement optimization. Methods (i) and (ii) work only at the C<sup> $\alpha$ </sup>-trace level and are strictly limited to modeling the 7TM bundle, while Method (iii) in principle can also be used for modeling EL and IL loops. These are non-conservative among the receptor types and much more obscure for modeling than the 7TM domain. All three methods give similar averaged shape of the 7TM bundle, Figure 4. Interestingly, the resulting bundles from (ii) and (iii) better overlap than (i) and (ii), despite close methodological relationship between the latter two.



Figure 4. Stereodiagram of overlapping TM bundles resulting from procedure: (i) green, (ii) blue and (iii) red. Extracellular view onto the membrane surface (TOP) and lateral view (BOTTOM). The conservative residues as indicated in Ref. [19] are marked with balls in Model (ii).

## 3. Biological Signal Transductuion via Vasopressin V2 Receptor

Vasopressin (AVP) and oxytocin (OT) are two similar nonapeptide hormones produced in the neurophysis and released to the blood in the pituitary posterior lobe. They differ only on the two amino acids X and X' in their otherwise common CYXQNCPX'G-NH<sub>2</sub>, where in AVP (X, X') = (F, R)sequence: and in OT(X, X') = (I, L). Major AVP activities consist of blood pressure control via the Vla receptors (VlaR) in blood vessels and urine concentration (antidiuresis) via the V2 receptors (V2R) in the kidney. Oxytocin controls labor and lactation in mammalian females via a common oxitocin receptor (OTR) in the uterus and the mammalian gland, respectively. V1aR, V2R and OTR, being 370-400 amino acid long, are typical members of the rhodopsin family of GPCRs, compare Figure 3. For the best-studied AVP/V2R system a number of mutations were identified, giving rise to the hereditary X-linked (i.e. carried by women but affecting boys) nephrogenic diabetes insipidus, consisting in a disability to concentrate the urine, resulting in an extensive diuresis and, possibly, death of dehydratation [29]. Other variants of nephrogenic diapetes insipidus, resulting from pathological deficiency of AVP, are cured by administration of V2R-selective AVP superagonist, desamino-[D-Arg<sup>9</sup>]AVP (DDAVP, desmopressin<sup>®</sup>) [29]. Both, the pathological mutations and model biochemical experiment, using mutagenesis [30, 31, 32] as a tool for studying V2R structure-activity relationships, warrant molecular modeling of V2R and its interaction with bioligands.

Our initial V2R model was obtained using Method (i), see above. The loops EL1-EL3, 1L1-IL3 and the N- and the C-termini were added using protein loopbuilding tools inherent in Sybyl suite of programs [33]. Initial ligand docking was attained in several ways, always respecting a complementarity in the electrostatic potentials of the V2R cleft, see below, and the ligand. The systems were



Figure 5. Optimized V2R/bioligand complexes. Only the extracellular parts are shown. V2R is grayshaded and the ligands are black. The receptor's interacting residues are labeled and their side chains exposed. A. V2R/AVP; B. V2R/selective peptide antagonist desGly<sup>9</sup>-[Mca<sup>1</sup>,D-Ile<sup>2</sup>,Ile<sup>4</sup>]AVP; C. V2R/selective nonpeptide antagonist OPC-31260.

equilibrated using a Constrained Simulated Annealing (CSA) protocol, with all but the 7TM C<sup> $\alpha$ </sup> atoms free to move. Optimal ligand docking modes were chosen using the ligand/receptor interaction energies and structure-activity data [34, 35] as the selection criteria. Our studies consisted of systems' relaxation using CSA in vacuo in the earlier works [36, 37, 38], and the molecular dynamics for the systems immersed in the fully hydrated phospholipid bilayer in the recent works [39, 40]. Details of computing and analyses are described elsewhere [36, 40].

From Figure 5 it is seen that any GPCR modeled to the RD template [26, 27] has a  $\sim$ 21Å deep cavity on the extracellular side, surrounded by TM3-TM7, with a narrower extension towards TM2. The cavity ends up on a floor from the hydrophobic residues TM3:M123, TM4:L170, TM5:V213,F214 and TM6:W284, F287,F288 in V2R. The cleft is large enough to accommodate the pressin ring (CYFQNC) of AVP and even more so to fit the OPC-31260 non-peptide antagonist. Most of the simulations, whether with a peptide ligand or not, converged to the docking modes typical of V2R/AVP [36]. However, OPC-31260 as much thinner than the AVP pressin ring, cannot fill up the entire V2R cleft and it adheres to the front side of the TM3-TM7 cavity in its most preferred arrangements, see Figure 5C [37].

In Figure 5 all V2R interacting residues are marked so that the significant receptorligand interactions could be seen. Both the V2R/peptide complexes develop a number of polar and nonpolar interactions with the cleft walls. Major interactions, common to both AVP and its peptide antagonist desGly<sup>9</sup>-[Mca<sup>1</sup>,D-Ile<sup>2</sup>,Ile<sup>4</sup>]AVP involve on the V2R part TM3:C112,V115-K116,Q119,M123; TM4:Q174; TM5:V206,A210,V213; TM6:W284,F287,F288,Q291 and TM7:F307,L310,A314,N317; see Figs. 5A and 5B. The Mca<sup>\*</sup>  $\beta$ , $\beta$ -pentamethylene moiety fits snugly a hydrophobic pocket formed by TM3:V115 and TM7:L310 and A314. The non-peptide antagonist OPC-31260 orients itself typically so that its long axis is nearly vertical and its HN(CH<sub>3</sub>)<sub>2</sub><sup>+</sup> is involved in an (bifurcated) ion bridge with one (two) of the numerous negatively charged Asp and/or Glu residues in ELs, see Figure 5. With this regard, it is interesting to notice that EL2 contains three carboxylates in V2R and two in V1aR, which may bear on the increased V2R/V1aR selectivity of the OPC-31260<sup>\*</sup> analogs with a cationic group in the equivalent place [35].

The tendency for all three ligands to dock within the same compartment of the V2R extracellular cavity, suggests a simple competitive mechanism for the antagonism toward V2R by both desGly<sup>9</sup>-[Mca<sup>1</sup>,D-Ile<sup>2</sup>,Ile<sup>4</sup>]AVP and OPC-31260. The V2R amino acid residues, involved in ligand binding, are invariant or conservative for the subfamily, or even invariant over the whole GPCR superfamily (TM3:C112, TM4:Q174, TM6:W284,F287 and TM7:N317). The invariant (conservative) residues within the subfamily may be pertinent to ligand binding while those invariant over the whole GPCR superfamily may have to do with the

<sup>\*</sup> Abbreviations: Mca β,β-cyclopenta-methylene-β-mercaptopropionyl; OPC-31260 [5-dimethylamino-1-{4-(2-methyl-benzoyl-amino)- benzoyl}-2,3,4,5-tetrahydro-1H-benzazepine.

signal transduction, putatively universal for the whole GPCR superfamily. Our results on agonist docking agree with those obtained by Mouillac et al for a related AVP/V1aR system. Furthermore, some of the equivalent V1aR residues have already been found critical for the ligand affinity [41].

In our most recent work [40] we performed comparative unconstrained molecular dynamics of the AVP/V2R complex and an empty V2R in the fully hydrated lecithine (dimyristoylphosphatidilcholine, DMPC) bilayer. In Figure 6 the interiors of the intracellular sides of empty V2R and its V2R/AVP complex are compared. Both images represent well-relaxed structures, resulting from averaging the last 300 ps of ~1500 ps total simulation in each case. It is seen that in the V2R/AVP complex there is a contiguous network of internal polar receptor residues, extending from the ligand to the cytosolic domain, whereas in the empty V2R a similar network is interrupted. The most prominent difference regards the TM3:Thr134-TM7:Tyr325 contact, present in the V2R/AVP complex but absent in the empty V2R. Interestingly, both residues belong to those universally conserved over the GPCR superfamily [4, 19], see Figure 3. Thus, the relaxed structures are compatible with the active and passive forms of V2R respectively, and possibly indicative of details of an allosteric signal transduction mechanism.



Figure 6. Space-filled networks of polar residues (blue) and prolines (green), spanning interior of V2R from AVP (thick gray backbone) to the conservative and important in signal transduction (see Figure 3) DRH sequence at the C-terminus of TM3 (standard colors: C,H gray, O red and N blue): in V2R/AVP complex (TOP) and in empty V2R (BOTTOM). It is seen that a contiguous network only preserves in the receptor-ligand complex. Note that the TM3:Thr134-TM7:Tyr325 (pink) contact is preset in the V2R/AVP complex while it is absent in the empty V2R.

### 4. Perspectives

Contemporary protein modeling is not advanced enough for full credibility. Rather, it hopefully may guide as to specific mutagenesis/affinity studies aimed at the verification of arising hypotheses. The afore-mentioned V2R residues, appearing to be responsible for ligand binding, should be among the first candidates for experiments of this kind. Progress in GPCR modeling may be expected from the following areas:

- (1) The Protein Structure Database at Brookhaven [42] is growing exponentially, now exceeding 7000 objects totally and 1000 having unique folds [43], thus providing a basis for analyses and taxonomy of structural protein motifs. The analysis of the accumulation rate of these motifs optimistically indicates that in 5-10 years, more or less simultaneously with the completion of the human genome project, the collection of the structural motifs may approach the state of saturation [43, 44], which in turn forecasts well for homology modeling.
- (2) Progress continues in the electron cryo-microscopy going down to lower and lower temperatures, towards the liquid helium. This will dramatically reduce a destructive effect of the electron beam thus improving the number of collected structure factors and eventually the resolution. A measure of success in this field may be the first high-resolution structure solution of bacteriorhodopsin (another 7TM integral membrane protein yet not a GPCR) [25], giving hope that other TM proteins will follow soon.
- (3) A new era for X-ray (micro)crystallography is coming, implementing cubic lipid phase [45]. This, together with the third-generation synchrotronic sources, providing for enormously strong X-ray radiation, forecast a possible breakthrough in the X-ray crystallography of integral membrane proteins [46, 47]. Two recent high-resolution structure solutions, using these new techniques for the most studied landmark protein bacteriorhodopsin [24, 48], argue in favor of this optimism.

If a break-through in the accumulation rate of the transmembrane protein motifs to the Protein Structure Database were indeed around the corner, then the basis for an increasingly rationalized homology modeling of GPCRs would grow rapidly.

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