Prediction of nanographene binding-scores to trout cellular receptors and cytochromes

Connolly, M., C., Navas, J.M. and Coll, J'.

Department of Environment. Instituto Nacional de Investigacion y Tecnología Agraria y Alimentaria, INIA. Madrid, Spain.

short title: nanographenes AHR and CYP bindings

Keywords: nanographene fragment; AHR; CYP; P450; trout; virtual binding; docking; ligands;

Connolly, Mona email: connolly.mona@inia.es orcid: 0000-0003-3574-8564

Navas, Jose María email: jmnavas@inia.es orcid: 0000-0002-7644-8499

Corresponding author Coll, Julio email: juliocollm@gmail.com orcid: 0000-0001-8496-3493

Abstract: To address the increasing concerns surrounding possible impacts of graphene-related materials on the aquatic environment, this study focused on computational predictions of binding between models of graphenes in the nm size range (nanographenes, nGs) and the aryl-hydrocarbon receptor (tAHR) and P450 cytochromes (tCYPs) of rainbow trout (*Oncorhynchus mykiss*). The tAHR plays a key role in the induction of detoxifying and early immune responses and tCYPs are essential for detoxifying planar hydrophobic chemicals such as nGs. After 3D modelling of those trout proteins, docking algorithms predicted the size-dependance profiles of nGs binding-scores to tAHR and tCYPs in the low nM range (high binding-affinities). Virtual oxidations of nGs to nGOs (carboxy-, epoxy- and/or hydroxy-oxidations) further lowered the corresponding binding-scores in level/type-oxidation manners. Among all the tCYPs, the tCYP3AR (the equivalent to human CYP3A4) was identified as a potential key interaction enzyme for nGs because of its lower binding-scores. These results implicate a possible processing pathway to be further probed through *in vitro* and *in vitro* experimentation. Together the information generated can be pivotal for the design of safer graphene-related materials for a variety of applications and help to understand their detoxification in aquatic vertebrates.

Introduction

Graphene-related materials (GRMs) have potential applications in a variety of human activities, from aeronautics to biomedicine, to electronics and in agriculture. This is causing a constant increase in the production of GRMs that will likely lead to releases to the environment during production, use and/or disposal 1. Although the current concentrations and toxicological hazards of GRM in the aquatic media are yet minimal, they are expected to increase with graphene production 2-4. Usually, graphene is not used in its pristine form but with a certain degree of oxidations (GOs). GOs have been shown to interact with other environmental pollutants, such as polyaromatic hydrocarbons (PAHs) causing an increase in cytotoxicity as estimated in fish cell lines 5. Once in the aquatic environment, residues of GOs will likely interact with a variety of biota but there is only a limited knowledge of the bio-reactions they might induce. Among these bioreactions, perturbations in detoxifying mechanisms ⁶ and immune responses ⁷⁻⁹ would have important impacts on vertebrates. To better understand the possible initiation of detoxyfying bio-reactions induced by or interfering with GOs, we have selected small fragments or nanographenes (nGs) to mimic degradation products of larger sheets. In this study we have focused on the possible effects of pristine nanographenes considering those as a single layer sheet < 100 nm lateral size without (nGs) and with different levels of oxidation (nGOs).

Previous work has shown that nGOs can adhere to the cellular plasma membrane, insert into the lipid bilayers and enter the cytoplasm ¹⁰. Once inside the cell, detoxification pathways could be activated that may hypothetically include receptor binding and induction of enzymes that cause a reduction of hydrophobicity by further oxidation (including carboxy- epoxy- and hydroxy-oxidation) to more hydrophilic metabolites which could more easily be excreted via the bile, urine or gills to prevent toxic concentrations and their derived bio-effects ^{11, 12}. We hypothesize that extracellularly, large graphenes (platelets) may begin their degradation by different mechanisms such as oxidation with reactive oxygen produced by peroxidases ^{13, 14}, leading to nGO. Alternatively, and although not yet demonstrated, different intramolecular imperfections in the graphene platelets could allow oxidations to occur extracellularly. Once inside cells, nGOs could bind to the aryl-hydrocarbon receptor (AHR) and induce oxidating cytochromes (CYPs), that will feed-back to further accelerate oxidation.

Taking into account the hypothesis mentioned above, we have computationally explored whether nGs/nGOs of ~25-200 rings could bind to intracellular AHR and/or CYPs with enough binding affinity to explain any downstream effects. Given the large differences among nGOs derivatives, it would be most convenient to select only those with the highest likelihood to elicit such bio-reactions that could be then demonstrated through *in vitro* or *in vivo* experimentation. Any reduction in the number of possibilities would make experimentation approaches more targeted and feasible. Therefore, to improve the likelihood of experimental success and to increase our understanding of possible detoxification mechanisms, *in silico* binding predictions between nGs/nGOs and 3D modeled AHR / CYPs has been performed.

For this work, rainbow trout (*Oncorhynchus mykiss*) was selected as a model vertebrate species because of their high sensitivity to environmental pollutants, and widespread use in ecotoxicological studies. Additionally, a number of their detoxifying and immune-related genes and/or functionalities have been studied. Therefore, this work specifically focuses on the trout aryl-hydrocarbon receptor (tAHR) and detoxification cytochrome enzymes such as CYPs (tCYPs).

Single layer graphene is constituted by a series of aromatic rings forming a planar structure. Therefore, Gs/GOs are structurally related to PAHs

which are also constituted by aromatic rings albeit PAHs have a much lower number of rings. Since the AHR is one of the first proteins to recognise the intracellular presence of PAHs, we have hypothesized that the AHR could also bind nGs/nGOs. Once bound to a ligand, the cytoplasmic AHR dissociates from HSP90 and other proteins, binds to the aryl-hydrocarbon receptor nuclear translocator protein (ARNT) 15 and translocates into the cell's nucleus. The cotranscriptional factor AHR/ARNT complex then interacts with xenobiotic genomic DNA response elements (XREs) to induce transcription of cyps and many other proteins ¹⁶. The recognition of ligands by PAHs has been mapped in mammalian AHRs to their PAS domain (PER, ARNT, SIM) which is common to other proteins of the same family of transcriptional factors. In particular, deletion analysis demonstrated that the binding-domain was localized in the amino-terminal part of AHR at residues 1-403. In contrast, deletion of 398-805 residues had no effect on ligand binding ^{17, 18}. Mouse AHR mutants at the 375 residue confirmed a reduction of binding of the prototypical ligands 19. Although all the above mentioned properties are most probably similar in trout, confirmatory studies are very scarce and some AHR downstream pathways may differ 20.

Detoxification of target aromatic molecules like PAHs, begins with the so called detoxification phase 1 by the addition of -COOH, -O, or -OH, by monooxygenases (predominant), flavoprotein monoxygenases, monoamine oxidases, epoxide hydrolases and/or reductases. Among all these possibilities, CYPs were chosen for this study because in vertebrates these oxidative microsomal-membrane heme-containing enzymes are the main participants in phase 1 detoxyfication 21. In addition, some of them are induced after ligand binding to AHR and have been studied in rainbow trout 22, to such an extent that induction of CYP1 by AHR activation is been used as a biomarker for hydrophobic contaminant exposure 23,24. A feed-back loop regulates AHR and CYPs transcription, increasing CYP1 down-regulates ahr and inhibition of CYP1 upregulates ahr 16. In human cells, inhibition of CYP1 up-regulates also helper T cells (and other immune cells) while down-regulating i/17 gene expression 25. Furthermore, some of the CYPs effects during infections resemble those of proinflammatory cytokines, further implicating CYPs in inflammation and immunology 26.

Putative CYPs predicted in their corresponding genomes (http://drnelson.uthsc.edu/cytochromeP450.html), showed species- and family-specific amino acid sequences ²², nevertheless with high tridimensional 3D structural similarities. CYPs are divided into those involved in xenobiotic catabolism (CYP1-4) and those implicated in metabolic biosynthesis (CYP5-51). Some CYPs are constitutively expressed but others are induced by PAHs ²⁷. Specifically in fish, many CYP enzymes are known to be implicated in fish metabolic biosynthesis such as that of hydroxycholesterols ²⁸, but also several CYP1-4 detoxyfying enzyme families have been detected ²². Therefore, it is expected that most foreign compounds introduced into the cellular environment of a fish body, including nGs/nGOs, could hypothetically interact with several CYPs as well as with other detoxifying enzymes. Furthermore, structurally distinct nGs/nGOs may have specific binding affinities with different CYPs with either inhibitory or synergistic results.

Therefore, this work focuses on prediction of binding-scores and conformations or binding-poses of pristine nGs and oxidated nGOs with tAHR and tCYPs. To our knowledge, no such computational predictions have been yet reported for any graphene-like or nGs/nGOs to tAHR/tCYPs 6.29-31.

Materials and Methods

Nanographene ligands

Graphene-like ligands were obtained by a similarity search in PubMed (https://pubchem.ncbi.nlm.nih.gov/#query=C1%5BC%40%40H%5D2N%3DN%5E C%40%40H%5D3%5BC%40H%5D1C1%3DC(C%3DCC%3DC1)%5BC%40H%5 D23&tab=similarity) by providing an 8 ring graphene-like molecule (SMILES= C1=CC2=C3C=CC4=CC=C5C=CC=C6C7=CC=C8C=CC(=C1)C2=C8C7=C3C4= C56) corresponding to Zinc ID 104923703 (http://zinc15.docking.org/). The corresponding downloaded sdf file manually curated, contained 86 small molecular weight graphene-like compounds.

To mimic graphene platelet degradation products, pdb models of nanographene (called nGs here, because of their 10-200 nm lateral side range) were designed and obtained using the open-source Phyton GOPY tool ithub.com/lourarum/GOPY). The nGs were obtained in different sizes (4 to 156 rings), and with different levels of oxidation (carboxylation -COOH, epoxy oxidation -O-, hydroxylation -OH and/or combinations). Oxygens were added to a maximum of ~1.6 Carbon/Oxygen C/O ratio, similar to those described in previous experimental work 32. While carboxylation can occur only at the C edges, both epoxyoxidation and hydroxilation may occur at each of the Cs inside the rings to be distributed randomly between the two faces of the planar nG sheet (see some depictions in Figure S3). In all cases, steric hindrance may reduce the number of theoretical possibilities. Ten random designs for each of the oxidation scenarios were computationally constructed for each oxidation state by modifications of the Phyton GOPY tool, which took into account all the requirements mentioned above 33. The resulting nanographene structures visualized in PyMOL showed a variety of numbers and intramolecular locations approximating the input numbers provided to the GOPY tool because of steric restrictions. Additionally, docking analysis rejected 10-20% of the structures specifically when 2 oxidations were too close in the same ring

Tridimensional trout AHR and CYP 3D models

The trout AHR (tAHR) was modeled using the SWISS- MODEL homology modeling (https://swissmodel.expasy.org/interactive). Structural similarities were expressed in Angstroms Å / number of common atoms, as estimated by 3D superposition with hAHR-1 in the CCP4 Molecular Graphics program vs2.10.11 (http://www.ccp4.ac.uk/MG) (Table 1)

The trout CYP (tCYP) enzymes selected for this work corresponded to those sequence-reviewed, that were available for Oncorynchus mykiss and downloaded from UNIPROT

(https://www.uniprot.org/uniprot/?query=reviewed:yes). They corresponded to most of the best studied tCYPs 22. Human eosinophil peroxidase or myeloperoxidase, was also included for comparison with previous work because to our knowledge it was the only CYP enzyme used in a previous nG oxidation computational study 34. The amino acid sequences were submitted to the SWISS- MODEL to obtain hypothetical 3D models. The coordinates of the heme and ligand binding pockets provided by the CYP human templates were copied from the human pdb to the modeled trout pdb file (Research Collaboratory for Structural Bioinformatics, RCSB, Protein Data Bank PDB). All modeled structures were visualized in PyMOL and PyRx . Structural similarities were studied as commented above by 3D superposition with tCYP1A1.Predicted binding pockets and α-helices were investigated using the seeSAR vs.10 program (https://www.biosolveit.de/SeeSAR/).

AutoDock Vina virtual docking

The AutoDock Vina program 35 included in the PyRx 0.9.8. package 36 (https://pyrx.sourceforge.io/) was used in e7 desk computers to predict Gibbs freeenergy (Δ G) as described before ^{28, 37, 38}, using grids including the whole protein molecules (blind docking) or the identified binding pockets when defined in the CYP templates. The *.sdf files were converted to *.pdbqt files by allowing ligand rotatable bonds, adding protonation and adding Gasteiger–Marsili partial atomic charges with one ffu energy minimization step carried out by the Open Babel program included into the PyRx package. Water molecules were not considered. Only the binding-poses with the lowest binding energy of each *.out.pdbqt were retained for further analysis. The output ΔG energies were converted to constant inhibition (Ki) values in molar concentrations (M), using the formula Ki = $\exp([\Delta G \times G])$ 1000] / [R \times T]) (R = 1.98 cal/mol, and T = 298 °C)³⁹. Final values were converted to nM. The predicted structures were visualized in PyRx and/or PyMOL (https://www.pymol.org/).

SeeSAR modeling

The seeSAR seeSAR vs.10 package

(https://www.biosolveit.de/SeeSAR/) 40-42 was used for binding pocket predictions and alternative visualization of bound complexes as described previously^{28, 37, 38}

Results

3D Modeling of trout AHR

One of the requirements for this study was to obtain a 3D model of the PAS domain of trout AHR (tAHR) based on the two amino acid sequences of tAHR available (97% identical) and some corresponding 3D solved structures. Since only residues 107-261 of human AHR (hAHR) were crystallographically solved and those were not enough to cover all the corresponding hAHR ligand binding domains, a template search was undertaken for a better template. Seven hAHR models were selected by the SWISS-model program using template PAS domains from diverse proteins including those from similar transcription factors. Among them, 6 models showed < 2 Å RMSD differences in their 3D structure alpha-carbons. The hAHR-1 model covering the highest number of amino acids of 357 residues was selected (Table 1, highlighted in grey background) to model the two tAHRs. The resulting modeled tAHRa and b structures were very similar (Table 1, last entries).

Table 1. Modelling of human and trout AHR

name	protein	#aa	SWISS	#aa	SI,	RMSD,
	sequence		template	3D modeled	%	Ä/#atoms
hAHR	NM_001621	848	4m4x	107-261	100	1.92/103
hAHR-1	NM_001621	848	5sys5	34-391	28.7	0.00/360
hAHR-2	NM_001621	848	4f3l	35-391	24.7	1.27/99
hAHR-3	NM_001621	848	4f3l	29-381	24.8	2.74/122
hAHR-4	NM_001621	848	5sy5	36-381	21.2	1.88/115
hAHR-5	NM_001621	848	4zpk	32-386	29.5	1.99/258
hAHR-6	NM_001621	848	4f3l	36-381	26.6	1.17/95
hAHR-7	NM_001621	848	5sy7	33-373	26.4	5.48/104
tAHRa	AF065137	1058	hAHR-1	34-391	71.2	0.38/348
tAHRb	AF065138	1059	hAHR-1	34-391	71.2	0.38/348

The sequences were obtained from the NUCCORE databank. Protein sequences from PAS domain of the hHRA (residues 1 to 420) were submitted to the SWISS-MODEL homology modelling, which automatically selected 7 possible templates with the highest sequence identity (SI). The hHRA-1 (highlighted grey background) was selected as model template for tAHRA and b. tHRAa and b sequences showed 97 % SI. hAHR, human AHR.
#aa, number of amino acids.
RMSD, Structural similarity in Å / number of common atoms by 3D superposing to hAHR-1 in CCP4_

Table 2. Modelling of trout CYPs compared to human myeloperoxidase hEPO

name	protein	#aa	SWISS	human	SI,	RMSD,	
	sequence		template	template	%	Å/#atoms	
tCYP1A1	Q92110	522	4i8v	CYP1A1	58.9	0.00/522	
tCYP1A3	Q92109	522	4i8v	CYP1A1	59.3	0.04/469	
tCYP2K1	Q92090	504	2pg6	CYP2A6	41.1	1.85/423	
tCYP2K3	093299	490	1nr6	CYP2D5	41.4	1.89/395	
tCYP2K4	O93297	504	2pg6	CYP2A6	40.7	1.86/426	
tCYP2M1	Q92088	499	1suo	CYP2B4	47.8	1.80/397	
tCYP3AR	O42563	518	1tqn	CYP3A4	55.9	2.29/377	
tCYP11A	Q07217	514	3n9y	CYP11A1	50.8	2.76/377	
tCYP17A	P30437	514	6b82	CYP17A1	75.7	1.86/418	
hEPO	P05164	745		1mhl			_

Only trout CYP protein sequences reviewed in UNIPROT were downloaded and modeled. Protein sequences were modeled as in Table 1. The coordinates of the heme and ligand binding pockets were copied from the human pdb to the modeled trout pdb file and visualized in PvMOL.

hEPO, human eosinophyl peroxidase or myeloperoxidase enzyme-degrading graphene, included for comparison with previous work 34

#aa, number of amino acids RMSD, Structural similarity.

3D Modeling of trout CYPs

Because of the absence of crystallization studies that solved the structures of trout CYPs (tCYPs), their hypothetical 3D structures were modeled for the first time (Table 2, Figure S1). Despite the differences in their amino acid sequences (Table S1), all the tCYP models have similar overall 3D structures as shown by their < 3 Å RMSD. The tCYP 3D structures have several α-helices, one conserved Cysteine, and an inner heme. Their carboxy-terminal helices contain a highly conserved domain (Table S1, red amino acids). Heme binding implicating residues ~100-140 and ~300-320 were in the pM range, as shown by seeSAR. An amino-terminal tunnel-like access (Figure S1, grey arrow) may be the main route for substrates/inhibitors to penetrate nearby the heme for optimal oxidation. A binding pocket predicted by seeSAR, was identified around the heme in all tCYPs (Figure S1, yellow pocket).

Computational binding of nG-like compounds to hAHR and tAHR

Most but not all nG-like compounds showed similar binding-scores to h and tAHR despite their differences in amino acid sequences (Figure 1A). Nevertheless, their corresponding nG binding-poses were different (Figure 1B and

Among the nG-like compounds there was a reduction of binding-scores down to 10⁻⁴ nM with increasing number of rings per molecule, in the following order, circumanthracene (13 rings), circumcoronene (19), circumvalene (24), nG (25) and circumcircumcoronene (37).

Since there were no differences between the binding-scores of tAHRa and b (not shown), the tAHRa model was selected for the rest of the work. Our approach predicted binding-scores in the 103 nM range for the hAHR prototypical agonist 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) (not shown).

Figure 1. Binding-scores of nG-like compounds to hAHR and tAHR A) Binding-scores to 83 nG-like compounds and tAHR. B) Drawing showing the best pose of 37-ring nG bound to hAHR. C) Drawing showing the best pose of 37-ring nG bound to tAHR

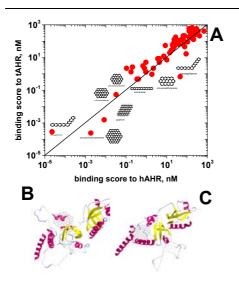
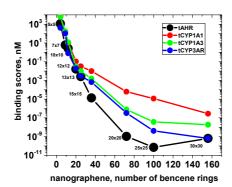


Figure 2. Influence of the number of rings of nG in their binding to tAHR and to tCYPs. nGs of different sizes were designed by the GOPY tool Black numbers, lateral sizes in nm of the nGs for inputs to the GOPY tool. Black circles, tAHR Red circles, tCYP1A1 Green circles, tCYP1A3. Blue circles, tCYP3AR.



Modeling of 20x20 nm nGs resulted in nGs of 72 rings down to binding-scores of >10-10 nM, compared to those of 25 nG or 37 circumcircumcoronene rings which bound to the hAHR / tAHR with binding-scores in the $\sim 10^{-3}$ nM range (Figure 1A). To further investigate the influence of nG size in the binding to tAHR and tCYPs, different sizes were designed and computationally tested by blind docking (PAS tAHR domain) or binding-pocket docking (tCYPs).

The results predicted that the lower binding-scores to tAHR corresponded to nGs > 100-rings. Larger nGs maintained these binding-scores. Binding to tCYPs showed a similar size-profiles as to tAHR, but in the 10-5-10-9 binding-score ranges (Figure 2, blue, green and red lines). Most tAHR binding to nGs mapped to its PAS ligand binding site. In contrast, most nGs binding to CYPs were localized on their surfaces away from their heme sites, suggesting some unspecific bindings (Figure S2). Only 4-9-ring nGs were mapped nearby to their heme site, most probably because only such small compounds could penetrate through the CYP tunnels to such internal location to be specifically oxidized (Figure

Models of 9 (7x7 nm, 32 Carbons) and 25 (13x13 nm, 77 Carbons)-ring nGs were selected for further studies, because significant binding-scores could be obtained in minimal computational times.

Computational binding of nGOs to tAHR

Carboxy (-COOH), epoxy (-O-) and hydroxy (-HO) oxidations were mimicked by adding them to the 9 and 25-ring nGs to randomly generate their corresponding nGOs using 1.6 Carbon/Oxygen C/O ratios 10 (see some of their structures in Figure S3).

In this test, docking conditions were adjusted to yield binding-scores of ~10-3 nM and ~101 nM for 25- and 9-rings nGs, respectively. Results with nGOs predicted 101-10-7 nM binding-scores for 25-rings (Figure 3,) and 100 nM for most 9rings (Figure 3, red- and grey-edged circles, respectively). In particular, epoxidation (-O-) alone or in combination with carboxylation (-COOH), was the most efficient process to reduce the binding-scores of 25-ring nGOs. In contrast, hydroxylation (-OH), and its combinations increased their binding-scores.

Mapping of the corresponding 3D binding-poses predicted that the amino terminal end of the PAS domain of tAHR was targeted by most 25- and 9rings nGOs (Figure 3C and B, respectively).

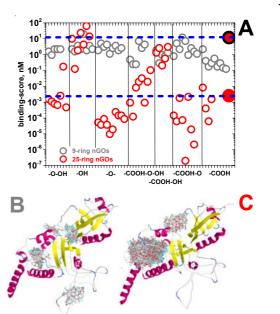


Figure 3. Influence of nG oxidation(nGO) in the binding-scores to tAHR. Oxidations with -COOH, -0-, -0H and combinations of them were randomly added at maximal $\,$ C/O \sim 1.6 ratios to 9 or 25-ring nG using the GOPY tool.

A) Grey-edged circles, 9-ring nGO.
Red-edged circles, 25-ring nGO.
Grey-edge, red filled circle, 9-ring nG. Red-edge red filled circle, 25-ring nG.

Black vertical lines, separation between different types of oxidations.

Dashed horizontal blue lines, nGs binding-scores to tAHR. B) Mapping of 9-ring nGOs bindings to tAHR.

C) Mapping of 25-ring nGOs bindings o tAHR.

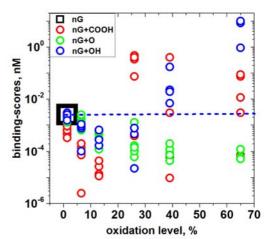


Figure 4. Influence of the level of oxidation in the binding of nGs to tAHR. Individual -COOH, -O-Off Dodd and Molecules were randomly added into 25 rings (77 Carbons) nGs by the GOPY tool. From 5-10 nG molecules were virtually oxidated per each level of oxidation. Due to steric problems when > 20-30 atoms were added, some of the resulting nGO structures when examined in PyMOL, only approximately confirmed the initial numbers supplied to the tool. Theoretical oxidations per nG molecule were expressed if % as calculated by the formula, 100 x number of output oxidative molecules per 77 Carbons. Black big square and blue-dashed horizontal line, binding-scores of 5x5 nm nGs (mean of n=5). red circles, nG+COOH. Green circles, nG+O. Blue circles, nG+OH

Computational binding of nGOs with different oxidation levels To study the influence of the levels of nGO oxidation on the

binding to tAHR, different numbers of oxygen-containing molecules were added to 25-ring nGs. Results showed that increasing the level of peroxidation (-O-) to 70 % caused a continuous reduction to 10-4 nM binding-scores (Figure 4, green circles). Increasing the level of carboxylation (-COOH) or hydroxilation (-OH) to <25 % reduced their binding-scores to ~10-5-10-6 nM, but increased them at higher oxidation levels (Figure 4, red and blue circles). Both nG and most nGO bindingscores to tAHR remained < 101 nM, which may be significant compared to the 103 nM binding-score of the AHR prototypical agonist TCDD under the same docking

Because of the nGs tendency to bind non-specifically to tCYPs (Figure S2), the size of the nGs were reduced to 5x5 nm (4 rings) and grids of 25 x 30 x25 Å surrounding the tCYPs heme were used for docking.

Under the above mentioned conditions, the nG binding-scores varied for each tCYPs molecular species from 102 to 104 nM (Figure 5, black-dashed horizontal lines). By increasing the level of nGOs oxidation to ~ 25 % most bindingscores decreased to different minimal levels for different tCYPs. However, increasing the level of most oxidations > 25 %, resulted in increased binding-scores for most tCYPs, except tCYP3AR. Thus, with >25 % oxidations, tCYP3AR bindingscores were further reduced to 10-2 by carboxylation (Figure 5, 3AR, red circles), and to a lower extent by peroxidation and hydroxylation.

Discussion

Lateral sizes of commercial powered graphene are of ~10 nm while the so called nanoplatelets range between 20-100 nm for oxidized graphene (GO) and between 100-1000 nm for carboxylated graphene 10. Our initial working hypothesis was that larger graphene fragments (e.g., platelets) are broken down and taken up by trout cells transformed into smaller graphene pieces of ~10-100 rings (graphenes in the nm size range, here called nGs). We hypothesized that once internalized by cells, nGs/nGOs may interact with microsomal tAHR activating phase I detoxification mechanisms, such as those implicating peroxidase-dependent reactive oxygen 13,14 and/or tCYPs enzymatic activities/tcyp gene transcription, to induce other bioeffects. All these possibilities remain largely unexplored.

To test such hypothesis by in vitro and in vivo experimentation, given the large numbers of different nGs/nGO derivatives, their numbers need to be reduced and possible candidates identified for further experimental studies. To do that, we proposed an in silico screening to select for those nGs with the highest binding affinities (lower binding-scores) to tAHR and tCYPs. We discovered that the maximal number of nG rings that tAHRs/tCYPs could bind is up to 25-rings with apparent binding-scores between 103-10-11 nM and mapping to the PAS tAHR specific binding site defined by its prototypical TCDD ligand.

Increasing hydrophilicity that facilitates detoxification of graphenes, is mostly caused by carboxylation, peroxidation and/or hydroxylation, but ringopening and reduction may also be implicated 43. Oxidation of nGs to nGOs by virtually adding -COOH, -O- and -OH such as those expected to be found in most graphenes used for biomedical applications, computationally predicted between 10-100-fold reduction in their nG binding-scores to tAHR depending on the numbers of oxidated carbons per molecule and the type of oxidation. Additionally, any possible implication of tCYPs in nG binding and subsequent oxidation may be sterically possible only with the smallest nGs according to the computational data. Predicted conformation or pose analysis showed that although nGs could bind tCYPs, most of those bindings seem to be unspecific or not specifically oxidative because of their excessive separation from the inner tCYP heme where oxidation is expected to be most active. Pose bindings nearby the tCYP heme could not be visualized for nGs > 4 rings. Only the minimal nGs of 4 rings were small enough to penetrate the inner heme located within the predicted binding pockets

With such size restrictions, among all the CYPs, the tCYP3AR was predicted to bind stronger than other tCYPs to nGOs, specifically to those which were carboxylated at their edges. Perhaps the higher implication of tCYP3AR in additional oxidations compared to other tCYPs may be due to its participation in the metabolism of endogenous substrates, such as steroids 43. According to the UNIPROT data base, tCYP3AR is coded by the trout gene cyp3a27, however 3D modeling choose the human hCRP3A4 as the closest isomer, suggesting that despite nucleotide sequence differences, tCYP3AR is equivalent to hCYP3A4. Although our knowledge of any tCYPs is still scarce, immunologically relatedness of fish CYP3A to hCYT3A4 and rat CYP3A has been demonstrated 44. However, since there is evidence that tCYP3A4 shows no significant bio-effects to seven known substrates of the corresponding hCYP3A4 45, the impact of substrate oxidation may differ among species. The hCYP3A subfamily is the most important of drug-metabolizing enzymes since it accounts for ~30 % of the total CYPs in the liver and metabolizes ~50 % of marketed drugs 43. In humans it is being expressed mainly in the liver where it accounts for 13 % of the total CYP content and has been implicated in the metabolism of \sim 4% of marketed drugs 43 . In contrast, few data are available for tCYP3AR.

The computational predictions identified the nGs molecular characteristics required to be suitable ligands for tAHR and therefore those with the higher potential to generate bio-effects. It may be hypothesized that subsequent translocation into the nucleus to induce the numerous tAHR-dependent genes would sustain the bases for a link between the environment and toxicological and immune responses at the cellular level. Although there are still no experimental evidences for that possibility, the present results indicate this may deserve futher explorations.

On the other hand, since vertebrate AHRs are expressed in many cells of both innate and adaptive immunity, the AHR may be one of the translators of environmental hydrophobic contamination into immunological responses. Experimental validation of such hypothesis, could be performed by in vitro and/or

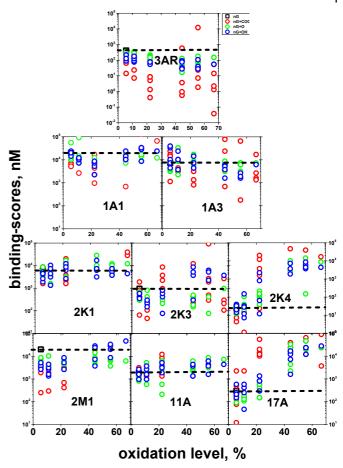


Figure 5. Influence of the level of oxidation in the binding of nGOs to tCYPs. Individual -COOH, -O-, -OH oxidant molecules were virtually and randomly added into 4 rings, 18 Cs nGs by the GOPY tool. From 5-10 nG molecules were virtually oxidated per each level of oxidation. Due to steric problems when > 20-30 atoms were added, some of the resulting structures examined in PyMOL only approximately confirmed the initial numbers supplied to the tool. Theoretical oxidations per nG molecule were expressed in % as calculated by the formula, 100 x number of oxidation molecules provided to the GOPY tool / 18 (n=5). The CYP family is in black bold lettering placed at around the 10² nM label for easy reference. Only those nGs showing binding affinities <10⁵ nM were shown. All the scales were equal except the wider lower scale down to 10-2 for tCYP3AR.
Black big square and dashed horizontal line, binding-scores of 5x5 nm nGs (mean of n=5) red circles, nGO-COOH

Green circles, nGO-O-Blue circles, nG-OH.

vivo assays by measuring the effect of synthetic nGs and their nGOs oxidated derivatives with different levels of oxidation, similar to those which have been investigated here using in silico screening.

Among the main difficulties to experimentally validate any hypothesis related to nG/nGO is the lack of such molecularly defined graphenes. An alternative to obtain the corresponding nGs/nGOs for experimental purposes could include not only chemical synthesis (if chemical synthesis could make it possible) but also strong sonication techniques or long peroxidation of graphene platelets. Techniques for removal of the largest fragments by ultracentrifugation and/or gel filtration chromatography are available. However, more detailed molecular characterization of such preparations than those routinely employed may also be required.

For further downstream experimentation, several in vitro assays such as those using subcellular fractions, fish cell lines, hepatocytes and/or tissues 24, could be used. Specifically to detect a variety of tAHR induced genes, for instance, RTqPCR could be used to detect up-/down-regulation of selected tcyps. Any induced tCYP1A and/or tCYP3A enzyme activities can also be monitored using ethoxyresorufin-O-deethylas(EROD) or benzyloxy-4-trifluoromethylcoumarin-Odebenzyloxylase (BFCOD) activity assays, respectively. To estimate possible induced immunological responses and/or to explain differences among AHR modulations observed across species⁴⁶, concentration-dependent effects on trout immunosuppression 25, inflammation (downregulation of ilb, crp, or upregulation of tgfb) and/or T cell and macrophage activation 47, may also be performed. Combining the information generated by in silico screening with future in vitro and in vivo experimentation, forms an integrative approach for unrevealling the bio-interactions and effects induced by nGs/nGOs and expanding our knowledge of these highly bio-interactive planar hydrophobic substances.

SUPPORTING INFORMATION

Table S1. Trout CYPs CLUSTAL O(1.2.4) sequence alignment

Table S1. Trout CYPs		
002000 000002 000000	MSLIEGLLQTSSTVTLLGTVLFLLVLYLRSSGSSSEGQ MVLMILPIIGSVSVSBGLVAIVTLGLVYMLMKYKHTEIPEGLKR	
093299 CP2K3_ONCMY	MULMILDITGSVSVSRGLVATVITICLVVMLMKVKHTRIDRGLKR	44
007217 CP11A ONCMY	MNVSWSVCRSSLALPACGLPSARHNSSMPVVROALSPDNSSTVON	45
Q92109 CP1A3_ONCMY	MWVSWSVCRSSLALPACGLPSARHNSSMPVVRQALSPDNSSTVQN MVLMILPIIGSVSASEGLVAMVTLCLVYMIMKYMHTEIPEGLKRMSLIEDILQTSSTVTLLGTVLFLLVLYLRSSGSSSEEQ	44
Q92090 CP2K1_ONCMY	MSLIEDILQTSSTVTLLGTVLFLLVLYLRSSGSSSEEQ	38
P30437 CP17A_ONCMY	LQVKLRRSLET	30
Q92088 CP2MI_ONCMY	MDVL-HILQTNFVSIIIGFVVIILL-WMNKGKQSN	33
042563 CP3AR_ONCMY		35
	•	
	GKEPPGPRPLPLLGNMLQLD-LKKPYCTLCELSKKYGSIFTFHFGPKKVVVLAGYKTV LPGPKPLPIIGNVLEVYNNPHLSLTAMSERYGSVFQIQIGMRPVVVLSGNETV	95 97
Q07217 CP11A_ONCMY	FSEIPGLWRNGLANLYSFWKLDGFRNIHRVMVHNFNTFGPIYREKIGYYDSVNIIKPEMP	105
Q92109 CP1A3_ONCMY	LPGPKPLPIIGNMLEVHNNPHLSLTAMSERYGSVF0I0IGMRPVVVLSGNETV	97
Q92090 CP2K1_ONCMY	GKEPPGPRPLPLLGNMLQLD-LKKPYCTLCELSKKYGS IFTVHFGPKKVVVLAGYKTV	95
P30437 CP17A_ONCMY	RGGPPSLPVFPLIGSLLSLRSNQAPHVLFQKLQQKYGHTYSLMMGPHTVILVNHHQHA SRLPPGPAPIPLLGNLLRMD-VKAPYKLYMELSKKYGSVFTVWLGSKPVVVISGYQAI	88 90
093297 CP2K4_ONCMY	GKEPPGPRPLPLLGNMLQLD-LKKPYCTLCELSKKYGS IFTVHFGSKKVVVLAGYKTV	95
042563 CP3AR_ONCMY	KMGIPGPKPLPYFGTMLEYKKGFTNFDTECFQKYGRIWGIYDGRQPVLCIMDKSMI	
002000 000000 000000	: :	1.40
093299 CP2K3_ONCMY	RQALVNQAED-FGDRD1TPVFYDF-NQGHGILFANGDSWREMRRFALTNL RQALIKQGED-FAGRPDLYSFKFI-NDGKSLAFSTDKAGVWRARRKLAMSAL	143
Q07217 CP11A_ONCMY	ATLEKA EGHYPKRI TVEAWTSYRDYRNRKYGVLIK NGEDWR SNRVI I NR EVI SPKV	161
Q92109 CP1A3_ONCMY	RQALIKQGED-FAGRSDLYSFKFI-NDGKSLAFSTDKAGVWRARRKLAMSAL KQALVNQAED-FGDRDITPVFYDF-NQGHGILFANGDSWKEMRRFALTNL	147
Q92090 CP2K1_ONCMY	KQALVNQAED-FGDRDITPVFYDF-NQGHGILFANGDSWKEMRRFALTNL	143
P30437 CP17A_ONCMY	KEVLLKKGKI-FAGRPRTVTTDLLTRDGKDIAFA-DYGATWRFHRKTVHGAL KDAFVTQGEE-FSGRANYPVIMTV-SKGYGVLVSSGKRSKDLRRFSLMTL	138
Q92088 CP2M1_ONCMY O93297 CP2K4_ONCMY	KQALVNQAED-FGERDITPAFYDF-NQGHGILFTNGDSWKEMRRFALTNL	143
042563 CP3AR_ONCMY	KTVLIKECYNIFTNRRNFHLNGELFDALSVAEDDTWRRIRSVLSPSFTSGRL	143
	the first of the second of the	
093299 CP2K3_ONCMY Q92110 CP1A1_ONCMY	-RDFGMG-KKGSEEKILEEIPYLIEVFEKHEGKAFDTTQSVLYAVSNIISA -RSFATL-EGTTPEYSCALEEHVCKEGEYLVKQLTSVMDVSGSFDPFRHIVVSVANVICG	192 205
007217 CP11A ONCMY		210
Q92109 CP1A3_ONCMY Q92090 CP2K1_ONCMY	$- \texttt{RSFATL} - \texttt{EGTTPEYS} \\ \textbf{C} \texttt{ALEEHVLKEGEYLVKQLTSVMDVSGSFDPFRHIVVSVANVICG}$	205
Q92090 CP2K1_ONCMY	LGMFYFLLDEVGQDFYARVHRKIERSGQDRWITDLSQELFKYALESVGS -RSFATL-SCTTPEYSGALEEHULKEGGFLVKQLTSVMDVSGSFDPFRHIVVSVANVIGG -RDFGMG-KKGSEKILEEIPYLLEVFEKHEGKAFDTTQSVLYAVSNIISA -CMFGEG-SASIEKIIGREALSLCDTLRESGSASLDLSPELTRAVTNVVCS	192
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY	-CMFGEG-SASIEKIICREALSLCDTLRES-GSASLDLSPELTRAVTNVVCS -KTECHC-PRSIERPVORFAKHIJKARGRYPDSVJNDVPII ONCUCNIJICO	187 187
093297 CP2K4_ONCMY	-KTFGMG-RRSIEERVQEEAKMLVKAFGEYRDSVVNPKELLCNCVGNVICS -RDFGMG-KKGSEEKILEEIPYLIEVLEKHEGKAFDTTQSVHHAVSNIISA	192
O42563 CP3AR_ONCMY	KEMFGIM-KQHSSTLLSGMKKQADKDQTIEVKEFFGPYSMDVVTS	187
002200 00222 02000	* : : : : : : : : : : : : : : : : : : :	246
093299 CP2K3_ONCMY Q92110 CP1A1_ONCMY	IVYGSRFEYTDPLFTGMADRAKESIHLTGSASIQMYNMFPWLGPWINN-LTRLKK-MCFGRRYSHDDQELLGLVNMSDEFGQVVGSGNPADFIPILRYLPNRTMKRFMD-	258
Q07217 CP11A_ONCMY	VLYGERLGLMLDYINPEAOHFIDCISLMFKTTSPMLYIPPAMLRRVGAKIWRDHVEAWDG	270
Q92109 CP1A3_ONCMY	MCFGRRYSHDDQELLGLVNMSDEFGQVVGSGNPADFIPILRYLPNRTMKRFMD-	258
Q92090 CP2K1_ONCMY	IVYGSRFEYTDPLFTGMADRAKESIHLTGSASIQMYNMFPWLGPWINN-LTRLKK-	246
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY	LCFSSSYCRGDPEFEAMLQFSQGIVDTVAKD-SLVDIFPWLQVFPNADLRLLKQ-IVFGHRFENDDPMFQLIQKAVDAYFNVLSSPIGAMYNMFPRIVWCFPGNHHEMFA-	240 242
093297 CP2K4_ONCMY	IVYGSRFEYTDPLFTGMVDRVNENVHLIGSASIQMYNMFPWLGPWINN-LTRLKK-	246
042563 CP3AR_ONCMY	TAFSVDIDSLNNPSDPFVSNVKKMLKFDLFNPLFLLVALFPFTGPILEKMKFSFFPT	244
O93299 CP2K3 ONCMY	:: :: NIADMKMEVTELVRGIKETLNPHMCR-GFVDSFLVRKQTLEESGHMDSFYHDDNL INDRFNNFVQKIVSEHYESYDKDNIR-DITDSLIDHCEDRKLDENANIQVSDEKI	300
Q92110 CP1A1_ONCMY	INDRFNNFVQKIVSEHYESYDKDNIR-DITDSLIDHCEDRKLDENANIQVSDEKI	312
007217 CP11A ONCMY	IFNOADRCIONIYRTMRODTNTHGKYPGVLASLLMLDKLSIEDI	314
Q92109 CP1A3_ONCMY Q92090 CP2K1_ONCMY	INDRFNNFVQKIVSEHYESYDKDNIR-DITDSLIDHCEDRKLDENANIQVSDEKI NIADMKMEVIELVRGLKETLNPHMCR-GFVDSFLVRKQTLEESGHMDSFYHDDNL	312
P30437 CP17A ONCMY	CVSTRDKLLOKKYEEHKSDYSDHEOR-DLLDALLRAKRSAENNNTARTTMETVGLSEDHL	300 299
P30437 CP17A ONCMY	CVSTRDKLLOKKYEEHKSDYSDHEOR-DLLDALLRAKRSAENNNTARTTMETVGLSEDHL	299
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY O93297 CP2K4 ONCMY	CVSITDKLLQKKYBEHKSDYSDHEQR-DLLDALLRAKRSAENNNTAEITMETVGLSEDHL IVNKAKVYIQEQAEIRLKTLNISEPQ-DFIEAFLVKMLEEKDDPNTEFNNGNM NVADLKMEVIELVRGLKETLNPHMCR-GFVDSFLVRKOTLEESGKMDSFYHDDNL	299 294 300
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY O93297 CP2K4 ONCMY	CVSTRDKLLOKKYEEHKSDYSDHEOR-DLLDALLRAKRSAENNNTARTTMETVGLSEDHL	299
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY O93297 CP2K4_ONCMY O42563 CP3AR_ONCMY	CVSIRDKLLQKKYEEHKSDYSDHEQR-DALDALLRAKESABNNNTAEITMETVGLSEDHI INVRAKVYIGGABIERLKTILSEG-DFIEBAFUWM-LEEKDODNTEFENDRI NVADLKMEVIELVRGLKETLAPIHWGR-GFVOSFLVEKGTLEESGKMDSFYHDDML AVTDFFYASLAKIKSGRDTGNSTNRV-DFLQLMIGSQKGSDTKTGEEQTKGLTDHEI :	299 294 300 300
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY O93297 CP2K4_ONCMY O42563 CP3AR_ONCMY	CVSIRDKLLQKKYEEHKSDYSDHEQR-DLLDALLRAKESABRINNTAEITMETVGLSDEHL TVINKAKVYIGAGAEITKIKTUS ISSQ-DFIEBATVAM-LEEKDODNTEFRINGIM NVADLKMEVIELVRGLKETIAPENGR-GFVDGFIVÆKQTLEESCKMDGFVHDDML AVTDFFYASLAKIKSGRDTGNSTNRV-DELQMIDSQKGSDTKTGEEQTKGLTDHEI VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISGVIG-SRQTLVEDRKNLFY	299 294 300 300
P30437 CP17A_ONCMY Q92088 CP2M_ONCMY 093297 CP2K4_ONCMY 042563 CP3AR_ONCMY 093299 CP2K3_ONCMY Q92110 CP1A1_ONCMY	CVSIRDKLLQKKYEEHKSDYSDHEQR-DLLDALLRAKESABRINNTAEITMETVGLSDEHL TUNKAKVYIGAGAEITKIKTUS ISSEQ-DFIEBATVAM-LEEKDODNTEFNINGIM NVADLKMEVIELVRGLKEFILNFENGER-GFVDSFLVRKQTLEESCKMDSFYHDDML AVTDFFYASLAKIKSGRDTGNSINRV-DFLLJMIDOQKGSDTKTGEEQTKGLITDHEI VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISGVIG-SRQTLVEDRKNLFY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIQSRLHQEKKEKVGMIRTPRISDKINLPL KSUTPH MAGGUTTSTITLIKWIYELAHDHOIG OFFI BKWAVARDSTYCOMLOWING	299 294 300 300
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY O93297 CP2K4_ONCMY O42563 CP3AR_ONCMY O93299 CP2K3_ONCMY Q92110 CP1A1_ONCMY Q97217 CP11A_ONCMY Q92109 CP1A3_ONCMY Q92109 CP1A3_ONCMY	CVSIRDKLLQKKYEEHKSDYSDHEQR-DLLDALLRAKESABRINNTAEITMETVGLSDEHL TUNKAKVYIGAGAEITKIKTUS ISSEQ-DFIEBATVAM-LEEKDODNTEFNINGIM NVADLKMEVIELVRGLKEFILNFENGER-GFVDSFLVRKQTLEESCKMDSFYHDDML AVTDFFYASLAKIKSGRDTGNSINRV-DFLLJMIDOQKGSDTKTGEEQTKGLITDHEI VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISGVIG-SRQTLVEDRKNLFY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIQSRLHQEKKEKVGMIRTPRISDKINLPL KSUTPH MAGGUTTSTITLIKWIYELAHDHOIG OFFI BKWAVARDSTYCOMLOWING	299 294 300 300 359 372 374 372
P30437 CP17A_ONCMY Q92088 CP2M1_ONCMY Q92087 CP2K4_ONCMY Q42563 CP3AR_ONCMY Q92190 CP2K3_ONCMY Q92110 CP1A1_ONCMY Q92107 CP11A_ONCMY Q92109 CP2K1_ONCMY Q92090 CP2K1_ONCMY	CVSIRDKLLQKKYEEHKSDYSDHEQR-DALDALLRAKESABRINNTAEITMETVGLSDEHL IVNKAKVYIOGAGEIRLKTURIS ESEQ-DFIEBATVEM-LEEKSOD-DNTEFINGIM NVADLKMEVIELVRGLKEFILNFENGE-GPVOSFIVEKÇTILESGKMDSFYHDDML AVTDFFYASLAKIKSGRDTGNSTINRV-DFIQLMIDSQKGSDTKTGEEQTKGLTDHEI VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKNLPY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIQSRLHQBLKEKVGMIRTPRLSDKINLDL VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIQSRLHQBLKEKVGMIRTPRLSDKINLDL VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIQSRLHQBLKEKVGMIRTPRLSDKINLDL VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIQSRLHQBLKEKVGMIRTPRLSDKINLDL VSVGVNLFSAGTDTTGTTLRGULLLMTKYPHIQDYQGBEISVG-SRQTLVEGBRKNLPY VSVGVNLFSAGTDTTGTTLRGULLLMTKYPHIQDYQGBEISVG-SRQTLVEGBRKNLPY VSVGVNLFSAGTDTTGTTLRGULLLMTKYPHIQDYQGBEISVG-SRQTLVEGBRKNLPY	299 294 300 300 359 372 374 372 359
P30437 [CP17A_DNCMY Q92088 [CP2M1_ONCMY 093297 [CP2K4_ONCMY 093299 [CP2K3_ONCMY 093299 [CP2K3_ONCMY Q92110 [CP1A1_ONCMY Q07217 [CP11A_ONCMY Q92109 [CP1A3_ONCMY Q92090 [CP2K1_ONCMY P30437 [CP17A_ONCMY P30437 [CP17A_ONCMY	CVSIRDKLLQKKYEEHKSDYSDHEQR-DALDALLBAKESABRINNTAEITMETVGLSDEIL IVNRAKVYIGGABIERLKTIJI SEEQ-DPI EBAFUWM-LEEKDODNTEFENIGMI NVADLKHEVIELVRGLEETLAPIHWER-GFVOSFUVEKÇTILEBSCKMDSFYHDDML AVTDFFYASLAKIKSGRDTONSTIRV-DFLQLMIDSQKSDTKTGEQTKGLITCHSI VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISGVIG-SRQTLVEDERKHLPY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIGBELHQELKEKVGWIRTPFRLSDKINLPL KASVTELMAGGVDTTSITLMTLYELAHHPDLQSELPAEVAVARQSTQGDMLQMLKHIPL VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDDVQDEEISBVIG-SRQTLVEDERKHLPL VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDDVQDEEISBVIG-SRQTLVEDERKHLPL VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDTQVQEEISBVIG-SRQTLVEDERKSLPY LUTVGDIFGAGWTTSTYLKWGLATALHHPHOQVQDEEISBVIG-SRQTLVEDERKSLPY LUTVGDIFGAGWTTSTYLKWGLATALHHPHOQVGOETOSELDSVCGRPTPOLSBRGSLPY	299 294 300 300 359 372 374 372 359 359
P30437 (CP17A_ONCMY 092088 (CP2M1_ONCMY 093297 (CP2K4_ONCMY 042563 (CP3AR_ONCMY 093299 (CP2K3_ONCMY 092110 (CP1A1_ONCMY 092101 (CP1A1_ONCMY 092090 (CP2K1_ONCMY P30437 (CP17A_ONCMY P30437 (CP17A_ONCMY 092088 (CP2M1_ONCMY 092088 (CP2M1_ONCMY	CVSIENKLLQKKYEEHKSDYSDHEQR-DALDALLRAKESABENNATABITMETVGLSDENLIVMKAKVYIGGABITIKKTUN ISEQ-DFIEBATVWM-LEEKDODNTEFNINGIM NVADLKMEVIELVRGLKEFTLAFEHWGR-GFVOSFLVEKGTLEESGKMDSFYHDDML AVTDFFYASLAKIKSGRDTONSTINEV-DFLQLMIDSQKGSDTKTGEEQTKGLTDHEI VFSVGNIDLFSAGTDTTGTTLRWGLLLMTKYPHIQDOVQEEISGGVIG-SRQTLVEDRKLDFV VGIVNDLFSAGTDTTGTTLRWGLLLMTKYPHIQDOVQEEISGGVIG-SRQTLVEDRKLDFV VGIVNDLFGAGFDTISTALSWAVVYLVAYPEIQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFDTISTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFDTISTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFDTISTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFDTISTTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFDTISTTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFTTTSTTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFTTTSTTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFTTTSTTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFTTTSTTALSWAVVYLVAYPETQSRLHQBLKEKVGMIFTFRISDKINLDFV VGIVNDLFGAGFTTTSTTALSWAVVYLVAYPETQSRLHQBLGSVGVETDSVIG-SRQFTLUPBV VGIVNDLFGAGFTTTSTTALSWAFTALMTHYHTGSSVQFTLDBVIG-SRVPTUDDRVKMPY VMTAMSLFAGFTTTSTSTLTSGFSHMIKYPHIQSSVQFLDBVIG-SRVPTUDDRVKMPY	299 294 300 300 359 372 374 372 359
P30437 [CP17A_DNCMY Q92088 [CP2M1_ONCMY 093297 [CP2K4_ONCMY 093299 [CP2K3_ONCMY 093299 [CP2K3_ONCMY Q92110 [CP1A1_ONCMY Q07217 [CP11A_ONCMY Q92109 [CP1A3_ONCMY Q92090 [CP2K1_ONCMY P30437 [CP17A_ONCMY P30437 [CP17A_ONCMY	CVSIRKLL(KKYEBHKSDYSDHEOR-DALDALDALDARERSABNNNTAEITMETVGLSDEHL IVNKAKVYLOGADEIRLKTULISEQ-DFIEBRUWM-LEEKDODNTEFNINGM NVADLXMEVIELVRGLEGETLMPIMOR-GFVDSFIVEKOTLEESCKMDSFYHDDML AVTDFFYASLAKIKSGEDTGSTNW-DFLQMIDDGKSDTKTGEGCTKGLTDHEI VSIVONLFSAMTIVTCTTLENGLLLMTKYBHIDOGVGBKISGVIG-SRQTLVSDBKHLDV VGIVONLFGAMTIVTCTTLENGLLLMTKYBHIDOGVGBKISGVIG-SRQTLVSDBKHLDV VGIVONLFGAMFTISTALSNAVVILVAVFETQERLHGELKEKVGMIRTPRLSDKINLDL VGIVONLFGAMFTISTALSNAVVILVAVFETQERLHGELKEKVGMIRTPRLSDKINLDL VGIVONLFGAMFTISTALSNAVVILVAVFETQERLHGELKEKVGMIRTPRLSDKINLDL VGIVONLFGAMFTISTALSNAVVILVAVFETQERLHGELKEKVGMIRTPRLSDKINLDL LMTVGDIFGAMVETTSTVLKNALAVLLMKYBHIDOGVGBKISGVIG-SRQTLVSDBKSLDV LMTVGDIFGAMFTSTSTLKSGSTMMIKYPHIDOVGBKISGVIG-SRQTVLSDBKSLDV LMTVGDIFGAMFTSTSTLKSGSTMMIKYPHIDOVGBKISGVIG-SRQTVLSDBKSLDV LSSGAMFIFAMTTTSTSTLRGSSTMMIKYPHIDOVGBKISGVIG-SRQTVLSDBKSLDV LSSGAMFIFAMTTTSTSTLRGSSTMMIKYPHIDOVGBKISGVIG-SRQTVLVSDBKNLDV LSSGAMFIFAMTTSTSTLRGSLMMIKYPHIDOVGBKISGVIG-SRQTVLVSDBKSLDV LSSGAMFIFAMTYTSSTLRGSLMMIKYPHIDOVGBKISGVIG-SRQTVLVSDBKALDV LSSGAMFIFAMTYTSSTRUKGARTANLANDHVMIKTLGEKTUNTPRINAFIGYETSBKHALDL	299 294 300 300 359 372 374 372 359 359 353
P30437 (D17A_ONOW) 972088 C29AL_ONOW] 093297 C22K4_ONOW] 093299 CP3K3_ONCW] 093299 CP2K3_ONCW] 0972110 C01A1_ONOW] 0972117 C011A_ONOW] 092109 C1A3_ONOW] 092090 C22K1_ONOW] 092088 C22K1_ONOW] 092083 C22K1_ONOW] 042563 C93AR_ONOW]	CVSIRKLLQKKYEEHKSDYSDHEQR-DALDALLRAKESABRNNTAEITMETVGLSDENLIVMRAKVYLQSABEIRKHTUS ISSEQ-DFIEBRUWM-LEEKDDPNTFERNGRM NVADLKMEVIELVRGLEETLAPIHWER-GFVOSFIVEKTILEESGKMDSFYHDDML AVTDFFYASLAKIKSGRDTONSTIRV-DFIQLMIDSQKSDTKTGEGCTKGLTDHDINL AVTDFYASLAKIKSGRDTONSTIRV-DFIQLMIDSQKSDTKTGEGCTKGLTDHDINL VSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISGVIG-SRQTLVEDRKNLPY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEGJGRHLMGELKEKVGWIRTPRLSDKINLPL KASVTELMAGGVDTTSTILWTLYELARHDDLQSELRAEVAVARQSTQCDMLCMLKHIPL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDDVQEEISRVIG-SRQTLVEDRKNLPY LWTVADIFGAGVTTSTYLKWGLLAVTHHDQVQEEISRVIG-SRQTLVEDRKNLPY VMTANSLFAAGTETTSSTLROSFLMMIKYPHIQSENGYEIDEVIG-SRQTVLVEDRKNLPY LWTSIGNLFGAGTTTTGTTLRWGLLLMKYFHIQDGYGEKLDSVG-SRQTVLVEDRKNLPY LWTSIGNLFGAGTTTTGTTLRWGLLLMKYFHIQDGYGEKLDSVG-SRQTVLVEDRKNLPY LESIGNLFGAGTTTTGTTLRWGLLLMKYFHIQSVQKEIDEVIG-SRQTVLVEDRKNLPY LESIGNLFGAGTTTTGTTLRWGLLLMKYFHIQSVQKEEDTVFG-SRQTVLVEDRKNLPY LESIGNLFGAGTTTGTTTGTTRGLLLLMKYFHIQDGYGESLDTVFG-SRQTVLVEDRKNLPY LESIGNLFGAGTTTTGTTLRWGLLLMKYFHIQDGYGESLDTVFG-SRQTVLVEDRKNLPY LESIGNLFGAGTTTTGTTLRWGLLLMKYFHIQDGYGESLDTVFG-SRQTVLVEDRKNLPY LESIGNLFGAGTTTTGTTLRWGLLLMKYFHIQDGYGESLDTVFFFRAFTLLBRAKLLLMKYFHIGATTHFAUTHFAUTHFAUTHFAUTHFAUTHFAUTHFAUTHF	299 294 300 300 359 372 374 372 359 359 353 359 360
P30437 (P17A_ONOW) 972088 (P2AL_ONOW) 093297 (P2K4_ONOW) 093299 (P2K3_ONOW) 093299 (P2K3_ONOW) 093299 (P2K3_ONOW) 093210 (P1AL_ONOW) 093210 (P1AL_ONOW) 093210 (P2K1_ONOW) 093291 (P2K1_ONOW) 093291 (P2K4_ONOW) 093291 (P2K4_ONOW) 042563 (P3AR_ONOW)	CVSIRKLL(QKKYEBHKSDYSDHEQR-DLLDALLBARESABRNNTAEITMETVGLSDEHL INVRAKVYLGGABIRLKITUS ISSEQ-DFIEBATVEM-LEEKDODNTEFNINGM NVADLXMEVIELVRGLEGTLNPINGE-GPVOSFIVEM-LEESGKMDSFYHDDML ANTDFYASLAKIKSGRDTGNSTINKV-DFLQMIDGQKSDTKTGBEQTKGLITDHSI VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKNLEV VGIVNDLFGAGFDTISTALSWAVVYLVAYPBIQBRINGELKKVGMIRTPRISDKINLEL KASVTSELMAGGVDTISTILMTLYSLARHFBLQBERHEGELKSKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV VSSYGNLFSAGTDTTGTTLRWGLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV VSSYGNLFSAGTDTTGTTLRWGLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV VSSYGNLFSAGTDTTGTTLRWGLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV VSSYGNLFSAGTDTTGTTLRWGLLMTKYPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV LSQAMIFIFAGTVTTGTTLRWGLLMAKVPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV LSQAMIFIFAGTVTTGTTLRWGLLMAKVPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV LSQAMIFIFAGTVTTGTTLRWGLLMAKVPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV LSQAMIFIFAGTVTTGTTLRWGLLMAKVPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV LSQAMIFIFAGTVTTGTTLRWGLLMAKVPHIQDQVQBEISKVIG-SRQTLVEDRKNLEV LSQAMIFIFAGTRAVGTTLRWGLLMAKVPHIQDGVGFIKK	299 294 300 300 359 372 374 372 359 359 360 406 432
P30437 (P17A_ONNMY) 093297 (P27A_ONNMY) 093297 (P27A_ONNMY) 093299 (P27A_ONNMY) 093299 (P27A_ONNMY) 093299 (P27A_ONNMY) 093210 (P1AA_ONNMY) 093210 (P1AA_ONNMY) 093210 (P1AA_ONNMY) 093210 (P1AA_ONNMY) 093297 (P27A_ONNMY) 093297 (P27A_ONNMY) 093299 (P3AA_ONNMY)	CVSIRKLL(QKKYEBHESDYSDHEQR-DALDALDALDARERSABNNNTAEITMETVGLSDEHL INVRAKVY1GGABIRLKITAIS ISEQ-DFIEBATUWM-LEEKDODNITEFINGKM NVADLXMEVIELVRGLEGETLNPINGE-GPVOSFIVEW-LEESCKMDSFYHDDML ANTDFYASIAKIKSGRDTGNSTINV-DFIQLMIDGQKSDTKTGEGQTKGLIDHBIL VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDGKUDHV VGIVNDLFGAGFDIISTALSWAVVYLVAYFBIGBRHGBLKEKVGMIRTPRISDKINLEL KASVTEIANGGVDTISTILLMTLYBLANHFDLQBERHGBLKEKVGMIRTPRISDKINLEL KASVTEIANGGVDTISTILLMTLYBLANHFDLQBERHGBLKEKVGMIRTPRISDKINLEL LMTVGDIFGAGVETTSTVLKWALAVLIHHDQVQGRIGBELDGVVGCDRTDQLSDRGGLDV LMTVGDIFGAGVETTSTVLKWALAVLIHHDQVQGRIGBELDGVVGCDRTDQLSDRGGLDV LPSIGNLFGAGTTTTSTTLRWGLLLMAKVPHIQDVQBETSRVIG-SRQTUVEDRENDLY LPSIGNLFGAGTTTTSTTLRWGLLLMAKVPHIQDVQBETSRVIG-SRQTUVEDRENDLY LPSIGNLFGAGTTTTTGTTLRWGLLLMAKVPHIQDVQBETSRVIG-SRQTUVEDRENDLY TDAVIHETGRLANIAPNSIPHTTSRDVTFGGGYFIKKDDSSWSSPHTL LBAFILEIFRHSSFLPFTIPHCTIKDTSLNGYFIFRDTVTROWGNARDPDVFPRPEKKY TRAVIHETGRLANIAPNSIPHTTSRDVTFGGYFIKK	299 294 300 300 359 372 374 372 359 359 360 406 432 433
P30437 (P17A, ONCHY 972088 C29AL, ONCHY 093297 C22K4_ONCHY 093299 CP3K3_ONCHY 097210 C11A1_ONCHY 097217 C911A, ONCHY 097218 C11A3_ONCHY 097209 C22K1_ONCHY 097208 C22K1_ONCHY 097209 C22K1_ONCHY 097209 C22K3_ONCHY 097209 C22K3_ONCHY 097209 C22K3_ONCHY 097210 C11A1_ONCHY 097217 C911A_ONCHY 097217 C911A_ONCHY 097217 C911A_ONCHY 097217 C911A_ONCHY 097217 C911A_ONCHY 097219 C92K3_ONCHY 097217 C911A_ONCHY 097217 C911A_ONCHY	CVSIRKLLQKKYEEHKSDYSDHEQR-DALDALLRAKESABRNNTAEITMETVGLSDENLIVMRAKVYLGGABIRIKKTUR ISEQ-DFIEBRIVMR-LEEKDDDNTFERNIGMN NVADLKKWEVIELVRGLEETLAPIHWER-GFVOSFUVRKOTLEESGKMDSFYHDDML AVTDFFYASLAKIKSGRDTONSTIRW-DFIQLMIDSQKSDTKTGEQTKGLTDHDINL AVTDFYASLAKIKSGRDTONSTIRW-DFIQLMIDSQKSDTKTGEQTKGLTDHDINL VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGEEISGVIG-SRQTLVEDRKNLPY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEDGERLHGELKEKKVGMIRTPRLSDKINLPL KASVTELMAGGVDTTSITLMTLYELARHPDLQSELRAEVAVARQSTQGTMLQMLKKHIPL VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDDVQEEISRVIG-SRQTLVEDRKNLPY VMTANSLFAAGTDTTGTTLRWGLLLMTKYPHIQDDVQEEISRVIG-SRQTLVEDRKNLPY VMTANSLFAAGTDTTGTTLRWGLLLMTKYPHIQDDVQEEISRVIG-SRQTLVEDRKNLPY VMTANSLFAAGTETTSSTLRQSFLMMIKYPHIQDSVQEEIDBVIG-SRQTLVEDRKNLPY LESIGNLFGAGTDTTGTTLRWGLLLMKYPHIQDVQEEISRVIG-SRQTLVEDRKNLPY LESIGNLFGAGTDTTGTTLRWGLLLMKYPHIQDVQEEISRVIG-SRQTLVEDRKNLPY LESIGNLFGAGTDTTGTTLRWGLLLMKYPHIQDVQEEISRVIG-SRQTLVEDRKNLPY LESIGNLFGAGTDTTGTTLRWGLLLMKYPHIQDVQEEISRVIG-SRQTLVEDRKNLPY LESIGNLFGAGTTTTGTTLRWGTLLMKYPHIQDVQEEISRVIG-SRQTLVEDRKNLPY LESIGNLFGAGTTTTGTTLRWGTLTMTSTLMYGTFFTDTTVFTLWGTWGTMPHOTTGTTLRWGTMTSTLMYGTTFTTGTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	299 294 300 300 372 374 372 359 353 360 406 432 433 432
P30437 (P17A, ONNOW) 972088 (P2AL, ONNOW) 093297 (P2K4, ONNOW) 093299 (P2K3, ONCOW) 093299 (P2K3, ONCOW) 093210 (P1AL, ONNOW) 072117 (P11A, ONNOW) P30437 (P1AL, ONNOW) P30437 (P1AL, ONNOW) 093299 (P2K4, ONNOW) 093299 (P2K4, ONNOW) 093291 (P1AL, ONNOW) 093299 (P2K3, ONNOW) 093299 (P2K3, ONNOW) 093299 (P3K3, ONNOW)	CVSIRKLL(QKKYEBHESDYSDHEQR-DALDALLRAKESABENNATAEITMETVGLSDEHL IVNKAKVY1GAGAEIRLKITAISEQ-DFIEBATUWM-LEEKDODNITEFNINGM NVADLXMEVIELVRGLEGTLAPHEQR-GFVDSFIVEW-LEESCKMDSFYHDDML ANTDFYASIAKIKSGRDTGNSTINV-DFIQLMIDGQKSDTKTGEGQTKGLITHBIL VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDGKUDHV VGIVNDLFGAGFDTISTALSNAVVYLVAYFBIGBRHGBLKEKVGMIRTPRISDKINLEL KASVTEIBANGGVDTTSITLANTLYELARHPBLQBEIREKVGMIRTPRISDKINLEL KASVTEIBANGGVDTTSITLANTLYELARHPBLQBEIREKVGMIRTPRISDKINLEL KASVTEIBANGGVDTTSTLLANTLYELARHPBLQBEIREKVGMIRTPRISDKINLEL LANTVOLFGAGVETTSTVLKWALAVLIHBDQVQDRIGBELGSVVGCDRTPQLSDKGSLDV VMTANSLFAGATTTTSTTLRGSFMMIKYFHIGDOVQBEISBVGG-SRQTLVEDGKALDW LPSIGNLFGAGTTTTTGTTLRWGLLLMAKYPHIQDQVGBTSBVGG-SRQTLVEDGKALDW LPSIGNLFGAGTTTTTGTTLRWGLLLMAKYPHIQDQVGBTSBVGG-SRQTLVEDGKALDW LPSIGNLFGAGTTTTTGTTLRWGLLLMAKYPHIQDQVGBTSBVGG-SRQTLVEDGKALDW TADVIHBTGRLAMIAPHSIPHTTSRDVTFGGGYFIKKDSSWESSPHTL LBAFILEIFRHSSFLPFTIPHCTIKDTSLNGYFIFKDTCVYFINWGWNHDEBLKKESSF TADVIHBTGRLAMIAPHSIPHTSRDVTFGGYFIKKDSSWESSPHTL LBAFILEIFRHSSFLPFTIPHCTIKDTSLNGYFIFKGTSVILLUTANGRGDPDVFPRPEKY LBAFILEIFRHSSFLPFTIPHCTIKDTSLNGYFIFKGTSVILLUTANGRGDPDVFPRPEKY LBAFILEIFRHSSFLPFTIPHCTIKDTSLNGYFIFKGTSVILLUTSVQNDRNDEDGELKKESSSF TADVIHBTGRAMIAPHSIPPTPHCTIKDTSLNGYFIFKGTSVILLUTSVQNDRNDEDGELKKESSSF TADVIHBTGRAMIAPHSIPPTFPHCTTKDTSLNGYFIFKGTSVILLUTSVQNDRNDEDGELKKESSSF TADVIHBTGRAMIAPHSIPPTFPHCTTKDTSLNGYFIFKGTSVILLUTSVQNDRENDESSNFTF	299 294 300 300 359 372 374 379 359 359 360 406 432 433 432 419
P30437 (2117A, ONCHY) 972088 (2241, ONCHY) 97207 (27244, ONCHY) 97207 (27244, ONCHY) 97209 (2724, ONCHY) 97209 (2724, ONCHY) 972109 (2711A, ONCHY) 972109 (2711A, ONCHY) 972090 (2724, ONCHY) 972090 (2724, ONCHY) 972091 (2724, ONCHY) 972091 (2724, ONCHY) 972091 (2724, ONCHY) 972091 (2724, ONCHY) 972090 (2724, ONCHY)	CVSIRDKLLQKKYEEHKSDYSDHEQR-DALDALLRAKESABRNNYTAEITMETVGLSDENLIVMRAKVYLGGABIERLKTHIS ISEQ-DPIEBAFUWM-LEEKDDDNTFERNIGMN NVADLKAKEVIELVGGABIERLKTHIS ISEQ-DPIEBAFUWM-LEEKDDDNTFERNIGMN NVADLKAKEVIELVGALERTIAPPHWQR-GFVOSFUVEKÇTILESSCKMDSFYHDDML AVTDFFYASLAKIKSGRDTONSTINEV-DFIQLMIDSQKGSDTKTGEQTKGLTDHDIL VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDGVQEEISGVIG-SRQTLVEDERKHLPY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEGIGRHLDGLKEKKVGMIRTPRISDKINLPL KASVTELMAGGVDTTSTILLWTLYELARHPDLQSELRAEVAVARQSTQGDMLQMLKKHIPL VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDDVQEEISRVIG-SRQTLVEDERKLPY UTVADLFGAGMPTISTALSWAVVYLVAYPEGIGRHLDGLKEKKVGMIRTPRISDKINLPL VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDOVQEEISRVIG-SRQTLVEDERKLPY VMTAMSLFAAGTETTSSTLRQSFLMMIKYPHIQDSVGFLEDEVIG-SRVTVVDDRVKMPY LESIGNLFGAGTDTTGTTLRWGLLLMAKYPHIQDOVQEEISRVIG-SRQTLVEDERKDLYD LESIGNLFGAGTDTTGTTLRWGLLLMAKYPHIQDOVQEEISRVIG-SRQTLVEDERKDLYD LSGAMHFIFAGYETSSTNSFLAYNLATNHHWMTKLQEEIDTVFPNKAPIQYEALMOMDY : : : : : : : : : : : : : : : : : : :	299 294 300 300 359 372 359 359 359 360 406 432 433 432 419 419
P30437 (D17A, ONNOW) 093297 (D2X4, ONNOW) 093297 (D2X4, ONNOW) 093299 (D2X3, ONCOW) 093299 (D2X3, ONCOW) 093299 (D2X1, ONNOW) 093291 (D1A1, ONNOW) 093290 (D2X1, ONNOW) 093290 (D2X1, ONNOW) 093297 (D2X4, ONNOW) 093297 (D2X4, ONNOW) 093297 (D2X1, ONNOW) 093297 (D2X1, ONNOW) 093297 (D2X1, ONNOW) 093297 (D2X1, ONNOW) 093299 (D2X1, ONNOW) 093297 (D2X1, ONNOW) 093298 (D2X1, ONNOW) 093297 (D2X1, ONNOW) 093297 (D2X1, ONNOW) 093297 (D2X1, ONNOW) 093297 (D2X1, ONNOW)	CVSIRKLLQKKYEEHKSDYSDHEQR-DALDALLRAKESABRNNTAEITMETVGLSDENLIVMRAKVYLGGABIRIKKTUS ISEQ-DPIEBAFUWM-LEEKDODNTFERNSMM NVADLKMEVIELVRGLEETLMPIHMER-GFVOSFUNGKTILESSCKMDSFYHDDML AVTOFFYASLAKIKSGRDTONSTIRV-DFIQLMIDSQKSDTKTGEQTKGLTDHDIN. AVTOFFYASLAKIKSGRDTONSTIRV-DFIQLMIDSQKSDTKTGEQTKGLTDHDIN. VFSVGNILFSAGTDTTGTTLRWGLLLMTKYPHIQDDVQEEISGVIG-SRQTLVEDRKHLPY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEDGERLHQELKEKKVGMIRTPRISDKINLPL KASVTELMAGGVDTTSITLMTLYELARHPDLQSELNBEVAVARQSTQGMLCMLKHIPL VGIVNDLFGAGFDTISTALSWAVVYLVAYPEDGERLHQELKEKKVGMIRTPRISDKINLPL VGIVNDLFGAGFDTISTALSWAVVYLVAYPEDGERLHQELKEKKVGMIRTPRISDKINLPL VGIVNDLFGAGFDTISTALSWATALATHHPDVQOTGEEISBVIG-SRQTLVEDBRKLPY VMTAMSLFAAGTDTTGTTLRWGLLLMAKYPHIQDVQEEISBVIG-SRQTLVEDBRKLPY VMTAMSLFAAGTETTSSTLRQSFLMMIKYPHIQDSVQFEEISBVIG-SRQTLVEDBRKDLYV VMTAMSLFAAGTETTSSTLRQSFLMMIKYPHIQDSVQFEEISBVIG-SRQTLVEDBRKDLYV LSGAMIFIFAGVSTSSTNSFLAYNLATNHHVMTKLQBEIDTVFPNKAPIQVSEAMMYNDLSKWSSTNSFLAWNLATNHHVMTKLQBEIDTVFPNKAPIQVSEAMMYNDLSKWSSTNSFLAWNLATNHHVMTKLQBEIDTVFPNKAPIQVSEAMMYNDLSKWSSTNSFLAWNLATNHHVMTKLQBEIDTVFPNKAPIQVSEAMMYNDLSFEESSTSTVSCLAKKSTLRLHPVANSL-QRYTTEEIVLQNYHIPGGTFIKKGTSVIPLLMSVLDHDEKSWSSPNTFT LANTHHSQLRAMIJPRNSVPHTTSRDVTFGGYFIKKGTSVIPLLMSVLDHDEKSWSSPNTFT TDAVIHHSTQRLAMIJPRNSVPHTTSRDVTFGGYFIKKGTSVIPLLMSVLDHDEKSWNSPENFT TDAVIHHSQLRAMIJSPNAVPHTSRDVTFGGYFIKKGTSVIPLLMSVLDHDEKSWNSPENFT TDAVIHHSQLRAMIJSPNAVPHTSRDVTFGGYFIKKGTSVIPLLMSVLDHDEKSWNSPENFT TDAVIHHSQLRAMIJSPNAVPHTSRDVTFGGYFIKKGTSVIPLLMSVLDHDEKSWNSPENFT TDAVIHHSQLRAMIJSPNAVPHTSRDVTFGGYFIKKGTSVIPLLMSVLQDDMEWSSNTFT	299 294 300 300 359 372 374 359 359 360 406 432 433 432 419 419 413 419
P30437 (2017A_ONNSW) 093297 (2024A_ONNSW) 093297 (2024A_ONNSW) 093299 (2023A_ONNSW) 093299 (2023A_ONNSW) 093299 (2023A_ONNSW) 093291 (2011A_ONNSW) 093290 (2024A_ONNSW) 093291 (2024A_ONNSW) 093291 (2024A_ONNSW) 093297 (2024A_ONNSW)	CVSIRNKLLQKKYEBHKSDYSDHEQR-DALDALDALDARARSABNNNTARITMETVGLSDEHL INNKAKVYIGGABIRIKKITUS ISSEQ-DFIEBARUWM-LEEKDODNITEFINGÖM NVADLKMEVIELVRGLEGETLAPIHQB-GSFVDSFLVKM-LEEKDDPNITEFINGÖM NVADLKMEVIELVRGLEGETLAPIHQB-GSFVDSFLVKGTLEBSGKMDSFYHDDML ANTDFYASLAKIKSGRDTONSTIRW-DFLQLMINGQKSDTKTGERGYKGLTDHDI VSYGNILFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEEISGVIG-SRQTLVEDRKHLPY VGIVNDLFGAGFPTISTALSWAVVYLVAYPEDGERLHQELKEKVGWIRTPFLSDKINLDL KASVTEHMAGGVDTTSTLLWITLYELARHPDLQSELRABVAVARQGTSGGMCMLMIKHTEL VSYGNILFSAGTDTTGTTLRWGLLLMIKYPHLQDQVGEISRVIG-SRQTLVEDRKHLPY USINNDLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVGEISRVIG-SRQTLVEDRKHLPY USINNLFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY UNTANSLFAAGTETTSSTLRQSFLMMIKYPHLQSVQFEELDVIG-SRVPTVDDRVKMPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKY-DVG-DVG-MAGNDDPUFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKY-SKONTYLDGLKMARDDPUFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKKGTSVIJGLMSKNAKDPWFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKKGTSVIJGLMSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSLANGLBDWFRERKENDEN TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLMSVLADDLRSKSNATP TOANHENGTHANIFFANDFFTSRDVTFQGYFIKKGTSVIJLMSVLADDLRSKSNATP T	299 294 300 300 359 372 374 372 359 360 406 432 419 419 419 419
P30437 (2017A_ONNSW) 093297 (2024A_ONNSW) 093297 (2024A_ONNSW) 093299 (2023A_ONNSW) 093299 (2023A_ONNSW) 093299 (2023A_ONNSW) 093291 (2011A_ONNSW) 093290 (2024A_ONNSW) 093291 (2024A_ONNSW) 093291 (2024A_ONNSW) 093297 (2024A_ONNSW)	CVSIRNKLLQKKYEBHKSDYSDHEQR-DALDALDALDARARSABNNNTARITMETVGLSDEHL INNKAKVYIGGABIRIKKITUS ISSEQ-DFIEBARUWM-LEEKDODNITEFINGÖM NVADLKMEVIELVRGLEGETLAPIHQB-GSFVDSFLVKM-LEEKDDPNITEFINGÖM NVADLKMEVIELVRGLEGETLAPIHQB-GSFVDSFLVKGTLEBSGKMDSFYHDDML ANTDFYASLAKIKSGRDTONSTIRW-DFLQLMINGQKSDTKTGERGYKGLTDHDI VSYGNILFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEEISGVIG-SRQTLVEDRKHLPY VGIVNDLFGAGFPTISTALSWAVVYLVAYPEDGERLHQELKEKVGWIRTPFLSDKINLDL KASVTEHMAGGVDTTSTLLWITLYELARHPDLQSELRABVAVARQGTSGGMCMLMIKHTEL VSYGNILFSAGTDTTGTTLRWGLLLMIKYPHLQDQVGEISRVIG-SRQTLVEDRKHLPY USINNDLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVGEISRVIG-SRQTLVEDRKHLPY USINNLFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY UNTANSLFAAGTETTSSTLRQSFLMMIKYPHLQSVQFEELDVIG-SRVPTVDDRVKMPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKY-DVG-DVG-MAGNDDPUFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKY-SKONTYLDGLKMARDDPUFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKKGTSVIJGLMSKNAKDPWFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKKGTSVIJGLMSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSLANGLBDWFRERKENDEN TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLMSVLADDLRSKSNATP TOANHENGTHANIFFANDFFTSRDVTFQGYFIKKGTSVIJLMSVLADDLRSKSNATP T	299 294 300 300 359 372 374 372 359 360 406 432 419 419 419 419
P30437 (2017A_ONNSW) 093297 (2024A_ONNSW) 093297 (2024A_ONNSW) 093299 (2023A_ONNSW) 093299 (2023A_ONNSW) 093299 (2023A_ONNSW) 093291 (2011A_ONNSW) 093290 (2024A_ONNSW) 093291 (2024A_ONNSW) 093291 (2024A_ONNSW) 093297 (2024A_ONNSW)	CVSIRNKLLQKKYEBHKSDYSDHEQR-DALDALDALDARARSABNNNTARITMETVGLSDEHL INNKAKVYIGGABIRIKKITUS ISSEQ-DFIEBARUWM-LEEKDODNITEFINGÖM NVADLKMEVIELVRGLEGETLAPIHQB-GSFVDSFLVKM-LEEKDDPNITEFINGÖM NVADLKMEVIELVRGLEGETLAPIHQB-GSFVDSFLVKGTLEBSGKMDSFYHDDML ANTDFYASLAKIKSGRDTONSTIRW-DFLQLMINGQKSDTKTGERGYKGLTDHDI VSYGNILFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEEISGVIG-SRQTLVEDRKHLPY VGIVNDLFGAGFPTISTALSWAVVYLVAYPEDGERLHQELKEKVGWIRTPFLSDKINLDL KASVTEHMAGGVDTTSTLLWITLYELARHPDLQSELRABVAVARQGTSGGMCMLMIKHTEL VSYGNILFSAGTDTTGTTLRWGLLLMIKYPHLQDQVGEISRVIG-SRQTLVEDRKHLPY USINNDLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVGEISRVIG-SRQTLVEDRKHLPY USINNLFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFSAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY UNTANSLFAAGTETTSSTLRQSFLMMIKYPHLQSVQFEELDVIG-SRVPTVDDRVKMPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTDTTGTTLRWGLLLMIKYPHLQDQVQEISRVIG-SRQTLVEDRKHLPY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKY-DVG-DVG-MAGNDDPUFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKY-SKONTYLDGLKMARDDPUFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKKGTSVIJGLMSKNAKDPWFPRERKY USINNLFGAGTANLAPMSDHTTSRDVTFQGYFIKKGTSVIJGLMSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSLANGLBDWFRERKENDEN TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKNAKDPMF TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLLMSVLADDLRSKSNATP TDAVIHETGRLANIFFANDFFTSRDVTFQGYFIKKGTSVIJLMSVLADDLRSKSNATP TOANHENGTHANIFFANDFFTSRDVTFQGYFIKKGTSVIJLMSVLADDLRSKSNATP T	299 294 300 300 359 372 374 372 359 360 406 432 419 419 419 419
P30437 (2017A_ONOMY) 093297 (2024A_ONOMY) 093297 (2024A_ONOMY) 093299 (2023A_ONOMY) 093299 (2023A_ONOMY) 093299 (2023A_ONOMY) 093290 (2024A_ONOMY) 093290 (2024A_ONOMY) 093290 (2024A_ONOMY) 093291 (2024A_ONOMY) 093291 (2024A_ONOMY) 093297 (2024A_ONOMY) 093297 (2024A_ONOMY) 093297 (2024A_ONOMY) 093299 (2024A_ONOMY)	CVSIRKLL(KKYEEHKSDYSDHEOR-DALDALLRAKESABRINNTAEITMETVGLSDEIL IVNKAKVYIGAGAEIRLKITAISEG-DFIERATVIM-LEEKODDNTEFNINGIM IVNAKAKVIGAGAEIRLKITAISEG-DFIERATVIM-LEEKODDNTEFNINGIM IVNAKOWIGAGEIRLKITAISEG-DFIERATVIM-TEKENDDNTEFNINGIM IVNAKOWIGAGEIRLKIKSGROTORITINGTKYGEGOTKGLTDHEIL ANTDEFYASIAKIKSGROTORITINGTKYGEGOTKGLTDHEIL SAVTERVASIAKIKSGROTORITIKWGLLLMIKYPHIQDQVQEEISGVIG-SRQTLVEDRINLEIL KASVTEHMAGGVDITSITALSAWAVVILVAYPEGIGRIHGELKEKVOMIRTPRISDKINLEIL KASVTEHMAGGVDITSITLAITLYELARHEDLQSELRAEVVANAGGSTGGOMGLMIKHTEL KASVTEHMAGGVDITSTILMITLYELARHEDLQSELRAEVVANAGGSTGGOMGLMIKHTEL KASVTEHMAGGVDITSTILMITLYELARHEDLQSELRAEVVANAGGSTGGOMGLMIKHTEL KASVTEHMAGGVDITSTILMITLYELARHEDLQSELRAEVVANAGGSTGGOMGCMIKMIKHTEL VSSVORIFSAGTDITGTTILRGALLLMIKYPHIQDQVQEEISKVIG-SRQTIVEDRIKKHEL VSSVORIFSAGTDITGTTILRGALLLMIKYPHIQDQVQEEISKVIG-SRQTIVEDRIKKHEL VSSVORIFSAGTDITGTTILRGALLLMIKYPHIQDQVQEEISKVIG-SRQTIVEDRIKKHEL VSSVORIFSAGTDITGTTILRGALLLMIKYPHIQDQVQEEISKVIG-SRQTIVEDRIKKHEL VSSVORIFSAGTDITGTTILRGALLLMIKYPHIQDQVQEEISKVIG-SRQTIVEDRIKKHEL VSSVORIFSAGTDITGTTILRGALLLMIKYPHIQDQVGEISKVIG-SRQTIVEDRIKKHEL LEGATILETERHANLAENSELPETIHGTILDTSLAGVFIFKGT	299 294 300 300 359 372 359 353 359 360 406 432 433 419 419 413 419 419 413 419 419 416 3492 487
P30437 (2017A, ONCHY) 093297 (2024A, ONCHY) 093297 (2024A, ONCHY) 093299 (2024A, ONCHY) 093299 (2024A, ONCHY) 093299 (2024A, ONCHY) 093299 (2024A, ONCHY) 093290 (2024A, ONCHY) 093290 (2024A, ONCHY) 093291 (2024A, ONCHY) 093297 (2024A, ONCHY) 093299 (2024A, ONCHY)	CVSIRKLL(KKYEEHKSDYSDHEOR-DLLDALLBARESABRNNTAEITMETVGLSDEHL IVNKAKVYIGGABIRIKKINIS ISSEQ-DFIEBATVEM-LEEKODDNTEFNINGM NVADLAKKEVIGGABIRIKKINIS ISSEQ-DFIEBATVEM-LEEKODDNTEFNINGM NVADLAKMEVIELVRGLEETLHPHORE-GFVOSFIVEM-LEEKODDNTEFNINGM NVADLAKSGROTORITHWELLIMIKY-DFILORIDGKSDTKTGERGYKGLTDHDI AVTOPFYASIAKIKSGROTORITHWOLLIMIKY-PHIQDQVOEEISGVIG-SRQTI-VEDRKHLPY VGIVNDLFGAGFFTISTALSWAVVYLVAYPEDGSRH.HGELKEKVGWIRTPRISDKINLEL KASVTEHMAGGVDTTSTILLWITLYELARHPDLQSELRAEVVANAGGTGGGMCHMINTHIS KASVTEHMAGGVDTTSTILLWITLYELARHPDLQSELRAEVVANAGGTGGGGGNETPGLISDESKINLEL KASVTEHMAGGVDTTSTILLWITLYELARHPDLQSELRAEVVANAGGTGGGGSTENGLMIKHKINLE KASVTEHMAGGVDTTSTILLWITLYELARHPDLQSELRAEVVANAGGTGGGGSTENGLMIKHKINLE KASVTEHMAGGVDTTSTILLWITLYELARHPDLQSGLAGEILGEKKVGWIRTPRISDKINLEL VSSVORLIFSAGTDTTGTTLRWGLLLMIKY-PHIQDQVOEEISKVIG-SRQTI-VEDRKHLEV VSTAWALFAGATTTTSTLRWGLLLMIKY-PHIQDQVOEEISKVIG-SRQTI-VEDRKHLEV VSTAWALFAGATTTTSTLRWGLLLMIKY-PHIQDQVOEEISKVIG-SRQTI-VEDRKHLEV LEGGMLFGAGTTTTTTLRWGLLLMAKY-PHIQDQVOEEISKVIG-SRQTI-VEDRKHLEV LEGGMLFGAGTAUTLABVSIGHTTSDAVTFGGYFT IKC	299 294 300 300 359 372 359 353 359 360 406 432 433 419 419 413 419 419 413 419 419 416 3492 487
P30437 (2017A, 0MNSW) 093297 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 093299 (2024A, 0MNSW) 093291 (2014A, 0MNSW) 093291 (2014A, 0MNSW) 093291 (2014A, 0MNSW) 093297 (2024A, 0MNSW)	CVSIRKLL(KKYEBHKSDYSDHEOR-DLLDALLRAKESABINNTAEITMETVGLSDEIL IVNKAKVYIGAGAEIRLKITAISEG-DFIERAFUNM-LEEKODDN-NTEFNINGIM NVADLKAKURUS GABEIRLKITAISEG-DFIERAFUNM-LEEKODDN-NTEFNINGIM NVADLKAKEVIELVRGLEETLAPHORG-GFVOSFIVENGTLEESCKMDSFYHDDML AVTDFFYASLAKIKSGEDTGSTINW-DFIQLATIONGKGSDTKTGEGCTKGLTDHIII VGIVANLFSAAKTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LAMTVAGAGAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LAMTVAGAGAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKXYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQDGVGESTAGVIG-SRQTLVSDEKKEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQTFTGAGTAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGA	299 294 300 300 372 374 375 359 359 360 406 432 433 419 419 413 419 419 447 463 487 497 497 497 497
P30437 (2017A, 0MNSW) 093297 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 093299 (2024A, 0MNSW) 093291 (2014A, 0MNSW) 093291 (2014A, 0MNSW) 093291 (2014A, 0MNSW) 093297 (2024A, 0MNSW)	CVSIRKLL(KKYEBHKSDYSDHEOR-DLLDALLRAKESABINNTAEITMETVGLSDEIL IVNKAKVYIGAGAEIRLKITAISEG-DFIERAFUNM-LEEKODDN-NTEFNINGIM NVADLKAKURUS GABEIRLKITAISEG-DFIERAFUNM-LEEKODDN-NTEFNINGIM NVADLKAKEVIELVRGLEETLAPHORG-GFVOSFIVENGTLEESCKMDSFYHDDML AVTDFFYASLAKIKSGEDTGSTINW-DFIQLATIONGKGSDTKTGEGCTKGLTDHIII VGIVANLFSAAKTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV VGIVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LAMTVAGAGAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LAMTVAGAGAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLAMTKYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKXYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQDGVGESTAGVIG-SRQTLVSDEKKLEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQDGVGESTAGVIG-SRQTLVSDEKKEV LYSVANLFGAAGTUTTGTTLRKGLLLMKAYBHIQTFTGAGTAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGA	299 294 300 300 372 374 372 359 359 359 360 406 432 433 432 419 413 419 419 419 449 476 478 478
P30437 (2017A_0NOW) 972088 C2244_0NOW) 0932297 C2244_0NOW) 0932297 C2244_0NOW) 0932299 C2243_0NCW] 0932299 C2243_0NCW] 0932290 C2241_0NOW) 0932290 C2241_0NOW) 0932290 C2241_0NOW) 0932290 C2244_0NOW] 0932390 C2244_0NOW] 0932390 C2244_0NOW] 0932390 C2244_0NOW]	CVSIRKLL(KKYEBHKSDYSDHEOR-DLLDALLRAKESABINNTAEITMETVGLSDEIL IVNKAKVYIGAGAEIRLKITAISEG-DFIERATVIMM-LEEKODDNITEFINGÖM NVADLKAKEVIGAGAEIRLKITAISEG-DFIERATVIMM-LEEKODDNITEFINGÖM NVADLKAKEVIGLUKGETIAPHENGE-GFVOSFIVENGTLEESCKMDSFYHDDMI AVTDFFYASIAKIKSGRDTGNSTINKV-DFI,OMIDOKGSDTKTGERGTKGLTDHEII VFSVONLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTVONLFGAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTVANSLFAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKENDSF TADVIHHTGGLAMIADPASTTTSRTUTGGYFTKGT	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 (2017A, 0MNSW) 093297 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 093291 (2024A, 0MNSW) 093291 (2024A, 0MNSW) 093291 (2024A, 0MNSW) 093297 (2024A, 0MNSW) 042563 (2034A, 0MNSW)	CVSIRKLL(KKYEBHKSDYSDHEOR-DLLDALLRAKESABINNTAEITMETVGLSDEIL IVNKAKVYIGAGAEIRLKITAISEG-DFIERATVIMM-LEEKODDNITEFINGÖM NVADLKAKEVIGAGAEIRLKITAISEG-DFIERATVIMM-LEEKODDNITEFINGÖM NVADLKAKEVIGLUKGETIAPHENGE-GFVOSFIVENGTLEESCKMDSFYHDDMI AVTDFFYASIAKIKSGRDTGNSTINKV-DFI,OMIDOKGSDTKTGERGTKGLTDHEII VFSVONLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV VGIVNDLFSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTVONLFGAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTVANSLFAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKULDV LSTSAGTUTTGTTLEWGLLLAMTKYPHIQDOVGEKISGVIG-SRQTLVEDRKENDSF TADVIHHTGGLAMIADPASTTTSRTUTGGYFTKGT	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 (2017A_ONNSWY 093297 (2024A_ONNSWY 093297 (2024A_ONNSWY 093299 (2024A_ONNSWY 093299 (2024A_ONNSWY 093299 (2024A_ONNSWY 093299 (2024A_ONNSWY 093290 (2024A_ONNSWY 093291 (2024A_ONNSWY	CVSTRINGLIQKKYEBHESDYSDHEOR-DALDALDALDARERSABNNNTAEITMETVGLSDBIL INVRAKVYIGGABIERLKITUS ISSEQ-DFIEBATUWM-LEEKDODNITERINGEN NVADLAKMEVIELVRGLEETLAPIHOR-GFVOSFIVENVEM-LEEKODDNITERINGEN NVADLAKMEVIELVRGLEETLAPIHOR-GFVOSFIVENVEM-LEESOKHDSFYHDDMI ANTDFYYASLAKIKSGRDTORISTINKU-DFLQAHIBOGKSDTKTGEBQTKGLITCHIS VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISSVIG-SRQTLVEDRKNILPY VGIVNDLFGAGFPTISTALSWAVVYLVAYPEIG BRIHQBLKEKVGWIRTPRISDKINLDL KASVTEHMAGGVDTTSTILWTLYELARHPDLQSELRAEVVANAGGSTGGMCHLMENTHISL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISSVIG-SRQTLVEDRKNILPY VGIVNDLFGAGFPTISTALSWAVVYLVAYPEIGSERLAPUSLKEKVGWIRTPRISDKINLDL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGEEISSVIG-SRQTLVEDRKNILPY VSTVANLFSAGTDTTGTTLRWGLLLMTKYPHIQDGTVGAEELGAFTGVGETRAGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTG	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 (2017A, ONOMY) 093297 (2024A, ONOMY) 093297 (2024A, ONOMY) 093299 (2024A, ONOMY) 093299 (2024A, ONOMY) 093299 (2011A, ONOMY) 093291 (2011A, ONOMY) 093291 (2011A, ONOMY) 093291 (2011A, ONOMY) 093297 (2024A, ONOMY) 093297 (2024A, ONOMY) 093297 (2024A, ONOMY) 093299 (2024A, ONOMY) 093297 (2024A, ONOMY) 093299 (2024A, ONOMY)	CVSITRKILLQKKYEBHKSDYSDHEQR-DLLDALLBALBARKSABNNNTABITMETVGLSDBIL IVNKAKVYIGAGABIRLKITAI SEQ-DFIEBALVMM-LEEKODDNITERNINGM NVADLAKMEVIELVRGLEGTLAPHNQR-GFVOSFIVENGTLEESGKMDSFYHDDML ANTDFYASIAKIKSGRDTGNSTINKY-DFIQUHIBOGKGSDTKTGEGCTKGLTDHEIL VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDGKLTDHIS VGVUNDLFGAGFDTISTALSWAVVYLVAYFBIQBRIHGELKEKVGMIRTPRISDKINLPL VGIVNDLFGAGFDTISTALSWAVVYLVAYFBIQBRIHGELKEKVGMIRTPRISDKINLPL KASVTEIANGGVDTISTILMTLYELARHFBLQBEILGELKEKVGMIRTPRISDKINLPL VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTTTTSTLRWGLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTTTTSTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDGVQBEISGVIG-SRQTLVEDRKHEND TADVIHRTGRLANIAPRSTPHTTSRDVTFGGGFFIKM	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 (2017A, ONOMY) 093297 (2024A, ONOMY) 093297 (2024A, ONOMY) 093299 (2024A, ONOMY) 093299 (2024A, ONOMY) 093299 (2011A, ONOMY) 093291 (2011A, ONOMY) 093291 (2011A, ONOMY) 093291 (2011A, ONOMY) 093297 (2024A, ONOMY) 093297 (2024A, ONOMY) 093297 (2024A, ONOMY) 093299 (2024A, ONOMY) 093297 (2024A, ONOMY) 093299 (2024A, ONOMY)	CVSITRKILLQKKYEBHKSDYSDHEQR-DLLDALLBALBARKSABNNNTABITMETVGLSDBIL IVNKAKVYIGAGABIRLKITAI SEQ-DFIEBALVMM-LEEKODDNITERNINGM NVADLAKMEVIELVRGLEGTLAPHNQR-GFVOSFIVENGTLEESGKMDSFYHDDML ANTDFYASIAKIKSGRDTGNSTINKY-DFIQUHIBOGKGSDTKTGEGCTKGLTDHEIL VFSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDGKLTDHIS VGVUNDLFGAGFDTISTALSWAVVYLVAYFBIQBRIHGELKEKVGMIRTPRISDKINLPL VGIVNDLFGAGFDTISTALSWAVVYLVAYFBIQBRIHGELKEKVGMIRTPRISDKINLPL KASVTEIANGGVDTISTILMTLYELARHFBLQBEILGELKEKVGMIRTPRISDKINLPL VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTDTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTTTTSTLRWGLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED VGSVGNLFSAGTTTTSTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLED LFSIGNLFGAGTTTTGTLRWGLLLMTKYPHIQDGVQBEISGVIG-SRQTLVEDRKHEND TADVIHRTGRLANIAPRSTPHTTSRDVTFGGGFFIKM	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 CP17A, ONCHY	CVSTRINLLQKKYEBHESDYSDHEOR -DLLDALLBARESABENNYTAETHETVGLSDEHL INNKAKYVIGOAB ETRIKTINI SEG-DFIEBENVEM-LEEKODD NITERINGEN NVADLKMEVIELVRGLEETLHPENGE-GFVOSFIVEM-LEEKODD NITERINGEN NVADLKMEVIELVRGLEETLHPENGE-GFVOSFIVEKOTLEESCKMDSFYHDDML ANTDFYASLAKIKSGRDTORISTINK-DFLQMINGOKSDTKTGEBQTKGLTDHDIL ANTDFYASLAKIKSGRDTORISTRUK-DFLQMINGOKSDTKTGEBQTKGLTDHDIL SVENGUNDER-GAGEPTISTALSWAVVYLVAYPEGIGREH.GELKEKVGMIRTPRESDKINLEL KASVTEHMAGGVDTTSTILMTLYELARHPDLQSELRAEVAVARQSTQGDMLQMLKMIDL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIDQDVQBEELSKVIG-SRQTILVEDRKHLEY VGIVNDLFGAGFDTISTALSWAVVYLVAYPEGIGREH.GELKEKVGMIRTPRESDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIDQDVQBEELSVIG-SRQTILVEDRKALBY VMTAWSIFAAGTDTTGTTLRWGLLLMTKYPHIDQDVQBEELSVIG-SRQTIVEDRKHLEY VMTAWSIFAAGTDTTGTTLRWGLLLMTKYPHIDQDVQBEELSVIG-SRQTIVEDRKHLEY VMTAWSIFAAGTETTSSTLROSEMMIKYPHIDGSVQEELDSVIG-SRQTIVEDRKHLEY VMTAWSIFAAGTETTSSTLROSEMMIKYPHIDGSVQEELDSVIG-SRQTIVEDRKHLEY VSSGNLFGAGTDTTGTTLRWGLLLMAKYPHIDQVQBEINGDTVFGFRENLY LESIGNLFGAGTDTTGTTLRWGLLLMAKYPHIDQVQBEINGDTVFGRRVHLEY VMTAWSIFAAGTETTSSTLROSEMMIKYPHIGSTUPGVEENDAWDRADELWEEDSSF VKGALKKELRHHPUAVSL-DENTIERDTTGGYFIKGTSVIPLOMQVNNEDPELWEEDSSF VKGALKKELRHHPUAVSL-QRYTIEETVINDSTLMSYFIP PROTCYFINOWQVNNEDPELWEEDSSF VKGALKKELRHHPUAVSL-QRYTIEETVINDSTLMSYFIP PROTCYFINOWQVNNEDPELWEEDSSF TOAVIHHTQHANIYPHSVPHTTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHSVPHTTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHSVPHTTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHALSPARAKTVEINGIVIFRACTUPLYPWTHIRDPENSDERSNTF TOAVIHHTQHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJQDBSWESBNTF TOAVIHHTQHANIYPHANISPHAPPHTSRDVTFGGYFIKKGTSVIPLLMSVLJAGHERPERFOD PROTCHTSRDATTSPH	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 CP17A, ONCHY	CVSITRKLL(QKKYEBHESDYSDHEQR-DLLDALLBARESABENNYTAEITMETVGLSDEHL IVNKAKVYLOGADEIRLKKILDISEQ-DFIERDIVEM-LEEKODDNITERNISM NVADLAKMEVIELVRGLEGETLHPHOGR-GFVOSFIVEM-LEEKODDNITERNISM NVADLAKMEVIELVRGLEGETLHPHOGR-GFVOSFIVEM-LEESOKMDSFYHDDML ANTDFYASLAKIKSGRDTGNSTINKY-DFLQLHDSQKSDTKTGEGCTKGLTDHEIL STYPSYGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISGVIG-SRQTLVEDRKHLEY VGIVNDLFGAGFDTISTALSWAVVYLVAYPBIQBRIHQBLKEKVGMIRTPRISDKINLEL KASVTSEHANGGVDTISTILMTLYELARHFBLQBEELRBYAVARQSTGCMILMHKNIEL VSSVGALFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VGIVNDLFGAGMFDTISTALSWAVVYLVAYPBIQBEILGBLKEKVGMIRTPRISDKINLEL KASVTSEHANGGVDTISTILMTLYELARHFBLQBEILGBLKEKVGMIRTPRISDKINLEL VSSVGALFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSVGALFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTTTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTTTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTTTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTTTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTTTTGTTLRWGLLLMTKYPHIQDQVQBEISRVIG-SRQTLVEDRKHLEY VSSAGNIFSAGTTTTGTTLRWGTT	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 CP17A, ONCHY	CVSITREMILLOKKYEBHESDYSDHEOR -DLLDALLBARESSABINNTAEITMETVGLSDEHL INVRAKVYIGGABIERKETIS ISEQ-DFIEBATUWM -LEEKDOD NITEFINGKIM NVADLAKMEVIELVRGLEETLNPIHMOR-GFVOSPIJVEKOTLEBSCKM DSFYHDDML ANTDFYASIAKIKSGRDTORSTINKY-DFIQUHIBOGKSD TKTGEGOTKGLTDHEIL STOPPHYSASIAKIKSGRDTORSTINKY-DFIQUHIBOGKSD TKTGEGOTKGLTDHEIL VSVSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISSVIG-SRQTLVEDEKNILEV VGIVNDLFGAGFDTISTALSMAVVYLVAYPEIGERLHGELKEKVGMIRTPRISDKINLEL KASVTSELMAGGVDTISTILMTLYELARHFBLQBEILGEKKVGMIRTPRISDKINLEL KASVTSELMAGGVDTISTILMTLYELARHFBLQBEILGEKKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLMTKYPHIQDQVGBEILGEKVGMIRTPRISDKINLEL LSGAMIFIEAGYTTSTYLKARGALLATHHFWORTHEIGEKVLFVERDKKNLEV LSGAMIFIEAGYTTSTYLKARGALLATHHFWORTHFORTHOOTHEIGEKVLFVERDKKNLEV LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHEIGEKVLFVERDKKNLEV LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHOOTHEIGEKVSSPHTL LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHOOTHEIGEKVSSPHTL LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHOOTHOOTHOOTHOOTHOOTHOOTHOOTHOOTH	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 CP17A, ONCHY	CVSTRINKLLQKKYEBHESDYSDHEOR—DALDALLBARESABENNYTAETHMETVGLSDEHEINKAKHVIGGABETRIKTUS ISSEQ—DFTEBETVENT—LEEKODD——NTEFNISHMENNADLAKKEVIELVRGLEETLHPHORGE-GFVUSFUTLESSCKM——DSFYHDDMI ANTOFFYASIAKIKSGRDTOSITINKU-DFLQUMI BOGKSD——TKTEBEQTKGLTDHIDI. VFSVGNIFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEETSGVIG-SRQTLVEDRKHLPY VGIVINDLE/GAGPFDTISTALSWAVVYLVAYPEDGREHQBLKEKVGMIRTPRISDKINLEL KASVTEHMAGOVDTTSTILLWTLYELARHPDLQSELARAVAVAQSTQGDMLCMLKMIBL VGIVINDLE/GAGPFDTISTALSWAVVYLVAYPEDGREHQBLKEKVGMIRTPRISDKINLEL KASVTEHMAGOVDTTSTILLWTLYELARHPDLQSELARAVAVAQSTQGDMLCMLKMIBL VGIVINDLE/GAGPFDTISTALSWAVVYLVAYPEDGREHQBLKEKVGWIRTPRISDKINLEL VSSVGNIFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTDTTGTTLRWGLLLMTKYPHIQDQVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTDTTGTTLRWGLLLMTKYPHIQDQVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQDSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQDSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQDSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQQSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQQSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQQSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQQSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQQSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSEMMIKYPHIQQSVQEETSKVIG-SRQTIVEDRKHSLYV UNTAWSLFAAGTETTSSTLRQSSTMSSLAWMIKATHALDENGETSKOTTSTLRGSSTARSTLAWGETSKATTAWSLAWMIKYPHIQATAVANGATATAWSLAWMIKYPHIQATAVANGATAWSLAWMIKYPHIQATAVANGATAWSLAWMIKYPHIQATAVANGATAWSLAWMIKYPHIQATAVANGATAWSLAWMIKYPHIQATAVANGATAWSLAWMIKYPHIQATAVANGATAWSLAWMIKATAVANGATAWATAWATAWATAWATAWATAWATAWATAWATAWATA	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49
P30437 (2017A, ONONY 972088 (2241, ONONY 972097 (2244, ONONY 972097 (2244, ONONY 972097 (2244, ONONY 972107 (2011A, ONONY 972109 (2011A, ONONY 972009 (2011A, ONONY 97209 (2011A,	CVSITREMILLOKKYEBHESDYSDHEOR -DLLDALLBARESSABINNTAEITMETVGLSDEHL INVRAKVYIGGABIERKETIS ISEQ-DFIEBATUWM -LEEKDOD NITEFINGKIM NVADLAKMEVIELVRGLEETLNPIHMOR-GFVOSPIJVEKOTLEBSCKM DSFYHDDML ANTDFYASIAKIKSGRDTORSTINKY-DFIQUHIBOGKSD TKTGEGOTKGLTDHEIL STOPPHYSASIAKIKSGRDTORSTINKY-DFIQUHIBOGKSD TKTGEGOTKGLTDHEIL VSVSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVQBEISSVIG-SRQTLVEDEKNILEV VGIVNDLFGAGFDTISTALSMAVVYLVAYPEIGERLHGELKEKVGMIRTPRISDKINLEL KASVTSELMAGGVDTISTILMTLYELARHFBLQBEILGEKKVGMIRTPRISDKINLEL KASVTSELMAGGVDTISTILMTLYELARHFBLQBEILGEKKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLLMTKYPHIQDQVGBEILGEKVGMIRTPRISDKINLEL VSSVGNLFSAGTDTTGTTLRWGLLMTKYPHIQDQVGBEILGEKVGMIRTPRISDKINLEL LSGAMIFIEAGYTTSTYLKARGALLATHHFWORTHEIGEKVLFVERDKKNLEV LSGAMIFIEAGYTTSTYLKARGALLATHHFWORTHFORTHOOTHEIGEKVLFVERDKKNLEV LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHEIGEKVLFVERDKKNLEV LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHOOTHEIGEKVSSPHTL LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHOOTHEIGEKVSSPHTL LSGAMIFIEAGYTTSTSTLKARGALLATHHFWORTHFORTHOOTHOOTHOOTHOOTHOOTHOOTHOOTHOOTHOOTH	299 294 300 300 372 374 359 359 360 406 432 433 4432 419 419 419 419 463 492 487 492 487 497 497 497 497 497 497 497 497 497 49

Conserved Cysteins are in bold and green backgrounds while other conserved amino acids in all trout CYPs and/or their similar surrounding amino acids to such positions are in bold red lettering. Similar conserved amino acids (:.).

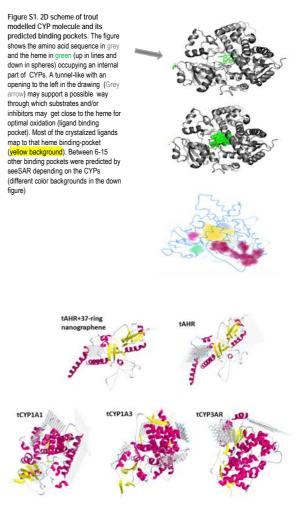


Figure S2. Drawings of nGs of different sizes bound to tAHR (up) and tCYPS (down). AutoDock Vina used a whole molecule grid (blind-docking). The nGs of 4 (5x5 nm), 9 (7x7 nm), 12 (10x10 nm), 20 (12x12 nm), 25 (13x13 nm), 36 (15x15 nm), 72 (20x20 nm), 100 (25x25 nm), and 156 (30x30 nm) rings were designed using the GOPY tool. Representative cartoons were made by combining one molecule of protein with several sizes of nG molecules and drawn in PyRx. The heme at the inner part of the CYP molecules have been removed for clarity.

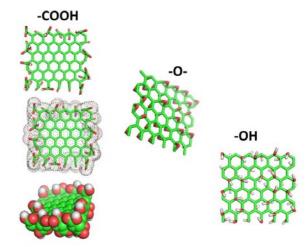


Figure S3. Cartoons of the nGOs of 25 rings (13x13 nm) designed by the GOPY tool. All the drawings were made in PyMOL.

Funding

, parch was funded in part by the European Union's Horizon 2020 research and innovation programme ad2. Grant Agreement n° 646221).

Competing interests
The authors declare that they have no competing interests

Authors' contributions

MC and JN, collaborated by critically discussing strategies and writing and correcting the manuscript. JC performed and analyzed the computational work and drafted the manuscript. Authors read and approved the

Acknowledgements
Thanks are due to Dra Ana Valdehita for her help to obtain additional seeSAR licenses. Mona Connolly received financing granted by the Community of Madrid (2018-T2/AMB-11392, Mode 2, Young Doctor

References

- ¹ Dasari Shareena, T.P., D. McShan, A.K. Dasmahapatra and P.B. Tchounwou, A Review on Graphene Based Nanomaterials in Biomedical Applications and Risks in Environment and Health Nanomicro Lett. 2018, 10. https://dx.doi.org/10.1007/s40820-018-0206-4
- ² Ema, M., M. Gamo and K. Honda A review of toxicity studies on graphene-based nanomaterials in laboratory animals Regul Toxicol Pharmacol. 2017, 85: 7-24. https://dx.doi.org/10.1016/j.yrtph.2017.01.011
- ³ Xiong, G., Y. Deng, X. Liao, J. Zhang, B. Cheng, Z. Cao and H. Lu.Graphene oxide nanoparticles induce hepatic dysfunction through the regulation of innate immune signaling in zebrafish
- (Danio rerio) Nanotoxicology. 2020: 1-16.https://dx.doi.org/10.1080/17435390.2020.1735552.

 4 Ou, L., B. Song, H. Liang, J. Liu, X. Feng, B. Deng, ... L. Shao.Toxicity of graphene-family nanoparticles: a general review of the origins and mechanisms Part Fibre Toxicol. 2016, 13: 57.https://dx.doi.org/10.1188/s12989-016-0168-y. [piii]
- s Jeneral review of the Gright and Herchanists Pairt Intel Policies (1906), 130-15. https://dx.doi.org/10.1186/s1298-016-0168-y [pii]]

 5 Lammel, T., P. Boisseaux and J.M. Navas Potentiating effect of graphene nanomaterials on aromatic environmental pollutant-induced cytochrome P450 1A expression in the topminnow fish hepatoma cell line PLHC-1 Environ Toxicol. 2015, 30: 1192-://dx.doi.ora/10.1002/tox.21991
- Pan, Y., C.E. Ong, Y.F. Pung and J.Y. Chieng. The current understanding of the interactions between nanoparticles and cytochrome P450 enzymes a literature-based review *Xenobiotica*. 2019, 49: 863-876. https://dx.doi.org/10.1080/00498254.2018.1503360
 Orecchioni, M., D. Bedognetif, F. Sgarrella, F.M. Marincola, A. Bianco and L.G. Delogu.Impact of carbon nanotubes and graphene on immune cells. *J Transl Med*. 2014, 12: 138.1479-5876-12-
- ora/10.1186/1479-5876-12-138
- 8 Orecchioni, M., D.A. Jasim, M. Pescatori, R. Manetti, C. Fozza, F. Sgarrella, . . . L.G. Delogu.Molecular and Genomic Impact of Large and Small Lateral Dimension Graphene Oxide Sheets on Human Immune Cells from Healthy Donors Adv Healthc Maler. 2016, 5: 276
- ⁹ Orecchioni, M., C. Menard-Moyon, L.G. Delogu and A. Bianco. Graphene and the immune system: Challenges and potentiality Adv Drug Deliv Rev. 2016, 105: 163-175. S0169-409X(16)30156-9 [piii] https://dx.doi.org/10.1016/j.addr.2016.05.014
- 10 Lammel, T., P. Boisseaux, M.L. Fernandez-Cruz and J.M. Navas.Internalization and cytotoxicity of Tammei, T., P. Bolsseaux, M.L. Fernandez-Cruz and J.M. Navas. Internalization and cytotoxicity or graphene oxide and carboxyl graphene nanoplatelets in the human hepatocellular carcinoma cell line Hep G2 Part Fibre Toxicol. 2013, 10: 27. <u>1743-8977-10-27 [pii] https://dx.doi.org/10.1186/1743-8977-10-27</u>
 Markovic, M., A. Kumar, I. Andjelkovic, S. Lath, J.K. Kirby, D. Losic, ... M.J. McLaughlin. Ecotoxicology.
- ... M.J. McLaughlin. Ecotoxicology of manufactured graphene oxide nanomaterials and derivation of preliminary guidelir values for freshwater environments *Environ Toxicol Chem.* 2018, 37: 1340-
- Markovic, M., I. Andelkovic, J. Shuster, L. Janik, A. Kumar, D. Losic and M.J. McLaughlin. Addressing challenges in providing a reliable ecotoxicology data for graphene-oxide (GO) using an algae (Raphidocelis subcapitata), and the trophic transfer consequence of GO-algae aggregates Chemosphere. 2020, 245: 125640. <u>S0045-6535(19)32880-2 (piil)</u>
 https://dx.doi.org/10.1016/j.chemosphere.2019.125640
- ¹³ Kurapati, R., C. Backes, C. Menard-Moyon, J.N. Coleman and A. Bianco White Graphene undergoes Peroxidase Degradation Angew Chem Int Ed Engl. 2016, 55: 5506-11. https://dx.doi.org/10.1002/3
- A. Kurapati, R. and A. Bianco. Peroxidase mimicking DNAzymes degrade graphene oxide Nanoscale. 2018, 10: 19316-19321. https://dx.doi.org/10.1039/c8nr06535g
 Grans, J., B. Wassmur and M.C. Celander. One-way inhibiting cross-talk between arylhydrocarbon receptor (AhR) and estrogen receptor (ER) signaling in primary cultures of rainbow trout hepatocytes. https://dx.doi.org/10.1002/c8-70.50766-445X/(10)00272-9 [pii]
- 16 Grans, J., B. Wassmur, M. Fernandez-Santoscoy, J. Zanette, B.R. Woodin, S.I. Karchner, . . . M.C. Celander. Regulation of pregnane-X-receptor, CYP3A and P-glycoprotein genes in the PCB-resistant killifish (Fundulus heteroclitus) population from New Bedford Harbor Aqual Toxicol. 2015, 159: 198-207. S0166-445X[14]00383-X [pii]
- ¹⁷ Fukunaga, B.N., M.R. Probst, S. Reisz-Porszasz and O. Hankinson.Identification of functional domains of the aryl hydrocarbon receptor J Biol Chem. 1995, 270: 29270 8. https://dx.doi.org/10.1074/jbc.270.49.29270

 18 Whitlock, J.P., Jr. Induction of cytochrome P4501A1 Annu Rev Pharmacol Toxicol. 1999, 39: 103-
- n/10 1146/an
- Poland, A., D. Palen and E. Glover Analysis of the four alleles of the murine aryl hydrocarbon receptor Mol Pharmacol. 1994, 46: 915-21.not doi
 Wassmur, B., J. Grans, P. Kling and M.C. Celander.Interactions of pharmaceuticals and other xenobiotics on hepatic pregnane X receptor and cytochrome P450 3A signaling pathway in rainbow trout (Oncorhynchus mykiss). Aqual Toxicol. 2010, 100: 91100. <u>S0166-445X(10)00261-4 [piil hitps://dx.doi.org/10.1016/j.aquatox.2010.07.013</u>
 ²¹ Renaud, H.J., J.Y. Cui, M. Khan and C.D. Klaassen.Tissue distribution and gender-divergent expression
- of 78 cytochrome P450 mRNAs in mice Toxicol Sci. 2011, 124: 261-77. kfr240 [pii]
- ²² Uno, T., M. Ishizuka and T. Itakura. Cytochrome P450 (CYP) in fish *Environ Toxicol Pharmacol*. 2012, 34 1-13. <u>\$1382-6689(12)00016-6 [pii] https://dx.doi.org/10.1016/j.elap.2012.02.004</u>
 ²³ Jonsson, M.E., K. Gao, J.A. Olsson, J.V. Goldstone and I. Brandt.Induction patterns of new CYP1 genes
- in environmentally exposed rainbow trout *Aquat Toxicol.* 2010, 98: 311-21. <u>S0166</u> 445X(10)00088-3 [piil https://dx.doi.org/10.1016/j.aquatox.2010.03.003
- ²⁴ Katagi, T.In vitro metabolism of pesticides and industrial chemicals in fish J Pestic Sci. 2020, 45: 1-15. https://dx.doi.org/10.1584/jpestics.D19-074

 25 Effner, R., J. Hiller, S. Eyerich, C. Traidi-Hoffmann, K. Brockow, M. Triggiani, . . .
- . J.T. Buters.Cytochrome P450s in human immune cells regulate IL-22 and c-Kit via an AHR feedback loop *Sci Rep.* 2017, 7: 44005. srep44005 [pii] http://dx.doi.org/10.1038/srep44005
- Rep. 2017, 7: 44005. Rep. 2017, 7: 44005. Srep44005 Stavropoulou, E., G.G. Pircalabioru and E. Bezirtzoglou. The Role of Cytochromes P450 in Infection Front Immunol. 2018, 9: 89. https://dx.doi.o

- ²⁷ Muntane-Relat, J., J.C. Ourlin, J. Domerque and P. Maurel, Differential effects of cytokines on the
- Muntane-Reiat, J., J.C. Culmin, J. Domergue and P. Maurel. Differential effects of cytokines on the inducible expression of CYP1A1, CYP1A2, and CYP3A4 in human hepatocytes in primary culture *Hepatology*. 1995, 22: 1143-53. https://dx.doi.org/S0270913995003569 [pii]
 Bello-Perez, M., A. Falco, B. Novoa, L. Perez and J. Coll. Hydroxycholesterol binds and enhances the anti-viral activities of zebrafish monomeric c-reactive protein isoforms *PLoS One*. 2019, 14: e0201509. https://dx.doi.org/10.1371/journal.pone.0201509
- ²⁹ Tian, S., Y. Djoumbou-Feunang, R. Greiner and D.S. Wishart CypReact: A Software Tool for in Silico Reactant Prediction for Human Cytochrome P450 Enzymes J Chem Inf Model. 2018, 58: 1282-1291. http://dx.doi.org/10.1021/acs.icim.8b0003
- 30 Tan, B.H., Y. Pan, A.N. Dong and C.E. Ong.In vitro and in silico Approaches to Study Cytochrome P450-Mediated Interactions J Pharm Pharm Sci. 2017, 20: 319
- 328. http://dx.doi.org/10.18433/J3434R
 Thang, T., Q. Chen, L. Li, L.A. Liu and D.Q. Wei. In silico prediction of cytochrome P450-mediated drug metabolism Comb Chem High Throughput Screen. 2011, 14: 388-95. BSP/CCHTS/E-Pub/00153 [pill https://dx.doi.org/10.2174/1/3862/0711795508412
 Lammel, T. and J.M. Navas. Graphene nanoplatelets spontaneously translocate into the cytosol and
- physically interact with cellular organelles in the fish cell line PLHC-1 Aqual Toxicol. 2014, 150: 55-65. S0166-445X(14)00066-6 [pii]
- ³³ Muraru, S., J.S. Burns and M. Ionita GOPY: a tool for building 2D graphene-based computational models SoftwareX. 2020, 12: 100586. https://doi.org/10.1016/j.softx.2020.100586
- ³⁴ Andon, F.T., A.A. Kapralov, N. Yanamala, W. Feng, A. Baygan, B.J. Chambers, ... V.E. Kagan. Biodegradation of single-walled carbon nanotubes by eosinophil peroxidase Small. 2013, 9: 2721-9, 2720. https://dx.doi.org/10.1002/smll.201202508
- 35 Trott, O. and A.J. Olson.AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading J Comput Chem. 2010, 31: 455-61, http://dx.doi.org/10.1002/icc.21334
- ³⁶ Dallakyan, S. and A.J. Olson.Small-molecule library screening by docking with PyRx Methods Mol Biol. 2015, 1263: 243-50. http://dx.doi.org/10.1007/978-1-4939-2269-7_19
- Blasco, R. and J.M. Coll. In silico screening for natural ligands to non-structural nsp7 conformers of SARS coronaviruses *ChemRxiv*. 2020. https://doi.org/10.26434/chemrxiv.12952115.v2
 Coll, J.M.Would it be possible to stabilize prefusion SARS-COV-2 spikes with ligands? *ChemRxiv*.
- 2020. <u>https://doi.org/10.26433//chemrxiv.13453919.v1</u>

 39 Shityakov, S. and C. Forster.In silico predictive model to determine vector-mediated transport
- properties for the blood-brain barrier choline transporter Adv Appl Bioinform Chem. 2014, 7: 23-36. http://dx.doi.org/10.2147/AABC.S63749
- ⁴⁰ Reau, M., F. Langenfeld, J.F. Zagury and M. Montes. Predicting the affinity of Farnesoid X Receptor ligands through a hierarchical ranking protocol: a D3R Grand Challenge 2 case study J Comput Aided Mol Des. 2018, 32: 231-238. 10.1007/s10822-017-0063-0 [pii]
- 41 Schneider, N., S. Hindle, G. Lange, R. Rilein, J. Albrecht, H. Briem, . . . M. Rarey. Substantial improvements in large-scale redocking and screening using the novel HYDE scoring function J Comput Aided Mol Des. 2012, 26: 701-23.
- ⁴² Schneider, N., G. Lange, S. Hindle, R. Klein and M. Rarey. A consistent description of HYdrogen bond and DEhydration energies in protein-ligand complexes: methods behind the HYDE scoring function *J. Comput Aided Mol Des.* 2013, 27: 15-29.
- 43 Martignoni, M., G.M. Groothuis and R. de Kanter. Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction Expert Opin Drug Metab Toxicol. 2006, 2: 875-94.https://dx.doi.org/10.1517/17425255.

 44 Celander, M., D.R. Buhler, L. Forlin, A. Goksoyr, C.L. Miranda, B.R. Woodin and J.J.
- Stegeman Immunochemical relationships of cytochrome P4503-Alike proteins in teleost fish Fish Physiol Biochem. 1996, 15: 323-32. 10.1007/BF02112359

 45 Connors, K.A., B. Du, P.N. Fitzsimmons, A.D. Hoffman, C.K. Chambliss, J.W. Nichols and B.W.
- Brooks.Comparative pharmaceutical metabolism by rainbow trout (Oncorhynchus mykiss) liver S9 fractions *Environ Toxicol Chem.* 2013, 32: 1810-
- ⁴⁶ Ambrosio, L.F., C. Insfran, X. Volpini, E. Acosta Rodriguez, H.M. Serra, F.J. Quintana, . . . C.C. Motran.Role of Aryl Hydrocarbon Receptor (AhR) in the Regulation of Immunity and Immunopathology During Trypanosoma cruzi Infection Front Immunol. 2019, 10: 631. http://dx.doi.org/10.3389/limmu.2019.00631
- 651. <u>http://dx.doi.org/10.3389/nmmu.2019.00631</u> 47 Abdullah, A., M. Maged, M.I. Hairul-Islam, I.A. Osama, H. Maha, A. Manal and H. Hamza.Activation of aryl hydrocarbon receptor signaling by a novel agonist ameliorates autoimmune encephalomyelitis *PLoS One.* 2019, 14: 0215981 PONF-D-18-33358 [pii]