Molecular tuning of sea anemone stinging

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Abstract

16 Jellyfish and sea anemones fire single-use, venom-covered barbs to immobilize prev or predators. We previously 17 showed that the anemone Nematostella vectensis uses a specialized voltage-gated calcium (Cav) channel to trigger 18 stinging in response to synergistic prey-derived chemicals and touch (Weir et al., 2020). Here we use experiments 19 and theory to find that stinging behavior is suited to distinct ecological niches. We find that the burrowing anemone 20 Nematostella uses uniquely strong Ca_V inactivation for precise control of predatory stinging. In contrast, the related 21 anemone Exaiptasia diaphana inhabits exposed environments to support photosynthetic endosymbionts. Consistent 22 with its niche, *Exaiptasia* indiscriminately stings for defense and expresses a Cay splice variant that confers weak 23 inactivation. Chimeric analyses reveal that $Ca_V\beta$ subunit adaptations regulate inactivation, suggesting an evolutionary 24 tuning mechanism for stinging behavior. These findings demonstrate how functional specialization of ion channel 25 structure contributes to distinct organismal behavior.

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28 Introduction

29 Sea anemones, jellyfish, corals, and hydrozoans of the Cnidarian phylum use specialized cells called nematocytes to 30 sting for predation or defense. Mechanical and chemical stimuli from prey or predators act synergistically on 31 nematocytes to mediate rapid discharge of a toxin-covered barb from its nematocyst organelle (Holstein and Tardent, 32 1984; Watson and Mire-Thibodeaux, 1994; Babonis and Martindale, 2014). Nematocyst discharge requires calcium 33 (Ca²⁺) influx and, as a one-time use organelle, is tightly controlled to prevent energetically wasteful stinging to 34 irrelevant stimuli (Lubbock et al., 1981; Gitter et al., 1994; Watson and Hessinger, 1994). We previously found that 35 the starlet sea anemone Nematostella vectensis uses a uniquely adapted voltage-gated Ca²⁺ channel (Ca_V) to integrate 36 simultaneously presented chemical and mechanical cues that elicit nematocyst discharge. Nematostella Cav exhibits unusually "strong" steady-state voltage-dependent inactivation at resting membrane voltages to reduce cellular 37 38 excitability and prevent stinging behavior in response to extraneous, non-prey touch signals. Chimeric analyses of 39 Nematostella and mammalian Ca_V showed that the auxiliary β subunit (Ca_V β) is required and sufficient for low-40 voltage steady-state inactivation in Nematostella Cay channel complexes. Cay inactivation is relieved by 41 hyperpolarization of the nematocyte membrane potential to very negative voltages through the effect of prey-derived 42 chemosensory signals that are synaptically transmitted from sensory neurons. Upon relieving Cav inactivation, direct 43 touch responses are amplified to trigger nematocyst discharge (Weir et al., 2020). Thus, single nematocytes integrate 44 synergistic cues to elicit a precise response, representing a unique cellular system to study how cells detect and 45 transduce signals to produce discrete behavior.

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While Ca_V-mediated sensory integration represents one mechanism by which nematocytes "decide" when to sting,
 the incredible diversity of cnidarian biology suggests that stinging behavior must be adapted to support the demands

49 of different lifestyles. Cnidarian taxa occupy diverse environmental niches and endure specific metabolic demands, 50 predatory challenges, and environmental pressures for survival, which results in distinct selective pressures on 51 nematocyte evolution (Beckmann and Özbek, 2012; Babonis et al., 2022). Nematostella vectensis and Exaiptasia 52 diaphana represent an example of closely related cnidarians with differing environmental niches and metabolic 53 demands (Darling et al., 2005; Bedgood et al., 2020). Nematostella are found in shallow brackish water of coastal 54 marshes where they are buried in the mud, hidden from predators, with only their tentacles exposed to catch 55 unsuspecting passing prey (Fraune et al., 2016). Thus, we hypothesize that their stinging is under tight regulation 56 adapted for opportunistic predation. In contrast, *Exaiptasia* are exposed to predators while living in shallow, open 57 ocean environments that provide sufficient sunlight for their endosymbionts to produce important photosynthetic 58 products and nutrients (Baumgarten et al., 2015). Considering these dramatically different ecological contexts, we 59 hypothesized that Cay-mediated regulation of nematocyte discharge has adapted to reflect the demands on stinging 60 behavior in these two anemones. We therefore probed the behavior of these related but distinct anemones and 61 investigated how subtle tuning of a shared molecular-regulatory mechanism drives adaptation in physiology and 62 behavior associated with niche diversification.

64 In this study, we find that the symbiotic anemone *Exaiptasia* stings in response to mechanical stimuli alone, 65 independent of predation pressure. This behavior serves as a stark contrast with Nematostella stinging, which is only 66 elicited by synergistic prey chemicals and touch. Markov decision process modeling coupled with behavioral 67 experiments revealed that *Nematostella* stings as an optimal predator, whereas *Exaiptasia* exhibits optimal defensive 68 stinging behavior. Consistent with indiscriminate stinging behavior, we discover that *Exaiptasia* nematocyte 69 physiology lacks the unusual Cav inactivation used by *Nematostella* to inactivate cells at rest and prevent responses 70 to touch in the absence of prey chemicals. "Weak" steady-state inactivation of Exaiptasia Cav is mediated by a splice 71 isoform of the beta subunit ($Ca_V\beta$) with a distinct N-terminus and allows for robust activation from resting membrane 72 potentials. Analysis of chimeric jellyfish and anemone channels reveals that Ca_v inactivation is broadly regulated by 73 the $Ca_V\beta$ N-terminus, suggesting an evolutionary tuning mechanism that could contribute to specific stinging 74 behavior across cnidarians. Thus, we propose Ca_v adaptations as one molecular mechanism that could shift predatory 75 versus defensive stinging in cnidarians. These results highlight how subtle adaptations in protein structure contribute 76 to complex organismal behavior.

78 Results

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79 *Comparative sea anemone stinging behavior*

80 In their natural habitat, Nematostella are hidden by burrowing within the sandy substrate and use an opportunistic 81 predatory strategy to capture prey with their tentacles. In contrast, symbiotic *Exaiptasia* are found within open waters 82 where they experience greater risk of predation and therefore must adopt a more defensive stance. Thus, we first 83 asked whether differences in ecological pressure are reflected by stinging behavior. Consistent with our previous 84 findings, we observed Nematostella stinging in response to simultaneously delivered prey extract and touch, 85 reflecting stinging control adapted for predation (Figure 1) (Weir et al., 2020). Strikingly, Exaiptasia tentacles instead 86 exhibited robust stinging even in the absence of prey chemicals (touch alone, Figure 1). Similar touch-evoked 87 stinging was observed for Exaiptasia acontia, which are defensive nematocyte-enriched structures that are ejected 88 and release toxins to repel predators (Lam et al., 2017). Considering the drastic differences in stinging behavior, we 89 wondered if *Exaiptasia*'s indiscriminate stinging reflects a distinct control strategy.

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To investigate whether different stinging behaviors might be suited for predation versus defense, we developed a normative theory aimed at predicting optimal stinging behavior as a function of nutritional state (see *Materials and Methods* for model details). We focused on stinging intensity, defined as the fraction of nematocysts discharged during a stinging event, and asked whether nutritional state would affect optimal predatory and defensive stinging. In the language of decision models, the intensity of stinging is an action, and it is chosen by the agent, or anemone. In our study, "choice" of stinging means modulation of behavior with nutritional state, rather than a cognitive process.

Each choice has associated costs and benefits that depend on the environment. Because anemones sting many times
over the course of their lives, an optimal behavior must account for overall costs and benefits after many events;
therefore, this is a sequential decision-making problem.

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101 We modeled the optimal stinging response to a given environment by using Markov decision processes (MDP). Each 102 anemone was modeled as an "agent" that must hedge the intensity of its stinging response. The environment, 103 including the identity of prey, predators, and the physiological state of the animals, defines the likelihood, costs, and 104 benefits of successful stinging. Specifically, intense stinging responses are costly since each fired nematocyst needs 105 to be regenerated. But they are also more likely to succeed because greater discharge of stinging barbs increases the 106 likelihood of contact and envenomation. The cost per nematocyte was first assumed to be constant and equivalent for 107 defensive and predatory stinging as nematocyst discharge requires regeneration in either case (Figure 2A, solid line, 108 filled circles). We assumed that the benefits of successful predatory stinging depend on the capture and consumption 109 of prey, which improves satiation (Figure 2B left). In contrast, stinging a predator for defense would not improve 110 nutritional state, hence the benefits of stinging would not depend on starvation (Figure 2C left). We then used the 111 model to predict optimal stinging that maximizes the sum of all future benefits while minimizing costs during starvation (i.e. maximizing the value function, see Materials and Methods). We then tested the prediction directly 112 113 against experiments with behaving animals.

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115 Using this approach, we found that optimal stinging strategies were completely different for predatory versus 116 defensive behavior. Regardless of the specific environment (likelihood to succeed and specific costs and benefits), 117 predatory stinging increased with starvation (Figure 2B right, solid lines, filled circles). To test our theory regarding 118 predatory stinging, we carried out simulations in which agents discharged a random fraction of nematocytes between 119 0 and 1, regardless of starvation. Random stinging was unsustainable over numerous events and agents quickly 120 reached maximal starvation state. Agents using optimal predatory stinging discharged more nematocysts when 121 starved and less when satiated, leading to sustained stinging behavior and survival. This was true even if they fired 122 the same fraction of nematocytes as the random agent (Figure 2D). In contrast, optimal stinging for defense stayed 123 constant with starvation (Figure 2B right, solid lines, filled circles). Importantly, while the precise optimal response 124 depended on the details of cost and reward that defined the MDP, the differences between increasing predatory 125 stinging versus unchanging defensive stinging were consistent and largely independent of assumptions associated 126 with each reward function (described in *Materials and Methods*, Figure 2—figure supplement 1-4). These results 127 reflect greater rewards to predatory anemones upon stinging during starvation, whereas defensive anemones sting at 128 a similar rate regardless of nutritional status. Thus, our model predicts robust differences in predatory versus 129 defensive stinging behavior.

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131 We next sought to experimentally test whether pressure to predate regulates stinging in Nematostella and Exaiptasia. 132 To do so, we fed both species of anemones copious amounts of prey (brine shrimp, Artemia nauplii) for 1-2 weeks 133 and then deprived them of food for 5 days. Following manipulation of prev availability, Nematostella significantly 134 increased stinging in response to starvation, while *Exaiptasia* stinging remained relatively constant despite complete 135 deprivation of prev (Figure 2E, symbols with error bars). The behavior was remarkably consistent with our normative 136 theory of optimal stinging strategies for predation versus defense (Figure 2E, filled circles). Furthermore, changes 137 in Nematostella and Exaiptasia stinging were not due to changes in the abundance of nematocytes because tentacles 138 from both animals were abundantly armed with nematocytes across feeding conditions (Figure 2-figure 139 supplement 5). The experimental behavior of *Exaiptasia* showed a slight decrease in stinging with starvation. To 140 account for this decrease we revisited the theory and assumed that the cost per nematocyte slightly increased with 141 starvation (Figure 2A, dashed lines and open circles). In this case, the optimal response slightly decreased for 142 defensive stinging but increased for predatory stinging (Figure 2B right, open circles and Figure 2C right, dashed 143 lines, open circles). In fact, the fit between theory and data for both Nematostella and Exaiptasia improved when the 144 cost increased slightly with starvation (Figure 2E, open circles). A more dramatic and less realistic increase of the

145 cost with starvation may lead to a decrease in predatory stinging (Figure 2—figure supplement 4). Thus, we 146 conclude that *Nematostella* controls stinging for opportunistic predation while *Exaiptasia* stinging is indiscriminate 147 and serves a greater defensive role for this symbiotic anemone.

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149 Sea anemones with different stinging behavior use distinct Ca_V channels

150 We next probed the physiological basis underlying these significantly different stinging behaviors. We previously 151 found that *Nematostella* stinging is triggered by a specialized Ca_V channel that exhibits strong inactivation at negative 152 voltages to prevent responses to extraneous non-prev mechanical stimuli (Weir et al., 2020). Ca^{2+} influx triggers an 153 increase in hydrostatic pressure inside the nematocyst capsule that forces the stinging thread to evert explosively at 154 an acceleration of up to 5.41×10^6 g, placing it among the fastest biological processes in existence (Lubbock and 155 Amos, 1981; Lubbock et al., 1981; Holstein and Tardent, 1984; Weber, 1990; Gitter et al., 1994; Tardent, 1995; 156 Nüchter et al., 2006). Similar to Nematostella, Exaiptasia stinging required extracellular Ca²⁺ and was abolished by 157 Cd^{2+} , a Ca_V channel blocker (Figure 3A). Consistent with a Ca^{2+} -dependent stinging mechanism, whole-cell patch 158 clamp recordings from nematocytes revealed the presence of voltage-gated inward currents that were blocked by 159 Cd^{2+} , suggesting that *Exaiptasia* nematocytes also use Ca_V channels to control stinging (Figure 3B). Indeed, Ca_V 160 currents in Exaiptasia nematocytes exhibited similar voltage-dependent activation properties compared with *Nematostella* nematocytes (Figure 3C). Thus, in agreement with previous findings, we conclude that Ca^{2+} influx via 161 162 Ca_V channels is broadly important for stinging.

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 Ca_V channels respond to positive membrane potentials by opening to conduct Ca^{2+} . However, sustained positive 164 voltage drives Cavs to transition to a non-conducting state (inactivation) that prevents re-activation until channels 165 166 return to a resting state induced by negative membrane potentials. In most cells, voltage-gated ion channel 167 inactivation prevents extended responses to repetitive or prolonged stimulation. Nematostella Cay, is unusual because 168 it inactivates at very negative voltages to prevent responses from resting potential, resulting in nematocytes that 169 cannot fire from rest (Weir et al., 2020). In contrast to Nematostella nematocytes in which half of all Cav channels 170 $(V_{i1/2})$ were inactivated at ~ -93mV, *Exaiptasia* nematocytes exhibited two distinct inactivation phenotypes: (1) 171 nematocytes with low-voltage threshold (low-V) inactivation similar to that of Nematostella (low-V, $V_{i1/2} = \sim$ -172 85mV); and (2) a distinct population with weak, high-voltage (high-V) threshold inactivation similar to its well-173 characterized mammalian orthologue (high-V, $V_{i1/2} = \sim -48$ mV) (Figure 3D). While we did not observe a correlation 174 with abundance or distinct cellular morphology (Östman, 2000; Kass-Simon and Scappaticci, 2002; Grajales and 175 Rodríguez, 2014), we could clearly distinguish the two populations based on these electrophysiological features. 176 Importantly, high-V nematocyte inactivation was minimal at resting voltages (~-70mV), so nearly all channels would 177 be available to amplify depolarizing signals, such as those elicited by touch. Thus, these markedly different 178 physiological properties correlate with distinct stinging behavior: Nematostella uses unusual low-voltage Cav 179 inactivation to integrate sensory cues for tightly regulated predatory stinging. In contrast, Exaiptasia employs a 180 population of nematocytes with weak Ca_v inactivation, consistent with direct activation from resting potentials and 181 stinging to touch alone.

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183 What is the molecular basis of distinct nematocyte physiology? Cav channels are made of at least three subunits: the 184 pore-forming α and auxiliary β and $\alpha 2\delta$ subunits. Transcriptomics revealed that nematocyte-enriched tentacles of 185 Exaiptasia expressed cachala, the pore-forming subunit homologous to that of the previously characterized 186 *Nematostella* nematocyte Ca_V channel (Figure 4—figure supplement 1). We also analyzed the Ca_V β subunit, Ca_V β , 187 which is required and sufficient for the unusual inactivation properties observed in Nematostella Ca_V (Weir et al., 188 2020) (Figure 4—figure supplement 1). From *Exaiptasia*, we identified two isoforms of $Ca_V\beta$: EdCa_V β 1 and 189 EdCa_V β 2. Droplet digital PCR assays of mRNA abundance showed that both isoforms are expressed throughout 190 Exaiptasia tissues, suggesting they could both be functionally important (Figure 4A-figure supplement 1B). To 191 localize $Ca_V\beta$, we used *in situ* hybridization to determine that distinct nematocyte populations expressed either 192 EdCav β 1 or EdCav β 2 mRNA (but not both) in the same cell (Figure 4B).

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194 Considering this expression profile, we wondered if the two $Ca_V\beta$ isoforms could mediate low-V and high-V 195 inactivation phenotypes in *Exaiptasia* nematocytes. To investigate this question, we heterologously expressed each 196 β subunit isoform with other well-characterized Ca_V subunits (mammalian Ca_V α and $\alpha 2\delta$) that express well in 197 heterologous systems. Both channels exhibited functional Cav currents with similar activation thresholds (Figure 198 **4C**). However, $EdCa_{v}\beta_{1}$ - and $EdCa_{v}\beta_{2}$ -containing channels significantly differed in their inactivation properties. 199 EdCa_V β 1 inactivated at negative voltages, similar to channels containing *Nematostella* Ca_V β (NveCa_V β). In contrast, 200 EdCa_V β 2 mediated Ca_V currents with weak inactivation, more like channels containing rat Ca_V β 2a (Figure 4C, D). 201 Thus, $EdCa_V\beta_1$ and $EdCa_V\beta_2$ confer strong, low-voltage and weak, high-voltage steady-state inactivation, 202 respectively, and are expressed in distinct nematocytes, consistent with low-V and high-V threshold inactivating 203 nematocyte populations. Genomic alignment revealed that alternative splicing at the N-terminus gives rise to 204 $EdCa_V\beta 1$ and $EdCa_V\beta 2$ isoforms, serving as a mechanism to dynamically tune nematocyte physiology and potentially 205 stinging behavior in contrast to adaptation through gene duplication and divergence (Figure 4E). Furthermore, by 206 expressing two functional variants, *Exaiptasia* could use distinct nematocyte populations for different behaviors, 207 including a less pronounced role for predation.

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209 Structural adaptations across cnidarian Ca_V channels

210 We next asked how variation in $Ca_V\beta$ structure mediates strong phenotypes by testing whether distinct protein 211 domains confer low or high voltage-dependent inactivation. We first compared rat rCavB2a and Nematostella 212 NveCa_V β , which have significantly different voltage-dependent properties (Weir et al., 2020). Swapping the well-213 characterized SH3, HOOK, and GK domains had no effect on inactivation, but the NveCa_vβ N-terminus was both 214 required and sufficient for low voltage-dependent inactivation (Figure 5A, B). Indeed, swapping only the N-terminus 215 of NveCa_V β was sufficient to shift rat rCav β 2a-conferred inactivation by ~ -75mV (Figure 5A, B). This finding is 216 consistent with the variation in EdCa_V β splice isoforms, in which differences in the N-terminus account for a ~ 40mV 217 difference in inactivation thresholds.

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219 To explore evolutionary relationships of $Ca_V\beta$, we constructed a phylogenetic tree of sequences from various 220 cnidarians including Nematostella vectensis (anemone, NveCa_V β), Exaiptasia diaphana (anemone, EdCa_V β 1 and 221 EdCa_V β 2), Cyanea capillata (jellyfish, CcCa_V β), Physalia physalis (hydrozoan, PpCa_V β), Clytia hemisphaerica 222 (iellvfish, ChCa_V β), Cassiopea xamachana (iellvfish, CxCa_V β), and the Rat β subunit (rCav β 2a) as an outgroup 223 (Figure 5C). Sequence comparison across all amino acid positions revealed that the N-terminus exhibited the greatest 224 sequence diversity (Figure 5D), consistent with previous findings showing extensive alternative splicing in this 225 region in other organisms (Helton and Horne, 2002; Helton et al., 2002; Takahashi et al., 2003; Foell et al., 2004; 226 Vendel et al., 2006; Ebert et al., 2008; Buraei and Yang, 2010; Siller et al., 2022). We found that all cnidarian Cayßs 227 conferred voltage-gated currents when co-expressed with $Ca_V\alpha$ and $\alpha 2\delta$ subunits and had relatively low voltage 228 thresholds for inactivation compared with rCav β 2 a or EdCav β 2 (Figure 5E, figure supplement 1A, figure 229 supplement 1B). Importantly, swapping the N-termini of each chidarian $Ca_V\beta$ onto EdCa_V β 2 was sufficient to shift 230 voltage-dependent inactivation to more negative values (Figure 5E, figure supplement 1C). Thus, alternative 231 splicing at the N-terminus could serve as a broad molecular mechanism for tuning Ca_V function. Collectively, these 232 findings substantiate the importance of $Ca_V\beta$ in modulating inactivation and suggest a mechanism that could 233 dynamically regulate a small region of only one subunit in the Ca_V protein complex to tune complex stinging behavior.

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235 Discussion

236 Collectively, our studies on cnidarian stinging, here and (Weir et al., 2020), reveal different behavior in the primarily

237 predatory anemone *Nematostella* versus the symbiotic anemone *Exaiptasia*. This study used a combination of theory

and experimentation to uncover the molecular basis of regulation of the divergent behavior of *Exaiptasia* that uses

- stinging primarily for defense. Indeed, *Exaiptasia* obtains a large fraction of its energy and nutrients from endosymbiotic algae (Muscatine et al., 1981; Shick and Dykens, 1984; Steen, 1988), thus reducing overall pressure
- 240 endosymbiolic algae (wuscaline et al., 1981; Snick and Dykens, 1984; Steen, 1988), thus reducing over

to predate. This finding is consistent with a common ecological theme in which symbiotic relationships are established whereby one partner provides food and the other provides shelter and defense (Lehnert et al., 2012; Bucher et al., 2016). Therefore, it is plausible that synergistic selection drives higher investment in defensive structures to protect symbiotic species.

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246 Our results demonstrate that molecular adaptations tune distinct stinging behavior: Nematostella $Ca_V\beta$ confers an 247 unusually low threshold for inactivation, basally inhibiting nematocytes unless they are exposed to synergistic prev 248 cues: chemical (hyperpolarizing to relieve inactivation) and mechanical (depolarizing to recruit available Cav 249 channels and elicit stinging) (Weir et al., 2020). These physiological mechanisms reflect a stinging strategy suited to 250 opportunistic predation by Nematostella, which burrow within shallow marshes and sting unsuspecting prev. 251 Consistent with the predictions of optimal control theory, Nematostella increased stinging with starvation, suggesting 252 that evolution has shaped its stinging response to maximize benefits for predation. In contrast, *Exaiptasia* nematocytes 253 contain a functionally specialized splice variant of $Ca_V\beta$ to mediate high threshold voltage-dependent Ca_V 254 inactivation, consistent with Ca_v channel availability to amplify depolarizing signals from rest and stinging in 255 response to touch alone. Thus, *Exaiptasia* physiology is consistent with an indiscriminate stinging strategy for 256 defense, necessary for survival in an exposed environment that facilitates endosymbiotic photosynthesis (Muscatine 257 et al., 1981; Shick and Dykens, 1984; Steen, 1988). Such stinging behavior is likely synergistic with physical escape 258 for some cnidarians (Pallasdies et al., 2019; Wang et al., 2023). Consistent with the predictions of optimal control 259 theory, Exaiptasia stinging was nearly independent of starvation, suggesting that evolution has shaped the stinging 260 response to maximize benefits for defense. Using molecular information gleaned from analyzing these two cnidarians, 261 we find that $Ca_{\nu}\beta$ variation across enidarians mediates differences in voltage-dependent inactivation, which could 262 contribute to differences in stinging behavior. Thus, our study provides an example by which alternative splicing 263 could account for adaptation across this diverse plethora of organisms and habitats.

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265 While theory predicts robust trends for optimal predation and defense independent of environment, the precise nature 266 of the predicted behavior does depend on the environment. In vivo, stinging is likely influenced by stimulus identity 267 and intensity, background turbulence, and other factors. For example, chidarians may have evolved distinct innate 268 responses for different prev and use chemical sensing to enact the appropriate stinging response. In this case, optimal 269 control theory can be used to predict the optimal response to known salient environmental cues. Alternatively, 270 cnidarians may learn that specific prey are palatable and easy to catch through repeated exposure (Botton-Amiot et 271 al., 2023). In this example, optimal control theory must be replaced by reinforcement learning as the likelihood of 272 successful predation and its cost and benefits (the environment) are unknown (Sutton and Barto, 2018). 273

274 Indeed, stinging is a complex process mediated by numerous molecular components and cell types that could be 275 subject to evolutionary change or acute modulation. Cnidarians occupy diverse ecological niches and experience 276 varying metabolic demands, predatory challenges, and other survival pressures that could influence stinging behavior. 277 Bevond cnidarians with stationary lifestyles that support photosynthetic endosymbionts (symbiotic anemones, corals, 278 sea pens) and those that use opportunistic "sit-and-wait" ambush predatory strategies (burrowing anemones, 279 siphonophores), others have evolved mobile lifestyles to actively capture prev (iellyfish) (Muscatine et al., 1981; 280 Shick and Dykens, 1984; Steen, 1988; Fraune et al., 2016; Damian-Serrano et al., 2022). Stinging by mobile 281 cnidarians could be subject to different physical demands, such as mechanical disturbance from increased turbulence 282 that could necessitate distinct molecular control. Furthermore, stinging can be influenced by acute factors such as 283 physiological state and various sensory cues, including chemicals, touch, or light (Pantin, 1942; Giebel et al., 1988; 284 Thorington and Hessinger, 1988; Watson and Hessinger, 1989; Plachetzki et al., 2012; Ozment et al., 2021; Aguilar-285 Camacho et al., 2023). Thus, further inquiry into modulation of stinging across physiological states such as nutritional 286 condition, altered symbiotic relationships, or developmental stages (Sandberg et al., 1971; Columbus-Shenkar et al., 287 2018) could reveal dynamic regulation by synaptic connections, hormones, or modulation of transcriptional or 288 translational programs (Westfall et al., 1998, 2002; Westfall, 2004; Weir et al., 2020). Importantly, across all these

- scenarios, nematocytes remain single-use cells, so it is essential that signaling cascades control discharge in response to the most salient environmental stimuli.
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As an early-branching metazoan lineage and sister group to Bilateria (Cartwright et al., 2007), cnidarians are a useful

293 model for probing origins of the nervous system and behavioral specialization (Steele et al., 2011, Jékely et al., 2015;

- 294 Pallasdies et al., 2019). Here we present a comparative approach across related cnidarians with distinct physiology
- and ecology to suggest that behavioral complexity emerges from subtle tuning of single proteins, even in non-
- 296 neuronal cells. Indeed, cnidarians pose a unique opportunity for the integrative exploration of the evolution of animal
- behavior. Even beyond neural computations, the emergence of novel cell types among diverse cnidarian body plans,
- sophisticated predator-prey interactions, and symbioses all contribute to biological novelty and niche expansion
- 299 (Technau and Steele, 2012). Overall, this work demonstrates how studying evolutionary novelties like stinging 300 behavior can yield broad insight into signal transduction, cellular decision making, and suggests that the evolution of
- 301 behavior should be examined across all tiers of biological organization.

302 Materials and Methods

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304 *Animals and Cells*

Starlet sea anemones (*Nematostella vectensis*) were provided by the Marine Biological Laboratory (Woods Hole, Massachusetts). Adult animals of both sexes were used and kept on a 14 hr light/10 hr dark cycle at 26°C in 1/3 natural sea water (NSW). *Exaiptasia spp.* were purchased through Carolina Biological Supply Company (Cat #162865). Adult animals of both sexes were used following being kept on either a 10 hr light/14 hr dark cycle at 26°C in natural sea water (NSW) or a 14 hr light/10 hr dark cycle at 26°C in natural sea water (NSW). *Cassiopea spp.* were purchased through Carolina Biological Supply Company (Cat #162936). Unless stated otherwise, all animals were fed freshly hatched brine shrimp (Artemia) twice a week.

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313 Exaiptasia diaphana were bleached through chemical methods (menthol-induced). Menthol (100mM in 100% 314 ethanol; Sigma-Aldrich) was added to NSW at a final concentration of 0.2mM (Matthews et al., 2016). The anemones 315 were incubated in the menthol/NSW treatment solution for a maximum of 8hr per day and outside of treatments 316 anemones were incubated in NSW. For 2 weeks, anemones were treated 4 days per week and kept in the dark 317 continuously starting from day 1 of treatment, aside from treatment changes. Animals were fed with Artemia 318 approximately twice per week between bleaching treatments, enabling successful bleaching with minimal mortality. 319 Their symbiotic status was assessed via fluorescence microscopy at the end of each week. For starvation experiments, 320 animals were fed to excess for 1-2 weeks before the trial and withheld food entirely during the trial period and given 321 water changes twice a week. 322

323 Nematostella nematocytes were isolated from tentacle tissue, which was harvested by anesthetizing animals in high 324 magnesium solution containing (mM): 140 NaCl, 3.3 Glucose, 3.3 KCl, 3.3 HEPES, 40 MgCl₂. Cells were isolated 325 from tentacles immediately prior to electrophysiology experiments by treatment with 0.05% Trypsin at 37°C for 15-326 20 min and mechanical dissociation in divalent free recording solution (mM): 140 NaCl, 3.3 Glucose, 3.3 KCl, 3.3 327 HEPES, pH 7.6. Dissociated cells were held on ice until use. Basitrichous isorhiza nematocytes were isolated from 328 tentacles and identified by the presence of a capsule with high refractive index containing a barbed thread, oblong 329 shape, and the presence of a cnidocil. Exaiptasia nematocytes were isolated from tentacle tissue immediately prior 330 to electrophysiology experiments by incubation in a heat shock dissociation solution with (in mM): 430 NaCl, 10 331 KCl, 150 sucrose, 5 NaEGTA, 10 HEPES, 10 glucose, pH 7.6 at 45°C for 15-20 min and mechanical dissociation in 332 the same solution. Dissociated cells were held on ice until use. Nematocytes were isolated from tentacles and 333 identified by the presence of a capsule with high refractive index, oblong shape, and the presence of one or multiple 334 apical cilia.

335

336 HEK293T cells (ATCC, Cat# CRL-3216, RRID:CVCL 0063, authenticated and validated as negative for 337 mycoplasma by vendor) were grown in DMEM, 10% fetal calf serum, and 1% penicillin/streptomycin at 37°C, 5% 338 CO2. For transfection, HEK293 cells were washed with Opti-MEM Reduced Serum Media (Gibco) and transfected 339 using lipofectamine 2000 (Invitrogen/Life Technologies Cat #11668019) according to the manufacturer's protocol. 340 1 ug each of M. musculus (mouse) cachala and rat cachald and one of a wide variety of beta subunits (Nematostella 341 vectensis cacnb2.1 (NveCa_V β), Rattus norvegicus (rat) cacnb2a (rCa_V β 2a), Exaiptasia diaphana Ca_V β s (EdCa_V β 1, 342 EdCa_V β 2), Cvanea capillata Ca_V β (CcCa_V β), Physalia physalis Ca_V β (PpCa_V β), Clytia hemisphaerica Ca_V β 343 (ChCa_V β), Cassiopea xamachana Ca_V β (CxCa_V β 2)) were coexpressed with 0.5 µg eGFP. We also assayed an array 344 of different EdCa_v β 2 mutants with N-termini from different animals by coexpressing 0.5 µg eGFP, 1 µg of M. 345 musculus (mouse) cacnala and rat cacna2dl, and one of a variety of beta subunits (Nematostella vectensis cacnb2.1 346 mutant (NveCa_V β -N), R. norvegicus (rat) cacnb2a mutant (rCa_V β -N), Exaiptasia diaphana Ca_V β mutants (EdCa_V β 1-347 N, EdCa_V β 2-N), Cvanea capillata Ca_V β mutant (CcCa_V β -N), Physalia physalis Ca_V β mutant (PpCa_V β -N), Clvtia 348 hemisphaerica $Ca_V\beta$ mutant (ChCa_V\beta-N), Cassiopea xamachana $Ca_V\beta$ mutant (CxCa_V\beta2-N)). To enhance channel

MEM for 6 hr at 37°C. Cell were then re-plated on coverslips, incubated for 1-2 hr at 37 °C, and then incubated at 30°C for 2-6 days before experiments. Rat *cacna2d1* (RRID: Addgene_26575) and *cacna1a* were gifts from D. Lipscombe (RRID: Addgene 26578) and *cacnb2a* was a gift from A. Dolphin (RRID: Addgene 107424).

353

354 Molecular biology

355 RNA was prepared from tentacles, body, and acontia tissues of WT and bleached adult *Exaiptasia* using published 356 methods (Stefanik et al., 2013). Each tissue was homogenized (Millipore Sigma Cat #Z359971) and RNA was 357 extracted using TRIzol Reagent (Thermo Fisher Cat #15596026), then after skipping the salt precipitation steps, RNA 358 was purified and concentrated with the RNA Clean & Concentrator-5 kit (Zymo Research). For ddPCR experiments, 359 droplet generation (OX200TM Droplet Generator BioRad Cat #1864002) and transfer of droplets to ddPCRTM 96-Well 360 Plates (Bio-Rad Cat #12001925) were performed according to manufacturer's instructions (Instruction Manual, 361 QX200TM Droplet Generator – Bio-Rad). Custom primers and probes and One-Step RT-ddPCR Advanced Kit for 362 Probes (Bio-Rad Cat #1864021) reaction reagents and Droplet Generation Oil for Probes (Bio-Rad Cat #1863005) 363 were sourced from Bio-Rad (see Key Resources Table for primer and probe sequences). The ddPCR plate was sealed 364 with a Pierceable Foil Heat Seal (Bio-Rad Cat #1814040) and the PX1[™] PCR Plate Sealer (Bio-Rad Cat #1814000). 365 Plates were transferred to a Bio-Rad Thermalcycler C1000 (Bio-Rad Cat #1851197). The cycling protocol was the 366 following: 45°C reverse transcription step for 60 minutes, 95°C enzyme activation step for 10 minutes followed by 367 40 cycles of a two-step cycling protocol (denaturation step of 95°C for 30 seconds and annealing/extension step of 368 58°C for 1 minute), 98°C enzyme deactivation step for 10 minutes, and holding at 12°C for an indefinite period before 369 transfer to the QX200 Droplet Generator. The plates were read with the Bio-Rad QX200 Droplet Generator & Reader 370 (Cat #1864003) and the RNA concentration per sample was processed using OuantaSoft (Bio-Rad Cat #1864011). 371 Data were exported to Microsoft Excel and Prism (Graphpad) for further statistical analysis.

372 Most plasmids, including Nematostella vectensis cacnb2.1 (NveCa_V β), Exaiptasia diaphana Ca_V β s (EdCa_V β 1, 373 EdCa_V β 2), Cvanea capillata Ca_V β (CcCa_V β), Physalia physalis Ca_V β (PpCa_V β), Clytia hemisphaerica Ca_V β 374 (ChCa_V β), Cassiopea xamachana Ca_V β (CxCa_V β 2)), Nematostella vectensis cacnb2.1 mutant (NveCa_V β -N), R. 375 norvegicus (rat) cacnb2a mutant (rCa_V β -N), Exaiptasia diaphana Ca_V β mutants (EdCa_V β 1-N, EdCa_V β 2-N), Cvanea 376 capillata Ca_V β mutant (CcCa_V β -N), *Physalia physalis* Ca_V β mutant (PpCa_V β -N), *Clytia hemisphaerica* Ca_V β mutant 377 (ChCa_V β -N), Cassiopea xamachana Ca_V β mutant (CxCa_V β 2-N), were synthesized by Genscript (Piscataway, NJ). 378 Sequence alignments were carried out using Clustal Omega. Wild type and Chimeric $Ca_V\beta$ sequences are listed in 379 Figure 5-- supplement table 1.

380

381Cnidarian beta sequences were obtained from RNA sequencing or NCBI: Nematostella vectensis cacnb2.1382(NveCa_Vβ) sequence (Weir et al., 2020), Exaiptasia diaphana Ca_Vβs from RNA sequencing and confirmation from383NCBI accession number KXJ28099.1 (EdCa_Vβ1) and NCBI accession number XP_020893045.1 (EdCa_Vβ2), Cyanea384capillata Ca_Vβ (CcCa_Vβ) from NCBI accession number <u>AAB87751.1</u> (Jeziorski et al., 1998), Physalia physalis Ca_Vβ385(PpCa_Vβ) from NCBI accession number <u>ABD59026</u> (Bouchard et al., 2006), Clytia hemisphaerica Ca_Vβ (ChCa_Vβ)386from the <u>MARIMBA database</u> (Leclère et al., 2019), Cassiopea xamachana Ca_Vβ (CxCa_Vβ2) from RNA sequencing387as TRINITY_DN5778_c3_g1_i5.p1.

388

389 *Transcriptomics*

390 *Exaiptasia* were anesthetized in 15% MgCl₂ NSW solution in a dish surrounded by an ice bath for 15 minutes. 391 Tentacle, body, and acontia tissue were dissected and flash frozen in the presence of liquid nitrogen. Cassiopea 392 xamachana were anesthetized in 10% MgCl₂ NSW solution in a dish surrounded by an ice bath for 15-20 minutes. 393 Oral arms, bell, and cassiosome tissues were dissected and flash frozen in the presence of liquid nitrogen. All tissues 394 were stored at -80°C until RNA extraction, library preparation, and RNA sequencing was performed by Genewiz 395 (Azenta) using a HiSeq (2x150 bp) platform. Reads were examined for base quality distribution, kmer frequencies 396 and adapter contamination by position in the read using fastqc (The Babraham Institute Bioinformatics Group), then 397 where relevant, Rcorrector was used to remove erroneous k-mers (Song and Florea, 2015) and the

398 FilterUncorrectablePEfastq python script from the Harvard Informatics group was used to discard read pairs. 399 TrimGalore (The Babraham Institute) was then used to remove adapter contamination in reads and where relevant, 400 Bowtie2 (Langmead and Salzberg, 2012) was used to remove reads originating from rRNA and Trinity was used to 401 assemble reference transcriptomes de novo (Grabherr et al., 2011). Transdecoder was used to identify open reading 402 frames (Haas, BJ) and Diamond used to annotate the transcriptome (Buchfink et al., 2015). Reads were pseudo-403 aligned and transcript abundance (TPM) was quantified using Kallisto (Brav et al., 2016) and our novel transcriptome 404 assemblies as a reference and visualization and alignments were performed with Geneious Prime software and/or 405 Clustal Omega (Madeira et al., 2022).

- 406
- 407 *Electrophysiology*

408 Recordings were carried out at room temperature using a MultiClamp 700B amplifier (Axon Instruments) and 409 digitized using a Digidata 1550B (Axon Instruments) interface and pClamp software (Axon Instruments). Whole-cell 410 recording data were filtered at 1kHz and sampled at 10kHz. Ca_V activation data were leak-subtracted online using a 411 p/4 protocol, and all membrane potentials were corrected for liquid junction potentials.

412

413 For whole-cell nematocyte recordings, borosilicate glass pipettes were polished to 8-10M Ω for *Nematostella* and 4-414 $6M\Omega$ for *Exaiptasia*, respectively. The standard *Nematostella* medium was used as the extracellular solution and 415 contained (in mM): 140 NaCl, 3.3 glucose, 3.3 KCl, 3.3 HEPES, 2 CaCl₂, 0.5 MgCl₂, pH 7.6, 260-280mOsm. The 416 standard Exaiptasia medium was used as extracellular solution and contained (in mM): 430 NaCl, 10 KCl, 10 CaCl₂, 417 50 MgCl₂, 10 HEPES, pH 7.6, 800-900mOsm. The intracellular solution for both Nematostella and Exaiptasia 418 contained (in mM); isolating inward currents (in mM); 500 cesium methanesulfonate, 4 MgCl₂, 10 CsEGTA, 10 419 HEPES, 30 sucrose, pH 7.6, 260-280mOsm for Nematostella and 800-900mOsm for Exaiptasia. For Nematostella 420 nematocyte recordings, voltage-dependent inactivation was measured during a 200ms activating pulse of -20mV 421 following a series of 1s pre-pulses ranging from -110mV to 30mV, holding at -110mV. Voltage-gated currents were 422 measured through a series of 200ms voltage pulses in 10mV increments from -110mV to 70mV, holding at -110mV. 423 For Exaiptasia nematocyte recordings, voltage-dependent inactivation was measured during a 200ms activating pulse 424 of 0mV following a series of 1s pre-pulses ranging from -110mV to 30mV, holding at -110mV. For both Nematostella 425 and Exaiptasia, voltage-gated currents were measured through a series of 200ms steps 200ms voltage pulses in 10mV increments from -110mV to 70mV, holding at -110mV. For Cd²⁺ experiments, 500µM Cd²⁺ (dissolved in water) was 426 427 applied locally and voltage-dependent activation was assessed through a single 200ms step to 0mV from a holding 428 potential of -110mV.

429

430 For whole-cell recordings in HEK293 cells, pipettes were $3-6M\Omega$. The standard extracellular solution contained (in 431 mM): 140 NaCl, 5 KCl, 10 HEPES, 2 CaCl₂, 2 MgCl₂, 10 Glucose, pH 7.4, 300-310mOsm. The intracellular solution 432 contained (in mM): 5 NaCl, 140 cesium methanesulfonate, 1 MgCl₂, 10 EGTA, 10 HEPES, 10 sucrose, pH 7.2, 300-433 310mOsm. For Ca²⁺ currents in heterologously expressed channels, voltage-dependent inactivation was measured in 434 one of two ways: (1) during an activating pulse of 0mV following a series of 1s pre-pulses ranging from -110mV to 435 50mV and holding potential of -80mV; or (2) during an activating pulse of 0mV following a series of 1s pre-pulses 436 ranging from -110mV to 80mV and holding potential of -90mV. Voltage-gated Ca²⁺ currents were measured in 437 response to 200ms voltage pulses in 10mV increments from -130mV to 80mV with -110mV holding potential. 438 Voltage-dependent inactivation was quantified as I/Imax, with Imax occurring at the voltage pulse following a -110mV 439 prepulse. In some instances, inactivation curves could not be fitted with a Boltzmann equation and were instead fitted 440 with an exponential. G-V relationships were derived from I-V curves by calculating G: $G=I_{CaV}/(V_m-E_{rev})$ and fit with 441 a Boltzmann equation. Data was processed and analyzed in Clampfit (pClamp 11 Software Suite, Molecular Devices) 442 and Microsoft Excel and Prism (GraphPad).

443

444 In situ hybridization (BaseScope)

445 Adult Exaiptasia were paralyzed in anesthetic solution (15% MgCl₂), rinsed in PBS, then embedded in Tissue-Tek 446 O.C.T. Compound (Sakura Cat #4583) in cryomolds (Sakura Tissue-Tek® Cryomold®, Intermediate, Cat #4566) 447 and flash frozen on dry ice and stored at -80°C. Cryostat sections (18-20µm) were adhered to Fisherbrand[™] 448 Superfrost[™] Plus Microscope Slides (Fisher Scientific Cat #12-550-15) and flash frozen on dry ice and stored at -449 80°C until used for BaseScope. The BaseScope Duplex Detection Reagent Kit (Advanced Cell Diagnostics Cat 450 #323800) and the manufacturer's manual (BaseScope Duplex Detection Reagent User Manual, ACDBio) was 451 followed to hybridize custom probes or positive control (Cat #700101) or negative control probes (Cat #700141) to 452 targets in tissue cryosections and amplify signals. Samples were imaged on an Olympus BX41 Phase Contrast & 453 Darkfield Microscope (Olympus Cat #BX41-PH-B) and images were acquired using the Olympus CellSens software 454 and Olympus DP25 5MP Color Firewire Camera.

455456 *Behavior*

457 Discharge of nematocysts was assessed based on well-established assays (Gitter et al., 1994; Watson and Hessinger, 458 1994; Weir et al., 2020). For assaying discharge, 5 mm round coverslips were coated with a solution of 25% gelatin 459 (w/v) dissolved in NSW (for *Exaiptasia*) or 1/3 NSW (for *Nematostella*) and allowed to cure 3-4 hr prior to use. 460 Coverslips were presented to the animal's tentacles for 5 seconds and then immediately imaged at 20X magnification 461 using a transmitted light source. To assay behavioral responses to prev-derived chemicals, freshly hatched brine 462 shrimp were flash frozen and ground to a powder with a mortar and pestle (Fisherbrand), then filtered through a 463 0.22µm syringe filter (VWR Cat #28145-501) and osmolarity adjusted for the specific anemone species. Coverslips 464 were submerged in prey extract for 10 seconds then immediately presented to the animal. Nematocytes visualized on 465 coverslips were only those that embedded in the gelatin after discharge. For experiments using pharmacological 466 agents such as CdCl₂, coverslips were submerged in a solution of 1M (*Exaiptasia*) or 10mM (*Nematostella*) Cd²⁺ in 467 milli-Q water for 10 seconds then immediately presented to the animal. After performing the experiments, the animals 468 were given several water changes to remove Cd^{2+} . Experiments carried out in the absence of extracellular Ca^{2+} were nominally Ca²⁺ free and did not include use of extracellular chelators. The region of the highest density of discharged 469 470 nematocytes on the coverslip was imaged at 20X. Images were acquired with MetaMorph Microscopy Automation 471 and Image Analysis Software (Molecular Devices) and the number of discharged nematocysts was counted by eve. 472 Images were processed in Fiji (ImageJ) (Schindelin et al., 2012). Exaiptasia and Nematostella tentacles were 473 examined by cutting a small portion of exposed tentacles and sandwiched between glass coverslips and then imaged 474 at 20X with the MetaMorph software.

475

476 *Phylogenetic and Genomic analyses*

477 To infer exon boundaries and isoforms, we aligned EdCavB1 (NCBI accession number LJWW01000015.1) and 478 EdCa_Vβ2 (NCBI accession number XM 021037386.2) to the Exaiptasia diaphana reference genome (BioProject 479 PRJNA261862) (Baumgarten et al., 2015) using GMAP version 2015-07-23 (Wu and Watanabe, 2005). For 480 phylogenetic analyses, we aligned nucleotide sequences with MAFFT v.7 (Katoh and Standley, 2013). We used 481 ModelFinder (Kalyaanamoorthy et al., 2017) to assess the best model of substitution for phylogenetic inference. We 482 estimated a maximum likelihood gene tree in IQ-TREE v2.0 (Minh et al., 2020). Support for clades was calculated 483 using ultrafast bootstrap approximation UFBoot2 (Hoang et al., 2018). Percentage of identity for amino acids was 484 calculated in overlapping windows.

485

486 *Mathematical model: Optimal control theory for the stinging response* 487

488 *Predatory stinging*. To model *Nematostella*, we assume the agent stings for predation. We thus introduce the state of 489 starvation, *s*, that ranges from 0 to 1; at s = 0 the agent is least starved and at s = 1 the agent is most starved (**Figure** 490 **2**— **figure supplement 1A top**). At each time step, the agent decides to perform an action (sting), *a*, representing 491 the intensity of the attack; *a* ranges from 0 to 1, and is experimentally compared to the fraction of nematocytes fired 492 in the behavioral assay. Each action has a cost that is proportional to the fraction of nematocytes that are fired, c(a) =

 $c_0 a$ where c_0 is the cost of discharging all nematocysts at once, or cost of full discharge, and we first consider c_0 493 494 constant. Each stinging event has a probability p(a) of achieving successful predation, where p(a) increases with a 495 (more intense attacks are more costly and more likely to succeed). A successful attack leads to the transition to the 496 next state s' where the agent is more satiated $s \rightarrow s' = s - 1$ whereas a failed attack leads to higher starvation state 497 $s \rightarrow s' = s + 1$. The most starved state is absorbing, which is equivalent to a point of no return. A reward r(s') is 498 assigned to the state of starvation reached upon attack, indicating its desirability (r(s')) is a decreasing function of s'), 499 and the most starved state entails a starvation penalty r(1) < 0. Without loss of generality, all costs and rewards are 500 normalized to the penalty of starvation, hence penalty of starvation is r(1) = -1. Our goal is to choose actions that 501 maximize the expected sum of all future net rewards (reward - cost) for each state, which is called the value function. 502 As customary in infinite horizon problems, we ensure convergence of the value function by introducing an effective 503 horizon, i.e. by discounting exponentially rewards that are further in the future with a discount rate $\gamma < 1$.

504 The optimal value of a state, $V^*(s)$ and the corresponding optimal action $a^*(s)$ are obtained by solving the Bellman 505 Optimality equation (Bellman, 2003), with the boundary condition $V^*(1) = 0$.

506

507
$$V^*(s) = \max_{a} (p(a)(r(s-1) - c(a) + \gamma V^*(s-1)) + (1 - p(a))(r(s+1) - c(a) + \gamma V^*(s+1))$$
(1)

508

509 $a^*(s) = \underset{a}{\operatorname{argmax}} (p(a)(r(s-1) - c(a) + \gamma V^*(s-1)) + (1 - p(a))(r(s+1) - c(a) + \gamma V^*(s+1)) (2)$

510

527

511 Predatory stinging increases with starvation. We solve Equations (1) and (2) numerically with the value iteration 512 algorithm (Sutton and Barto, 2018) and analytically under the assumption that $a^*(s)$ varies slowly with s (see 513 Asymptotics for predatory stinging). The asymptotic solution reproduces well the numerical results (compare lines and full circles in **Figure 2B right**, where we used $c_0 = 1$ and $p = p_M(2 - a^2)$ and $p_M = 0.8$ and showcased two different functional forms for r(s), $r(s) = 10 \operatorname{atan}(1-s)$; $r(s) = 5 \cos\left(\frac{s\pi}{2}\right)$. We also explored how well the 514 515 516 asymptotic result can capture the trend of the numerical result by varying the parameters in these three different forms 517 for the reward (Figure 2—figure supplement 2). The asymptotic solution shows that the stinging response increases 518 with starvation under broad conditions and not only for specific forms of rewards r, transitions p and costs c, (i.e. as 519 long as r(s) and p(a) are concave functions and c(a) is convex, see Asymptotics for predatory stinging). To 520 exemplify the importance of acting optimally to save resources, we considered two agents, one acting optimally and one acting randomly i.e. shooting with a number of nematocysts uniformly distributed between a_{min} and a_{max} . Both 521 522 agents start at the same starvation state (s = 0.9 in Figure 2D) and use on average the same number of nematocysts. 523 but the random agent reaches starvation typically in tens of steps, whereas the optimal agent converges to a steady 524 state (around s = 0.3 in the figure) and hardly ever reaches severe starvation. Predatory stinging increases with 525 starvation even when costs increase moderately with starvation; it will eventually decrease with starvation when cost 526 increase is exceedingly steep (see Asymptotics for predatory stinging – changing cost).

528 Asymptotics for predatory stinging. Short-hand notation: $a^* \equiv a^*(s)$. When $a^* \in (0, 1)$ we obtain it by zeroing the 529 derivative with respect to a in Equation (1):

530
$$-c'(a^*) + p'(a^*)[r(s-1) + \gamma V^*(s-1)] - p'(a^*)[r(s+1) + \gamma V^*(s+1)] = 0$$

531
$$[r(s-1) + \gamma V^*(s-1)] = r(s+1) + \gamma V^*(s+1) + \frac{c'(a^*)}{p'(a^*)}$$
(3)

532 Plugging Equation (3) into the Bellman Equation (1) we obtain:

533
$$V^*(s) = -c(a^*) + r(s+1) + \gamma V^*(s+1) + p(a^*) \frac{c'(a^*)}{p'(a^*)}$$
(4)

534 From Equation (3) there is also

535
$$V^*(s-1) = V^*(s+1) + \frac{1}{\gamma} [r(s+1) - r(s-1)] + \frac{c'(a^*)}{p'(a^*)}$$
(5)

Equations (4) and (5) are two equations in the four unknowns $V^*(s)$, $V^*(s+1)$, $V^*(s-1)$ and $a^*(s)$. These equations can be solved iteratively by coupling all states and using the boundary conditions on the absorbing state. However, the exact iterative solution is not particularly instructive. Instead, we will make a simplifying assumption that leads to a good approximation that can be used to gather a qualitative understanding of the prediction. Assume that $a^*(s)$ varies slowly with s so that $a^* \equiv a^*(s) \approx a^*(s+1) \approx a^*(s-1)$ (better approximations may be achieved by assuming a first order expansion). Then we obtain a third equation by writing Equation (4) for the state $\bar{s} = s - 1$

543
$$V^*(s-1) = -c(a^*) + r(s) + \gamma V^*(s) + p(a^*) \frac{c'(a^*)}{p'(a^*)}$$
(6)

544 We can then repeat the trick to obtain a fourth equation. To this end, we first eliminate $V^*(s-1)$ by combining 545 Equations (5) and (6):

546
$$V^*(s+1) = K(a^*) \frac{\gamma}{1-\gamma^2} - \frac{r(s+1)}{\gamma} + \frac{r(s-1)}{\gamma(1-\gamma^2)} + \frac{r(s)}{1-\gamma^2}$$
(7)

547
$$K(a^*) = -c(a^*)\frac{1+\gamma}{\gamma} + \frac{c'(a^*)}{p'(a^*)}\left(p(a^*)\frac{1+\gamma}{\gamma} - \frac{1}{\gamma^2}\right)$$
(8)

548 Repeating the trick, we can write Equation (7) for $\bar{s} = s - 1$ and using that $a^*(s - 1) = a^*(s)$ we obtain a fourth 549 equation to close the system:

550
$$V^*(s) = K(a^*) \frac{\gamma}{1-\gamma^2} - \frac{r(s)}{\gamma} + \frac{r(s-2)}{\gamma(1-\gamma^2)} + \frac{r(s-1)}{1-\gamma^2}$$
(9)

551 The system is now closed with the 4 Equations (4), (5), (6), (9) in the 4 unknowns $V^*(s)$, $V^*(s + 1)$, $V^*(s - 1)$ and 552 $a^*(s)$. We solve for a^* by eliminating $V^*(s)$ from Equations (4) and (9) and plugging the expression for $V^*(s + 1)$ 553 from Equation (7). After some (tedious) algebra, we obtain that a^* satisfies the simple relation:

$$\frac{p'(a^*)}{c'(a^*)} = \frac{1-\gamma}{-\Delta r(s)} \tag{10}$$

555 Both the asymptotic solution from Equation (10) and the numerical solution from value iteration are used in the main 556 text (Figure 2B right, symbols and lines respectively). We showcase the robust match between the asymptotic and 557 numerical solutions to Equation (1) by using a variety of functional forms of the reward function and varying the 558 parameters (Figure 2-figure supplement 2). The asymptotics break down if abrupt changes in the rewards and 559 transition rates are assumed, which leads to exceeding slopes in the optimal policy (data not shown). Equation (12) 560 has a non-trivial solution $0 < a^* < 1$ when c' > 0, r(s) is a decreasing function, and p(a) is an increasing function. 561 If we additionally assume that r is concave, and p'/c' is a decreasing function of a (for example, p is strictly concave 562 and c is convex), then Equation (12) prescribes that a^* increases with s, as seen graphically in Figure 2—figure 563 supplement 1A bottom. Hence independently of the specific functional forms of c, p, and r, as long as these broad 564 assumptions are valid, optimal stinging for predation entails more intense attacks as starvation increases. For different 565 assumptions of reward function r(s), cost function c(a), and probability p(a), we can easily substitute the specific 566 expressions into Equation (10) and solve for a^* for every *s*.

567 Asymptotics for predatory stinging – changing cost. We applied a cost to predatory stinging that increases with 568 starvation. We found numerically that predatory stinging still increases for moderate increase of $c_0(s)$ with s. The 569 result is exemplified in Figure 2C using the same functional form for $c_0(s)$ of the defensive stinging (Figure 2B, 570

open circles). For a more intense increase of $c_0(s)$ with s predatory stinging eventually decreases with starvation (see 571 Figure 2-figure supplement 4, for a comparison with 4 different cost functions from numerical solutions of 572 Equations (1) and (2)).

These results can be easily understood from our asymptotic solution (10), which appears to still hold when $c = c_0(s)a$ 573 574 (data not shown -- a formal proof of the asymptotic solution for this case and further consequences for Markov 575 Decision Processes are beyond the scope of the current paper). Indeed, if c increases slightly with s, the light blue 576 curve in Figure 2—figure supplement 3 slightly shifts downward with s. If the shift is sufficiently small, its 577 intersection with the green curves still occurs for increasing values of a (dashed line in Figure 2—figure supplement 578 3). However, a dramatic increase of c with s will shift the light-blue curve downward considerably, and the 579 intersection will eventually move backward (dotted line in Figure 2—figure supplement 3). In plain words, when 580 the cost of nematocyst discharge for starved animals is dramatically larger than for well-fed animals, the benefits of 581 predation are eventually outweighed by its cost and the animals will sting less with starvation (exemplified in Figure 582 **2—figure supplement 4**, green and vellow curves). Note that the most extreme increase of cost with starvation is 583 unrealistic as it entails that the cost of stinging is nearly irrelevant when well fed and outweighs the benefits of feeding 584 when starving (see green and yellow cost functions in Figure 2-figure supplement 4A). This scenario may become 585 more relevant upon severe starvation, which we do not explore experimentally.

586

587 Defensive stinging. To model Exaiptasia, we assume the agent stings for defense, thus the associated Markov process 588 models transitions between the states of safety, which we indicate with L, and danger, which we indicate with D589 (Figure 2S1B top). The state of starvation is not affected by stinging and instead is dictated by a separate process 590 that relies on symbionts and which we do not model. Similar to the previous model, the agent chooses an action, a_{i} 591 representing the intensity of the attack. Each attack has a likelihood to succeed p(a) and an associated cost c(a) =592 $c_0 a$ where c_0 is the cost of full discharge of all nematocysts at once. A successful attack allows the animal to remain 593 in state L and receive a unit reward; a failed attack leads to state D and penalty -1. F is an absorbing state hence 594 $V^*(F) = 0$. The optimal value and action in state L follow:

595

$$V^{*}(L) = \max_{a} (p(a)(-c_{0}a + \gamma V^{*}(L) + 1) + (1 - p(a))(-1 - c_{0}a))$$
(11)
$$a^{*}(L) = \operatorname*{argmax}_{a} (p(a)(-c_{0}a + \gamma V^{*}(L) + 1) + (1 - p(a))(-1 - c_{0}a))$$

598

599 Analytic solution for defensive stinging. Zeroing the derivative of the argument on the r.h.s. of equation (11) leads to 600 $-c_0 + p'(a^*)(\gamma V^*(L) + 2) = 0$ 601

$$V^*(L) = -c_0 a^* + p(a^*)(\gamma V^*(L) + 1) + (1 - p(a^*))$$

Here, p(a) is the probability of success of action a and it ranges from p(0) = 0 to $p(1) = p_M < 1$. Combining these 602 603 equations we obtain an implicit algebraic equation for a^* :

604
$$(\gamma p(a^*) - 1) \left(\frac{c'(a^*)}{p'(a^*)} - 1\right) = \gamma c(a^*) + \gamma \left(1 - p(a^*)\right) - 1$$
 (12)

Assuming the specific form $p = p_M a(2 - a)$ in Equation (12) leads to the constant optimal action: $a^* = K - \sqrt{K^2 - A}$, where $K = \frac{2-\gamma}{c_0\gamma}$ and $A = -\frac{1}{\gamma p_M} + 2K$. If c_0 is constant, there is a non-trivial optimal action as long as $c_0 < \infty$ 605 606 607 $2p_M(2-\gamma)$ and clearly the optimal action does not depend on starvation (constant solution in Figure 2E right, with $c_0 = 1; \gamma = 0.99 \text{ and } p_M = 0.8).$ 608

609

610 Defensive stinging - increasing cost. Stinging predators does not improve nutritional state, thus transitions among 611 different starvation states are not modelled for defensive stinging, but instead rely heavily on symbionts. However, 612 to capture subtle effects of starvation on defensive stinging, we note that the cost of discharging nematocysts may 613 still depend parametrically on whatever state of starvation the agent happens to be in. In this case, $c_0 = c_0(s)$ and under the assumption that the cost increases with starvation, we find that optimal defensive stinging always decreases 614 with starvation, for any functional form of p. Indeed, equation (12) with $c_s(a) = c(s, a)$ simply reads: 615

616
$$(\gamma p(a^*) - 1) \left(\frac{\partial_a c_s(a^*)}{p'(a^*)} - 1 \right) = \gamma c_s(a^*) + \gamma \left(1 - p(a^*) \right) - 1$$
 (13)

617 where $\partial_a c$ is now a partial derivative with respect to a. For $c = c_0(s)$ and $p = p_M a(2 - a)$, the solution is $a^*(s) = 618$ 618 $K(s) - \sqrt{K(s)^2 - C(s)}$ where $K = \varepsilon/c_0(s)$; $\varepsilon = (2 - \gamma)/\gamma$, $C(s) = -1/(p_M \gamma) + 2\varepsilon/c_0(s)$ and it exists for 619 $c_0(s) < 2p_M(2 - \gamma)$. Outside these boundaries, the solution is either $a^* = 0$ or $a^* = 1$ and it is obtained by 620 comparing V(L) for these two choices of action and choosing the one that maximizes V. This solution is decreasing 621 as can be easily demonstrated by deriving with respect to s. We used this solution for $a^*(s)$ to match the experimental 622 data and obtained a fit for the cost function shown in **Figure 2A** (empty circles).

While we discussed a specific case for the choices of p and a above, optimal defensive stinging decreases with s in much more general conditions. Indeed, a^* decreases or remains constant with s using the same broad classes of functions discussed for predatory stinging (p(a) is concave and c is convex in a; either p or c can be linear in a, but not both) and assuming additionally that $dc_0/ds \ge 0$ i.e. that the cost does not decrease with starvation. Rearranging Equation (13) we note that a^* is defined by the point where:

$$628 \qquad \frac{1 - \gamma p(a^*)}{p'(a^*)} \partial_a c_s(a^*) + \gamma c_s(a^*) = 2 - \gamma \tag{14}$$

The l.h.s. of Equation (14) is an increasing function of *a* as seen by deriving with respect to *a* and using the assumptions: p < 1; $p'' \le 0$; $c' \ge 0$ and $c'' \ge 0$. Because $c_s(a)$ increases with *s*, the intersection of the l.h.s. with the constant value $2 - \gamma$ occurs at lower and lower values of *a* as *s* increases (see graphical representation Figure **2S1B bottom).** Thus under the same broad assumptions for the functional forms of *c* and *p*, stinging for predation increases with starvation, whereas stinging for defense remains constant or decreases with starvation.

634 *Statistical analysis*

Data were analyzed with Clampfit (Axon Instruments), Prism (GraphPad), or QuantaSoft (BioRad Laboratories) and are represented as mean \pm sem. *n* represents independent experiments for the number of cells/patches or behavioral trials. Data were considered significant if p < 0.05 using paired or unpaired two-tailed Student's t-tests or one- or two-way ANOVAs. All significance tests were justified considering the experimental design and we assumed normal distribution and variance, as is common for similar experiments. Sample sizes were chosen based on the number of independent experiments required for statistical significance and technical feasibility.

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642 Data availability

Deep sequencing data are available via the Sequence Read Archive (SRA) repository under the BioProject accession code PRJNA945904. All plasmids are available upon request. Further requests for resources and reagents should be directed to and will be fulfilled by the corresponding author, NWB (<u>nbellono@harvard.edu</u>). The Matlab code to obtain the optimal predicted stinging according to our Markov Decision Process is available from https://zenodo.org/record/8177567.

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649 Acknowledgments: We thank B. Walsh and P. Kilian for assistance with animal husbandry, A. Whipple and D. 650 Loftus with guidance for ddPCR experiments, A. Grearson for illustrations and photographs, K. Koenig and M. 651 Martindale, and the Marine Biological Laboratory for providing animals. We also thank the Harvard Center for 652 Biological Imaging (RRID:SCR 018673), Histology Core at the Harvard Department of Stem Cell and Regenerative 653 Biology, and The Bauer Core Facility at Harvard University for infrastructure and experimental support. This research 654 was supported by grants to NWB from the New York Stem Cell Foundation, Searle Scholars Program, and the NIH 655 (R35GM142697), fellowships to LH from NSF Graduate Research Fellowship Program and Physics of Living 656 Systems (PoLS) Graduate Fellowship and the Simmons Award at the Harvard Center for Biological Imaging, grants

to AS from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation

- programme (grant agreement No 101002724 RIDING), the Air Force Office of Scientific Research under award
 number FA8655-20-1-7028, and the National Institutes of Health (NIH) under award number R01DC018789.
- Author Contributions: LH, CAA, SPK, KW, and NWB contributed to physiological studies. LH contributed to
 behavioral, histological, and molecular studies. LH and WV contributed to phylogenetic, transcriptomic, and genomic
 studies. YQ and AS contributed to mathematical modelling studies. All authors were involved with writing or
 reviewing the manuscript.
- 665
- 666 **Competing Interests:** The authors declare no competing financial interests.
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817 Figure 1. Comparative sea anemone stinging behavior.

- A) *Nematostella vectensis* stings with tentacles while *Exaiptasia diaphana* also stings with acontia filaments that are ejected from its body for defense. *Left: Nematostella* nematocyte discharge was only observed in response to simultaneous prey chemicals and touch stimuli. *Middle, Right: Exaiptasia* nematocyte discharge 821
 from tentacles and acontia occurred irrespective of prey cues (touch alone). Scale bar = 50µm.
 - **B)** *Nematostella* nematocyte discharge was elicited by simultaneous touch and prey chemical stimuli (n = 10 trials). *Exaiptasia* tentacle (n = 10) and acontia (n = 13) nematocytes discharged only to touch, with or without prey chemicals. p < 0.05 for *Nematostella*, paired two-tailed student's t-test. Data represented as mean \pm sem.

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828 Figure 2. Nematostella stinging is regulated by predation while *Exaiptasia* stings for defense.

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- 829 A) The cost of stinging is $c = c_o a$, where c_o is the cost for full nematocyte discharge and it either does not 830 change (solid lines filled circles) or increases slightly (dashed lines empty circles) with starvation state. These 831 symbols are used throughout the figure to represent each cost function. The increasing cost is obtained by 832 fitting the Exaiptasia behavior (*see fitting procedure in Materials and Methods*).
- 833 B) Left: Nematostella burrows in the substrate and stings for predation. Center: Desirability of nutritional state, 834 or reward, decreases with starvation. Two examples are shown: example 1, $r(s) = 10 \tan^{-1} (1-s)$; example 2, $r(s) = 5 \cos\left(\frac{s\pi}{2}\right)$. Right: Predicted optimal stinging obtained by solving equation (1) with 835 836 numerical simulations (circles) and approximate analytical solutions (lines) assuming: $p(a) = p_M a(2 - a)$ 837 and $p_M = 0.8$; $c = c_0 a$ with cost for full discharge c_0 matching panel A (full circles and solid lines for 838 constant cost; empty circles for increasing cost); reward in Left panels (colors match). For all reward and 839 cost functions, optimal predatory stinging increases with starvation under broad assumptions (see Materials 840 and Methods).
 - C) Left: Exaiptasia diaphana relies heavily on endosymbiotic algae for nutrients and stings primarily for defense. Center: We assumed there are two states, safety (L), and danger (D). The state of safety can transition to danger, but not the other way around. We assumed the agent obtains reward 1 in state L and penalty -1 in state D. Right: Predicted optimal stinging obtained by solving equation (2) with numerical simulations (circles) and analytical solutions (lines). Styles match the costs in panel A; we assume $p(a) = p_M a(2 a)$ and $p_M = 0.8$ as before. Optimal defensive stinging is constant or decreases with starvation under broad assumptions (see Materials and Methods).
- 848 **D**) Examples of optimal (blue) versus random (black) predatory stinging. Each agent (anemone) starts with s =849 0.9, and stings sequentially for many events (represented on the *x* axis). The random agent almost always 850 reaches maximal starvation before 50 events (grey lines, five examples shown). In comparison, the optimal 851 agent effectively never starves due to a successful stinging strategy optimized for predation (blue lines, five 852 examples shown, parameters as in panel B, curve with matching color).
- E) Left: Nematostella nematocyte discharge was affected by prey availability while Exaiptasia stung at a similar rate regardless of feeding. p < 0.0001 for Nematostella, two-way ANOVA with post hoc Bonferroni test (n = 10 animals, data represented as mean ± sem). Right: Experimental data (circles with error bars representing standard deviation) are well fit by normalized optimal nematocyst discharge predicted from MDP models for both Exaiptasia (orange full and empty circles for constant and increasing cost, panel A) and Nematostella (light blue full and empty circles for constant and increasing cost, panel A and desirability 2 in panel B). We

- 859 match the last experimental data point to s = 0.5, the precise value of this parameter is irrelevant as long as
- 860 it is smaller than 1, representing that animals are not severely starved during the experiment.



865 Figure 2—figure supplement 1. Sketch of Markov Decision Processes model and predictions for stinging.

- A) Directed graph representing the Markov Decision Process for predatory stinging (*top*) including states of
 starvation s, actions a, and transitions to adjacent states depending on the probability to catch prey p(a).
 Graphical representation of the result that optimal predatory stinging increases with starvation (*bottom*).
- 869B)Directed graph representing the Markov Decision Process for defensive stinging (top) including states of
safety and danger L and D, actions a, and transitions between L and D depending on the probability to
successfully stinging the predator p(a). Graphical representation of the result that the optimal defensive
stinging decreases with starvation (bottom).



Figure 2—figure supplement 2. Optimal policy predicted by Bellman's theory for the MDP sketched in Figure
 2—figure supplement 1A.

Left: three choices of concave reward functions r(s'): $r(s) = k \cos(s\pi/2)$, upper left; r = k(1 - 50s2) + 60, middle left; $r = k \tan - 1(5(1 - s)/(\pi/10))$, lower left. Solid and dashed lines correspond to two choices of the parameter k for each reward as in the legend. The cost of full dischare is constant $c_0 = 1.5$ and the likelihood of successful discharge is $p = p_M a(2 - a)$ with $p_M = 0.6$.

Right: the asymptotic solution for the optimal policy $a^*(s)$ (solid and dashed lines matching the corresponding reward on the left) reproduces well the numerical solution obtained from solving Bellman's Equation (1) with the value iteration algorithm (crosses and circles correspond to the solid and dashed rewards on the left). Optimal nematocyst discharge increases with the starvation state, independently on the shape of the reward function.

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Figure 2—figure supplement 3. Sketch of theoretical prediction for predatory stinging with increasing cost. Similar to Figure 2-figure supplement 1A bottom, for the case where the cost per nematocyte varies with starvation $c = c_0(s)a$. Moderate increase in the cost per starvation (dashed light-blue line) do not affect the qualitative results as the green curve still intersects the light-blue curve for increasing values of a^* (marked by dashed dark-blue line). More dramatic increases of cost with starvation (light-blue dotted line) do lead to a decrease in predatory stinging with starvation as the intercept now moves backward with increasing s (marked by dark-blue dotted line).

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915 Figure 2—figure supplement 4. Effects of a moderately vs dramatically increasing cost with starvation.

For a constant cost of full discharge or moderately increasing cost with starvation, predatory stinging always increases, whereas defensive stinging decreases or stays constant (results discussed in main text, **Figure 2**, and reproduced here for comparison, red and blue curves in Panels A-C. For predation, we use desirability 2 from **Figure 2B**). When the cost function increases dramatically with starvation (panel A, yellow and green lines), defensive stinging keeps decreasing with starvation (panel C, right), but now also predatory stinging decreases with starvation (panel B, right, yellow and green lines). Results are obtained with numerical simulations.

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928 929 Figure 2-figure supplement 5. Modulation of Nematostella and Exaiptasia stinging is not due to changes in

930 the abundance of nematocytes.

- 931 Nematocytes were highly abundant in tentacles from Nematostella (top) and Exaiptasia (bottom) before and after
- 932 starvation. Representative of n = 3 animals. Scale bar = $50 \mu m$.



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937 Figure 3. Exaiptasia nematocyte voltage-gated Ca²⁺ currents exhibit minimal steady-state inactivation 938 compared with Nematostella.

- 939 A) Touch-elicited *Exaiptasia* tentacle nematocyte discharge was blocked in the absence of Ca^{2+} (p < 0.01, paired 940 two-tailed student's t-test, n = 9 animals) or by addition of the Ca_V channel blocker Cd²⁺ (500 μ M, p < 0.05, 941 paired two-tailed student's t-test, n = 6 animals). Scale bar = 50 μ m.
 - **B)** Top: Representative patch clamp experiment from an *Exaiptasia* nematocyte. Scale bar = 20µm. Bottom: Nematocyte voltage-gated currents elicited by a maximally activating 0mV pulse were blocked by Cd^{2+} (n = 3 cells, p < 0.01, paired two-tailed student's t-test).
 - C) Nematocyte voltage-gated currents elicited by -120mV (black) or 0mV pulses (colored). Conductancevoltage curves for *Nematostella* nematocyte ($V_{al/2} = -26.54 \pm 0.78$ mV, n = 3) and *Exaiptasia* nematocyte $(V_{a1/2} = -12.47 \pm 0.70 \text{mV}, n = 3).$
- 948 **D)** Nematocyte voltage-gated currents elicited by a maximally activating voltage pulse following 1 s pre-pulses 949 to -110 mV (max current, black), -50 mV (colored), or 20 mV (inactivated, no current). Nematostella 950 nematocytes inactivated at very negative voltages ($V_{i1/2} = -93.22 \pm 0.42 \text{mV}$, n = 7) while *Exaiptasia* 951 contained two populations of nematocytes: low-voltage threshold ($V_{1/2} = -84.94 \pm 0.70$ mV, n = 4), and high-952 voltage threshold ($V_{i1/2} = -48.17 \pm 3.32 \text{mV}$, n = 3). Data represented as mean \pm sem.

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955 Figure 4. *Exaiptasia* expresses a Ca_v β subunit splice isoform that confers weak voltage-dependent inactivation.

- A) ddPCR ratio of concentrations of $Ca_V \beta$ subunit 1 and 2 mRNAs was similar in tentacle (n = 5), body (n = 5), and acontia (n = 4 animals) tissue samples.
- **B)** EdCa_v β 1 and EdCa_v β 2 localized to distinct nematocytes in *Exaiptasia* tentacle cross section, as visualized by BaseScope *in situ* hybridization. Representative nematocyte expressing EdCa_v β 1 (green) or EdCa_v β 2 (red). Representative of 3 animals.
- C) Voltage-gated currents from heterologously-expressed chimeric mammalian Ca_V (mCa_V) with different β subunits: rat (*Rattus norvegicus*), *Nematostella* (Nve), *Exaiptasia* EdCa_Vβ1 or EdCa_Vβ2. *Top*: Currents elicited by voltage pulses to -120mV (no current, black) and maximally activating 0mV (colored). *Bottom*: Voltage-gated currents elicited by a maximally activating voltage pulse following 1 s pre-pulses to -110 mV (max current, black), -50 mV (colored), or 20 mV (inactivated, no current, black). Scale bars = 100pA, 50ms.
 - **D**) *Exaiptasia* Ca_V β subunit splice isoforms confer distinct inactivation: *Nematostella* β subunit (V_{i1/2} = -68.93 \pm 1.53mV, n = 5) and Rat β 2a subunit (V_{i1/2} = -2.98 \pm 13.51mV, n = 12) and EdCa_V β 1 (V_{i1/2} = -56.76 \pm 3.18mV, n = 8), and EdCa_V β 2 (V_{i1/2} = -18.84 \pm 8.00mV, n = 5 cells). Data represented as mean \pm sem.
- 969 E) Genomic alignment of *Exaiptasia* β subunit isoforms showed that alternative splicing of the N-terminus 970 region was associated with distinct inactivation: Ca_V β 1 (long N-term) had low-voltage steady-state 971 inactivation similar to *Nematostella*, while Ca_V β 2 (short N-term) exhibited more depolarized steady-state 972 inactivation, matching its mammalian orthologue. Genomic loci listed above sequence. 973
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976 Figure 4—figure supplement 1. Transcriptomic and molecular analyses of *Exaiptasia* β subunit isoforms.

- 977A) mRNA expression (transcripts per million, TPM) of voltage-gated calcium (Ca_V) channel α and β subunits978in *Exaiptasia* tentacle (nematocyte abundant, blue), body (nematocyte non-abundant, red), bleached (minimal979symbionts) tentacle (light blue), bleached body (light red) tissues. The Ca_V α subunit was identified by980homology to the sequence of the cnidarian Ca_V2.1 homolog found enriched in *Nematostella* nematocyte-rich981tissues (Weir et al., 2020). NompC, the putative mechanoreceptor in *Nematostella* nematocytes (Schüler et982al., 2015; Weir et al., 2020), was also detected in *Exaiptasia* tentacles.
 - B) Representative plots of fluorescent amplitude across event number (droplet events) from amplification of unique regions of EdCa_vβ1 (Ch1, *Top*) and EdCa_vβ2 (Ch2, *Bottom*) sequences using droplet digital PCR (ddPCR, Bio-Rad Laboratories). Individual lanes correspond to tentacle RNA, body RNA, acontia RNA, and no template control (NTC). Blue and green points indicate positive PCR droplets after thresholding and gray points indicate negative droplets.
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991 Figure 5. Cnidarian Ca_v β subunit N-termini confer unique inactivation properties.

- C) Voltage-gated currents from heterologously expressed Ca_v channels with *Nematostella*-rat chimeric β subunits demonstrate that the *Nematostella* N-terminus is sufficient to drive inactivation at negative voltages. Currents shown in response to 10 mV voltage pulses following 1 s pre-pulses to -130 mV (max current, black), -50 mV (colored), or 0 mV (inactivated, no current, black). Scale bars = 100pA, 50ms.
- 996 D) Diagram of Ca_V *Nematostella*-rat β subunit domain swaps and resulting V_{i1/2} values. The *Nematostella* β 997 subunit N-terminus is required and sufficient for uniquely hyperpolarized Ca_V inactivation properties (p < 998 0.001 for average V_{i1/2} values across mutant beta subunits, one-way ANOVA with post-hoc Tukey test, n = 999 2-8 cells).
 - E) Phylogenetic tree of β subunit sequences obtained from several species of cnidarians. Abbreviations of species: Nve, *Nematostella vectensis*; Ed, *Exaiptasia diaphana*; Cc, *Cyanea capillata* (jellyfish); Pp, *Physalia physalis* (siphonophore); Ch, *Clytia hemisphaerica* (jellyfish); Cx, *Cassiopea xamachana* (jellyfish); r, *Rattus norvegicus*.
- 1004 F) *Top*: Percentage of identity between amino acid sequences across β subunit protein domains for NveCa_v β , 1005 EdCa_v β 1, EdCa_v β 2, CcCa_v β , PpCa_v β , ChCa_v β , CxCa_v β 2, rCa_v β 2. *Bottom*: Fraction of identity of amino 1006 acids across sites of the β subunit protein. Cnidarian Ca_v β N-termini shift depolarized, weak voltage-1007 dependent inactivation of Ca_v channels containing EdCa_v β 2 to more negative voltages. Voltage-dependent

1008	inactivation (V _{i1/2}) of heterologously-expressed Ca _v s with WT EdCa _v β 2, β subunits from the indicated
1009	cnidarians, and chimeras with their N-termini on EdCa _V $\beta 2$ (p < 0.0001 for average V _{i1/2} values with
1010	multiple comparisons against WT EdCavB2 mean, one-way ANOVA with Bartlett's test and post-hoc
1011	Tukey test, $n = 4-9$ cells). Data represented as mean \pm sem.



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Figure 5—figure supplement 1. Voltage-dependent activation of Ca_v channels is conserved across cnidarian β subunits.

1017 A) *Top*: Voltage-gated currents from heterologously-expressed chimeric Cavs with the indicated β subunits elicited by voltage pulses to -120mV (no current, black) and 0mV (colored). Abbreviations of species: Nve, *Nematostella vectensis*; Ed, *Exaiptasia diaphana*; Cc, *Cyanea capillata* (jellyfish); Pp, *Physalia physalis* (siphonophore); Ch, *Clytia hemisphaerica* (jellyfish); Cx, *Cassiopea xamachana* (jellyfish); r, *Rattus norvegicus. Bottom*: Voltage-gated currents elicited by a maximally activating voltage pulse following 1 s pre-pulses to -110 mV (max current, black), -50 mV (colored), or 20 mV (inactivated, no current, black).
 1023 Scalebars = 100pA, 50ms.

1024B) Activation and inactivation curves for heterologously-expressed chimeric Cavs with different β subunits.1025Activation: $rCa_V\beta 2 V_{a1/2} = -19.76 \pm 1.16mV$, n = 12; NveCa_Vβ $V_{a1/2} = -23.07 \pm 1.16mV$, n = 5; EdCa_Vβ11026 $V_{a1/2} = -18.27 \pm 1.08mV$, n = 8; EdCa_Vβ2 $V_{a1/2} = -14.22 \pm 1.46mV$, n = 5; CcCa_Vβ $V_{a1/2} = -18.47 \pm 1.59mV$,

- 1027 n = 6; $CxCa_V\beta V_{a1/2} = -28.89 \pm 1.54mV$, n = 15; $PpCa_V\beta V_{a1/2} = -15.29 \pm 1.23mV$, n = 10; $ChCa_V\beta V_{a1/$
- 1028 $10.30 \pm 1.04 \text{mV}, n = 12. \text{ rCav}\beta 2 \text{ V}_{i1/2} = -2.98 \pm 13.51 \text{mV}, n = 12; \text{ NveCav}\beta \text{ V}_{i1/2} = -68.93 \pm 1.53 \text{mV}, n = 5;$
- 1029 $EdCa_{V}\beta 1 V_{i1/2} = -56.76 \pm 3.18 \text{mV}, n = 8; EdCa_{V}\beta 2 V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ subunit } V_{i1/2} = -18.84 \pm 8.00 \text{mV}, n = 5; CcCa_{V}\beta \text{ su$
- $1030 \qquad \qquad 47.81 \pm 5.57 \text{mV}, \text{n} = 6; \text{CxCa}_{\text{V}}\beta \text{ V}_{\text{i}1/2} = -87.75 \pm 1.72 \text{mV}, \text{n} = 15; \text{PpCa}_{\text{V}}\beta \text{ V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{n} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -99.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -90.80 \pm 0.92 \text{mV}, \text{m} = 10; \text{m} \text{V}_{\text{i}1/2} = -90.80 \text{m} \text{V$
- 1031 ChCa_V β V_{i1/2} = -70.25 ± 4.67mV, n = 12 cells.
- 1032 C) Diagram of $Ca_V \beta$ subunit domain swaps and the length of the N-terminus swapped in amino acids.
- 1033 **D)** Cnidarian Ca_v β N-termini do not greatly affect voltage-dependent activation of Ca_v channels containing
- 1034 EdCav β 2. Voltage-dependent activation (V_{a1/2}) of heterologously-expressed Cavs with WT EdCav β 2, β
- 1035 subunits from the indicated cnidarians, and chimeras with their N-termini on EdCa_V β 2, p = 0.5830 for
- 1036 average $V_{i1/2}$ values across mutant beta subunits, one-way ANOVA with Bartlett's test and post-hoc Tukey
- 1037 test, n = 4-7 cells. Data represented as mean \pm sem.

1038 Figure 5—supplement table 1: Wild type and Chimeric $Ca_v\beta$ amino acid sequences.

Protein name	Amino Acid Sequence
Exaiptasia	MAQDFALSNRDIELDSLEHDSTGSSTPSEIQRWHMYSDRSGRVVCKDSEPAYRASD
diaphana	TSSVDEDKETSRRELERRAWEALQAARSKPVAFAVRTNIAYEGSEDDDSPVHGAA
Ca _v β1	VSFNVKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPSKLKSLQQVGPATGGRPV
$(EdCa_V\beta 1)$	RGSSKTVFHFNDMVNQAQSPTNTSPSRHSSASVDAENGMEYNEEEQHSPTSPTSKT
	STLPRSASGNTVTSQSAPGQQGKSKKAFFKKQEQLPPYDVVPSMRPIVLVGPSLKG
	YEVTDMMQKALFDYMKHQFSGRVLISRVTSDISLAKRSNLANPSKRNIIERSNSKN
	SGLAEVQQEIERIFELSRGLNLVVLDCDTVNHPTQLAKTSLAPLVVYVKISAPKVLQ
	RLIKTRGKTQSRALNVQLVAAEKLAQCSEDLYDLILDETQLQDACHHLGEFLESY
	WRATHPPNQPGSRPPNMQQSTPQYNVIEAGERPSVYL
Exaiptasia	MGNTDSVQSFTKDSEPAYRASDTSSVDEDKETSRRELERRAWEALQAARSKPVAF
diaphana	AVRTNIAYEGSEDDDSPVHGAAVSFNVKDFLHVKEKFNDDWWIGRVVKEGCDIG
Ca _v β2	FIPTPSKLKSLQQVGPATGGRPVRGSSKTVFHFNDMVNQAQSPTNTSPSRHSSASV
$(EdCa_V\beta 2)$	VDAENGMEYNEEEQHSPTSPTSKTSTLPRSASGNTVTSQSAPGQQGKSKKAFFKKQ
	EQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALFDYMKHQFSGRVLISRVTSDI
	SLAKRSNLANPSKRNIIERSNSKNSGLAEVQQEIERIFELSRGLNLVVLDCDTVNHPT
	QLAKTSLAPLVVYVKISAPKVLQRLIKTRGKTQSRALNVQLVAAEKLAQCSEDLY
	DLILDETQLQDACHHLGEFLESYWRATHPPNQPGSRPPNMQQSTPQYNVIEAGERP
	SVYL
Cyanea	MWFGTKKSKDSERRKRQPIDVYREQALSVNPAYIWGDDLDSRKTSGTSSEYGEDD
Capillata	IEQIRVQALEQLAAARVKPVAFAMRANYGYNGAEDDDSPIHGMALSFEPKDFLHI
Ca _v β	KEKFNNDWLIGRVVREGCDIGFIPSPSKLESLRLSGLAGRKMRQSSTSSNLHLQDAF
$(CcCa_V\beta)$	SASSPSEDRQNSFDDESLPPSSPVKSVNPGVIGQPNSKTAKKGIFKKNDSLPPYDVV
	PSMRPVIFVGPSLKGYEVTDMMQKALFDYLKHRFQGRIVITRVTADISTAKKSTIQ
	NLAKKPIIKERGATQASQEVNQEIERIFELCRNLQLVVLDSYTVNYPAQVAKTSLAP
	IIVYIKISSPKVLTRLVKSRGKSQSKNLNVQLVAAVKLGQCSEDMYDVVLDETQLE
	DACEHLGEFLEAYWRAAHPSQSNFGAAGAPGSFTANGQPVVVNYNSMDPFSAQS
Physalia	MV1ASYNVPLDN1SA1HSFNYPHAFLL1HSSCSYHSNEGFINSS1EVDIVDENDFKP
physalis Ca _v p	LFEGNSNEPHCQKKVISFSSLLDNVVAPIWYFFEMGDEFDSKKISGISSEYGEEDVE
(PpCa _v p)	ALKVQALEQLAAAASKPVAFAVKANYGYNGSEDEDCPVNGMAVSFEAKDCLHIK
	VKFNNDWWIGKVVKEGHDIGFIPSASKLDNIKQSGISGKLKLKQS51S5NMINLEDQ
	SQPLSKEQDNKSPSEEKGISFDDDSPASPLKNPSGSSLIANNNNNNSNIASNVNNSQ
	PKUKKUIFKKSENLPPYDVVPSMKPIIFVUPSLKUYEVOOEIEDIEELOPSMOLV
	VLDCESINHPSQVANISLAPIIAWIKIASPNVLIKLIKSKUKSQINHLNFQLVAAENL
	COSIGNVNGCGOVNGTDODHI DTAOV
Cassionaa	
Cassiopea	M = V = V = V = V = V = V = V = V = V =
C_{2} B	
Cavp	
(CACavp)	DVVPSMRPIII VGPSI KGYFVTDMMOK AI EDEI KHDEDGDIGITDVTADIGI AKDGV
	I NNDSKHIIJERSNTRSSI AEVOSEJERIJELARTI OJ VAL DADTINHDAOJ SKTSLAR
	IVVIKITSPKVI ORI IKSRGKSOSKHI NVOIAASEKI AOODDEMEDIII DENOI EDAO
	FHI Δ FYI FΔ YWK Δ THPPSSTPDNDI I NRTM Δ ΤΔ ΔΙ Δ Δ CDΔ DVCNI ΛCDVI Δ CCDΛ
	PI DRATGEHASVHEYPGEI GOPPGI YPSNHPPGRAGTI RAI SRODTEDADTOGON
	SAYTEPGDSCVDMFTDPSEGPGDPAGGGTPPAROGSWEFFEDVFFEMTDNRNR
	GRNK ARYCAEGGGPVLGRNKNELEGWGOGVYIR

Clytia	MMHGSOTEPAISSMTSERNHKNI, SHGSRTSINSORSTNKK VNSHVSEDESTA APSS
hemisphaerica	KKPGALSA AGGKKSVDDNESSSVI OTVEALRWOKKA AOKKKKPDDEOOMYMHS
Cauß	MSGALGSUGDEEDGRKTSGTSSEVGDGEDLEALRU ALEKU OAARTRPVAEAVRA
$(ChCa_{\nu}\beta)$	NYGYNGSEDDDSPVHGMAVSEEKDDCI HIKDKENKDWWIGRVVKEGHNIGEVPS
(ChCayp)	PDKI ESIROSGVSGKI KMROSSTSSNMNI HDDPONORSPI GEAGGNNSEDDETVN
	COVENING SOLUTION SOLUTIAN SOLUTIAN SOLUTION SOLUTION SOLUTIAN S
	SI VKIVSTESINI INININI INSENAQKOKKOI KKINEQEHI I IVII SIVIKI III VOI SE VCVEVTDMMOVAI EDVI VIDECEDIIETDVNADICI AVDONI NNONDODNEDVVCNI
	COACLAEVOEEVNDIEELCDSSOLVULDCDTINNDSOURTSLADUVAIVIASDVULT
	DUKADLAE VQEE VINKIFELUKSSQL V VLDUDI IININPSQVIK I SLAPI I VAINIASPK VLI DUKADUKADVKIH NIOMIA ADKI SOCNEEMEDVVI DENOLEDA CEHL CEELEAV
	KLIKSKUKINŲ V KILINIŲ IVIIAADKLSŲ CINELIVIED V V LDEINŲ LEDACEILUEFLEA I WIDA AVIDOA OECI, ISOENIOCEUNOCODNICA OVNOVOTDODNI, DTAOV
Norman de la de 11 m	
Nemalosiella	MEPEPGLSEQUIELDSLEQV51A55FH5DIQKH1NDGKEA5KFIGADDFNKD5DPA1
vectensis	KASDISSIEEDKEISKKELEKKAWDALQAAKSKPVAFAVKINLKIDUSEDDDSPVH
cacnb2.1	GAAVSFEAKDFLHVKEKFNDDWWIGKVVKEGCDIGFIPIPSKLKSLQQIGGIASGK
(ΝνΕβ)	GMRNSKRDVFQFDMVNQAQSP1N1SPSRHSS1SVDAENGVEYDDDQQSP1SP1NK
	TLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLK
	GYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTNMSNPGKQTIMERTKN
	KNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVYIKIAAPKV
	LQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEETQLDDACEHLGEFLES
	YWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVYL
Rat cacnb2a	MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK
(Rat β)	AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL
	VKEGCEIGFIPSPVKLENMRLQHEQRAKQGKFYSSKSGGNSSSSLGDIVPSSRKSTPP
	SSAIDIDATGLDAEENDIPANHRSPKPSANSVTSPHSKEKRMPFFKKTEHTPPYDVV
	PSMRPVVLVGPSLKGYEVTDMMQKALFDFLKHRFEGRISITRVTADISLAKRSVLN
	NPSKHAIIERSNTRSSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIIV
	YVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDA
	CEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTD
	RSAPRSASQAEEEPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRD
	SAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDH
	NECSKQRSRHKSKDRYCDKEGEVISKRRSEAGEWNRDVYIRQ
Rat β with	MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK
NVE Hook	AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL
	VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS
	RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG
	LFKKQEQLPPYDVVPSMRPVVLVGPSLKGYEVTDMMQKALFDFLKHRFEGRISITR
	VTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIFELARTLQLVVLDADTIN
	HPAOLSKTSLAPIIVYVKISSPKVLORLIKSRGKSOAKHLNVOMVAADKLAOCPPO
	ESFDVILDENOLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTL
	ASNSOGSOGDORTDRSAPRSASOAEEEPCLEPVKKSOHRSSSATHONHRSGTGRGL
	SROETFDSETOESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREP
	RHRTRDMGRDODHNECSKORSRHKSKDRYCDKEGEVISKRRSEAGEWNRDVYIR
	0
NVE β with	NEPEPGL SEODIEL DSLEOVSTASSFHSDIOR HYNDGREASRFIGADD FNRDSDPAY
Rat Hook	RASDTSSIEEDRETSRRELERRAWDALOAARSKPVAFAVRTNLRYDGSEDDDSPV
	HGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLOHEOR
	AKOGKFYSSKSGGNSSSSI GDIVPSSRKSTPPSSAIDIDATGI DAFENDIPANHRSPK
	PSANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPIVI VGPSI KGYFVTDMMOK
	ALL DEMKHRESGRVI LARVTSDISL AKRTNMSNPGKOTIMERTKNKNTGI AFVOO
	FIERIFEI ARGI NI VVI DOFTVNIHOTOL AKTELADMIVVIKIAADKVI ODI IKTOOKE
	OSPNI SIOLVA AEKI AOCSEDMVDI VI FETOL DDACEHI CEELESVWD ATUDDNO
	PGSRPPNVOPSNSTPOVNVIEGGERPSVVI
Pat B with	
NVE CV	ΙΊΙ ΥΥΟΌΟΕΥΠΙΝΝΝΥΝΥΘΙΟΘΑΡΟΤΙΟΝΕΟΡΥΘΕΕΡΙΝΕΑΥΚΚΕΑΕΚΥΑΥΑU ΑΚΤΚΟΥΛΕΛΥΡΤΝΙΛΡΥΘΑΛΟΕΡΡΙΟΙΟΥΡΩΜΑΙΩΕΕΛΥΡΕΙ ΠΥΛΕΚΕΝΙΝΡΙΔΙΩΩΟΙ
INVEUK	AT ITT VAFA VT IN VT I SAAQEDD V F V POMAISFEATDFLH V KEKFINND W WIGRL

domain VKEQCEIGFTISTVALEDNMLQHEQKARQUERY TSAKSOGNSSSSLDJUYSSKKS JF PSSADIDATGLDAEENDIFANIRSYKPSANSVTSPISKEKARMPFFKKTEHTPYDV VPSMRPIVLVGPSLKGYEYTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTN MSNPCKQTIMERTKNKNTGLAEVQQEIFRIETI-ARGLNI.VVLDCFTVNHPTQLAKT SLAPMIVYIKIAAPKVLQRLIKTRGKSOSRILSIQLVAAEKLAQCSEDMVDLVLEET QLDDACEHLGEFLSSVWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVL MEPEPGLSEQDIELDSLEQVSTASSTHSDIQENTYNDGREASRFIGADDFNRDSDPAY Rat GK RASDTSSIEEDRETSRRELERRAWDAI.QAARSKPVAFAVRTNLRYDGSEDDSPV domain HGAAVSFEAKDFLHVKEKFYDDWWGRVVKEGCDIGFTDYFNKLKSLQQIGGTASG RGMRNSKRDVFQFDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTN KTLPRSASGTTVSSQFGTATGTQGFKKGLFKKGCIFKWCDZBACHLADYLEAY KSGEGSQAHLLNVQWAADKLAQCPPQESTPULDENQLEACEHLADYLEAY WKATHPPSSNI.PNPLI.SRTLATSTLPI.SPTLASNSQGSQGDQTDRSAPRSASQAEF EPCLEPVKKSQHRSSATHQNIRSGTGGGLSAGGGETPSSETGSSRDSAYVEPKEDYS HEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHK SKDRYCDKEGFUTSSKLSLQQIGGTEPTSSTDSDSVEVEDDSWVIRQ Rat 5' on NVE β MQCCGLVHRRRVKVSGSADSTSRSPSDSDVSIEEDREAVRREAERQAQAQLEK NVE β MQCCGLVHRRRVKVSGSADSTSRSPSDSDVSIEEDREAVRREAERQAQAQLEK NVE β AKTRPVAFAVRTNLRYDGSBDDSPYBRINKTITPSSASGTTVSSQCTATGTQGKFKKG LFKKQEQLPPYDVVSMRPVLVGPSLKGVEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNNSNPGQTTMERTKNNNTGLAEVQQEERFFELARGLNLVVLD CCCLIVHRRRVKYGGADSTSRPSDSDVSIEEDREAVRR	1 '	VWEGGEIGEIDEDWWLENNMLOUEODAWGGWCGGWGGGGGGGGGGGGGGGGGGGGGGG
PSSAIDIDATGI DALE-NIJPANIHKSPKPSANSV ISPHSKERKMPT-KK THTPPT/DJAKT VPSMRPTVLVGPSLKQVEYTDMMQKALLDEMKIRFSGRVLLARVTSDISLAKKIN MSNPCKQTIMERTKNKNTGLAEVQQEIERIFELARGI.NLVVLDCETVNHPTQLAKT SLAPMIVYUKIKALRVU/QRLIKTRGKSQSRNLSJOLVAAEKLAQCSEDMYDLVLEET QLDDACEHLGFELSSYWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVYL NVF β with MEPPFQI SEQDIELDS LQVSTASSHISDIQRHYNDGREASRFIGADDFNNDSDPAY Rat GK RASDTSSIEEDRETSRKELERRAWDALQAARSKYVAFAVRTNLRYDGSEDDDSPV domain HGAAVSFEADDH JVKEKFNDDWWGRVVKEGCDIGFIPTPSKLKSLQUGGTASG RGMKNSKRDVFQFDMVNQQQSPTNTSPSRHSTSVDAENGVEYDDDQQSPTSPTN KTLPRSASGTVSSOPGTATGTQGKPKKGLFKKQEQLPYDVVPSMRPVVLVGPSL KGYFVTDMMQKALFDFLARTQCVLDADTINIPAQLSKTSLAPHVYVKISSPKVLQRL KSSLAEVOSEERRIFELARTLQLVVLDADTINIPAQLSKTSLAPHVYVKISSPKVLQRL KSSGRSQAKHLNVQMVAADKLAQCPPOFSFDVILDFSETQESRDSAYVEPKEDYS HEHVDRYVPHREHNIREESRISSNGHRIRREPRIHTRDMGRQDDHNCCSKQRSRHK SKDRVCDKFGEVISKRSPAGEWNDVYRQ WKATHFPSSNLPPPLLSRTLATSTLYLDSLASGGSGODORDRSAPRSASQAEE FPCLFPVKKSQHRSSSATHQNHRSGTGRGI SRQETFDSETQESRDSAYVEPKEDYS HEHVDRYVPHREHNIREESRNGHRINDVYRQ Rat 5' on MQCCGLVFRRVVSYGSADSYTSRPSDSDVSLEEDRAVRREAERQQQAQLEK KATKPVAFAVTRUKYDOSEDDDSRLSEQAKGRNKKDVFQFDMVNQAQSPTNTSPS RAtSTSVDAENGVEYDDDQQSPTSTINKTLPRSASGTTVSSQPGTATGTQGKFKG L	domain	VKEGCEIGFIPSPVKLENMRLQHEQKAKQGKFYSSKSGGNSSSSLGDIVPSSKKSIP
VPSMRPIVLVGPSLKGYEVTDMMQKALLDEMKHRESGRVLLARVTSDISLAKRTN MSNPGKQTIMERTKNKNTGLAEVQQEIERHELARGLNLVVLDCETVNHPTQLAKT SLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMVDLVLEET QLDDACEHLGEFLESYWRATHIPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVL MEPEFGLSEQDIELDSLEQVSTASSTHSDIQCHYNDGREASRFIGADDFNRDSDPAY Rat GK RASDTSSIEEDRETSRRELERAWDALQAARSKPVAFAVRTNLRYDGGEGRFSVL domain MEPEFGLSEQDIELDSLEQVSTASSTHSDIQCHYNDGREASRFIGADDFNRDSDPAY RATGK RGMRNSKRDVQFDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTN KTLPRSASGTTVSSQPGTATGTQGRPKKGLEKKQEQLPYDVVPSMRPVLVGPSL KGYEVTDMMQKALPDFLKHRPEGRISTIRVTADISLAKRSVLNPSKHAIERSNTR SSLAEVQSEIRHFLARTIQLVVLDADTINNPAQLSKTSLAPIVVYVSSRSVLQRL KSRGKSQAKHLNVQMVAADKLAQCPPQESPUDLEDACEHLADYLEAY WKATHIPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEE EPCLFPVKKSQHKSSSATHQNHRSGTGRGLSRQETEDSETQESRDSAYVPKEDYS HEHVDRYVPHREHNIREESHSSNCHRHREPRHRTRDMGRDQHNECSKQRSRHK SKDRYCDKEGEVISKRRSEAGEWNRDYYIRQ Rat 5' on MQCCGLVHRRRVRYSGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK AKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFFAKDFLHVKEFKNDDWWIGRV VKEGCDIGFPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTINKTLPRSASGTVTSSQPGTATGTQGKFKKG LFKKQEQLPPDVVPSMRPIVLVGPSLKGVETDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKLAAPKVLQRLIKTRGKSQSRNLSIQLVAAELAQ CSEDMYDLVLEETQLDDACEHLGFFLESYWRATHPPNQFGSRPFNVQPSNSTPQY VVIEGGRFPSVYL Rat 5' + SH3 MQCCGLVHRRRVVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK AKTKPVAFAVRTNYRSAAQEDDYPVPGMAISEFAKDFLHVKEKFNDDWWIGRL VKEGCEGIFIPSFKLKSLQQUGGTASGRGMRNSKRDVVQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTINKTLPRSASGTTVSSQCFTATGTQGKFKKG LFKKQEQLPPPDVVPSMRPVLVQFSLKGPKVDMASRDVAQAQELFMVQASSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQCFTATGTQGKFKKG LFKKKQEQLPPPDVVPSMRPVLVQFSLKGPKVDMASRDVQVPSNSTPQY VVIEGGRFPSVYL NVE β <td></td> <td>PSSAIDIDATGLDAEENDIPANHRSPKPSANSVTSPHSKEKRMPFFKKTEHTPPYDV</td>		PSSAIDIDATGLDAEENDIPANHRSPKPSANSVTSPHSKEKRMPFFKKTEHTPPYDV
MSNPGKQTIMERTKNIKNTGLAE/QQEIERIFELARGLNI.VVLDCETVNHPTQLAKT SLAPMIVYTKIAAPKVLQRI.KTRGKSQSRNI.SIQLVAAEKLAQCSEDMYDLVLEET QLDDACEHLGEFLESYWRATHPENQPGSRPPNVQPSNSTFQYNVUEGEDMYDLVLEET MFPEPGLSFQDIELDSI.EQVSTASSFHSDIQRHYNDGRASRFIGADDPRRDSDPAY Rat GK RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPV domain HGFAVSFEAKDFLHVKEKFNDDWWIGRVKEGCDIGFIPTPSKLKSLQQIGGTASG RGMRNSRDVFQFDDWVQAQSPTNTSPSRHSTSVDAENGVEYDDDQQSFTSPTN KTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPVVLVGPSL KGYEVTDMMQKALFPFLKHRFFGRISITRVTADISTSVDAENGVEYDDDQQSFTSPTN KTLPRSASGTVVSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPVVLVGPSL KGYEVTDMMQKALFPFLKHRFFGRISITRVTADISTSVDAENGVEYDDQQSFTSPTN KTLPRSASGTVVSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPVVLVGPSL KGYEVTDMMQKALFPFLKHRTRDVTRVDSSGSQGQDQTDRSAPRSASQAEE EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYS HEHVDRYVPHREINHRESSISSAGHRINEPRHRTRDMGRDQDINECSKQRSRISSQAEE EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETTMSDQGRTDRSAPRSASQAEE FVCLEFVKSQHRSSSATHQNHRSGTGRGLSRQETTVSDQGTATGTQGCKPKKQ KKGCLPPYDVPYSMRPVLVGPSLKGYEVTDMMQKALDFMKHRFGRVLIA NVE β MQCCGLVHRRWRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK NVE β MCCGGLPPTYVPSMRPVLVGPSLKGYEVTDMMQKALDFMKHRFGRVLIA NVE β MQCCGLVHRRWRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK NVE β MCCGGLVHRRWRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK <td></td> <td>VPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTN</td>		VPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTN
SLAPMIVYIKIAAPKVLQRLIKITRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEET QLDDACEHLGEFLESVWRATHPRNQPGSRPPNVQPNNVPGSRFPQYNVIEGGERPSVYL NVE β with MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY Rat GK RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPV IGANVSFEAKDFLHVKEKFADDWWIGRVVKEGCDIGFIPTPSKLKSLQQGGTASG RGMRNSKRDVPQFDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQSSFTSPTN KTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPVVLVGPSI. KGYEVTDMMQKALFDFLKRFEGRISTRVTADISLAKRSVLNNPSKHAITERSNTR SSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPITYVKISSPKVLQRL IKSRGKSQAKHLNVQWVAADKLAQCPPQESPDVILDENQLEDACEHLASVVEPKEDYS HEHVDRYVPHREHNHRESSISSNGHRHREPRHRTRDMGRQDDINECSKQRSRHK SKDRYCDKEGEVISKRRSEAGEWNRDYVIRQ Rat 5' on MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDRFAVRREAFRQAQAQLEK NVE β RKKEPVAFAVRTNLRYDGSEDDDSPTINKTLPRSASGTTVSSQPGTATGTQGRPKKG LFKKQFQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RYTSDISLAKRTMNSNPCKQTIMERTKNNKTGLAEVQQEIERIFFLARGLNLVLQ CETVNHPTQLAKTSLAPMIVYIKAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CEDMYDLVDLEETQLDDACEHLGEFLESYWAATHPNNQPGSRPNVQPSNSTPQY NVE β RATSTSVDAENGVEYDDDQQSPTSPINKTLPRSASGTTVSSQPGTATGTQGRPKKG <td></td> <td>MSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKT</td>		MSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKT
QLDDACEHLGEFLESYWRATHPPNQPGSRPFNVQPSNSTPQYNVLGGERPSVYL NVE β with ME9PEQI SEQUELDSI LEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY Rat GK RASDTSSIEEDRETSRELERRAWDALQAARSKPVAFAVKTNLRYDGSEDDDSPV domain HGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPSKLSQQIGGTASG RGMRNSRDVFQEDDWVQAQSPTNTSPSRHSTSVDAENGVEYDDDQQSFTSPTN KTLPSASGTVSSQPGTATGTQGKPKKGLFKKQEQI PPYDVVPSMRPVVLVGPSI. KGVEVTDMMQKALFPFLKRFEGRISTRVTADDISLAKKSVLNNPSKHAIIERSNTR SSLAEVQSEIERIFELARTLQUVVLDADTINHPAQLSKTSLAPINYVKISSPKVLQRL KSRGKSQAKHLNVQMVAADKLAQCPPQESFDVLDENQLEDACEHLADYLEAY WKATHPYSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGQQRTDRSARPSASQAEE EPCLEPVKKSQHRSSATHQNHRSGTGRGLSRQETFDSETDESKDSAYVEPKEDYS HEHVDRYVPHREINNRESENSSNGHRHREPRHRTRDMGRDQDINECSKQRSRH SDRYCDKEGEVISKRSFAGEWRDYYRQ MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK		SLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEET
ΝVE β with Rat GK MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RATGK Rat GK RASDTSSIEEDRTSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPV GAAVSFEAKDFI-HVKEKFNDDWUGRVVKGCDIGFIPTSKI.KSI.QQIGGTASG RGMRNSKRDVFQFDMVNQAQSPTNTSPSRHSSTSVDAENGVFYDDDQQSPTSPTN KTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPVVLVGPSI. KGYEVIDMMQKALFDFLKHRFEGRISITRVTADISLAKKSVLNNPSKHAILERSNTR SSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRI. IKSRGKSQAKHI.NVQWVAADKI.AQCPPQESFDVILDENQIEDACTEHLAPIYLEAY WKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEE EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYS HEHVDBYVPHREHNHREESHSSNGHRHEPFHRTRDMGRDQDNNECSKQRSRHK SKDRYCDKEGEVISKRSEAGEWNRDYTRQ Rat 5' on NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDDSDVSLEEDREAVRREAERQAQAQLEK AXTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKNDQWIGRV VKEGCDIGFIPTSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQRSTLJQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERSYYI. Rat 5' + SH3 MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRI. VKEGCUIGHPTPNUVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEERHFELARGLNLVVLD CETVNPTPLQLATSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERSYYI. NVE 5' HSH35 VDAENGVEYDDDQQSPTSPTINKTLPRSASGTTVSSQGRTATGTQGKPKKG LFKKQEQLPPTVDVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEERHFELARGLNLVVLD CETVNPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERSYYL NVE 5' + SH3 on Rat β MFEPEGLSEQDIFLDSLEQVSTASS		QLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVYL
Rat GK RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPV domain RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPV domain RGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGHPTTSKLKSUQQIGGTASG RGMRNSRDVYEDDWVQAQSTTNISPSRHSTSVDAENGVEYDDDQQSFTSPTN KTPRSASCTTVSSOPGTATGTQGKPKKGLFKKQEQLPPYDVVPSNRPVVLVGPSL KGYEVTDMMQKALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTR SSLÄEVQSEIERIFELARTLQIVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRI. KSRGKSQAKHLNVQMVAADKLAQCPPQESPDVLDENQLEDACEHADYLEAY WKATHPPSSNLPPNI JSRTLATSTLPI.SPTLASNSQGSQGDQRTDRSAPSSASQAFE EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYS HEHVDRYVPHRENNHRESHSSNCHRHEPPHRTRDMGRDQDINECSKQESRH NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK NVE β MQCCGLVPYDDVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLLA RvTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKLAAPKVLQRLIKTRGKSQSRNLSQLVAAEKLAQ Rat 5' + SH3 On NVE β MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK ATTKPVAFAVRTNNRYSAQEDDVPVCMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTTTSPS Rat 5' + SH3 MQCCGLVHRRRVNSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK ATT	NVE ß with	MEPEPGL SEODIEL DSLEOVSTASSFHSDIOR HYNDGREASRFIGADDENRDSDPAY
Mathon High Add Strandbard domain HGAAVSFEAKDFLHVKEKENDDWUGRVVKEGCDIGFIPTPSKLKSLQQIGGTASG RGMRNSKRDVFQFDMVNQAQSPTNTSPSRHSSTSVDAENGVVDDDQQSPTSPTN KTLPRASGTTVSSQPGTATGTOGKPKKGLFKKO5QLPPTDVVDPSMRPVUVGPSL KGYEVTDMMQKALFDFLKHRFEGRISTRVTADISLAKRSVLNNPSKHAIIERSNTR SSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIUVYKISSPKVLQRL IKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADVLEAY WKATHPPSSNLPNPLISRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAFE EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYS HEHVDRYVPHREINNHRESNSCHRHREPRHRTRDMGRDQDHNECSKQRSRHK SKDRYCDKEGEVISKRRSEAGEWNRDVYIRQ Rat 5' on MQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK AKTKPVAFAVRTNLRYDGSEDDDSPVHGAVSFEAKDFLHVKEKFNDDWWIGRV VKEGCDIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFOFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGRQTIMERTKNKNTGLAEVQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYKIAAPKVLQRLIKTGKSQSSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVEGGEFISPSVL Rat 5' + SH3 MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK on NVE β NVE GGEIFPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTNFGLAEVQEHERIFELARGLNLVLD CETVNHPTQLAKTSLAPMIVYKIAAPKVLQRLIKTGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVEGGEFISSVLI NVE 5' + MEPEPGI SEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNKTSAAQEDDDPVP PGMAISEAADDFLHVKEKFNDDWWIGRUVKEGGCGIGFPSPKLENMRLHREPRFKVLJA SANSVTSPHSKEKRMIPFKKTEHTPDVDVPSRRPVLENMRLGHEQAK KQGKFYSSKSGGNSSSSLGDIVPSSRSSTPSSAJDIDATGLAAERDIPANRSSAQAEEPDY SANSVTSPHSKEKRMPFFKKTEHTPDVVVSSRSTPSSAJDIDATGLAACKSQAKHL NVWGMAADKLAQCPPQESEDVILDENQLEAACHLANVRSAQAEEPDOFPNH	Rat GK	RASDTSSIFFDRETSRREI FRRAWDAL OA ARSKPVAFAVRTNI RYDGSEDDDSPV
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SSLAEVQSEIERIFELARTLQUVVLDADTINHPAQUSKTSLAPIVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGQQRTDRSAPRSASQAEEEPCLEPVKKSQRRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRKKSKDRYCDKEGEVISKRSEAGEWNRDVYIRQRat 5' onMQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQQAQQLEKAKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPSKLKSLQUGGTASGRGMRNSKRDVFQEDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLKGVEVTDMMQKALLDFMKHRFSGRVLIARvTSDISLAKTTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVE βAKTKPVAFAVRTNVRYSAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTINTSPSRhtSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKTTNSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVVIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVEGGERPSVYLNVEGST+SMEPEPOLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPKVLENMRLQHEQAAKQCKFYSSKSGGRSSSSLGDVPSSKSVLDNTSKSKLAPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVXEKFNDDWWIGRLVKEGCEIGFIPSPVVLENMRLQHEQAAKQKKFYSSKSGGRGISSSSLGDVSSSSGQDQRTDRSAP		KGYEVIDMMQKALFDFLKHRFEGRISIIRVIADISLAKRSVLNNPSKHAIIERSNIR
IKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACHLADTLEAY WKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEE EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDVS HEHVDRYVPHREHNHRESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHK SKDRYCDKEGEVISKRRSEAGEWNRDVYIRQRat 5' on NVE βMQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRV VKEGCDIGFIPTPSKLSI.QQIGGTASGRGMRNSKRDVPQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKFKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVVIKIAAPKVLQRI.KTRGSQSRNI.SIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSV1LRat 5' + SH3 on NVE βMQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWVIGRL VKEGCEIGHPSPSKLKSLQQIGGTASGRGMRNSKRDVPQEDMVNQQSPTNTSPS RHSSTS VDAENGVEYDDDQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTLAKSLAPUVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTLAKSLAPUVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKGCGCEIGFPSPVVLENMRLQHEQRA KQGKFSSKSGGNSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKERMPFFKKTEHTPPVDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDELKHRFEGRISTRVTADISLAKRSVLNPSKHAIBENSTRSLAEVQSEIERF ELARTLQLVVLDADTINHPAQLSKTSLAPIUVYKISSPKVLLENMRLQHEQRA KQGKFYSSKSGGRSSSLGDIVPSSRKSTPNSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKERMPFFKKTEHTPPDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDELKHRFEGRISTRVTADISLAKRSVLNPSKHAIBENDFANRSKDRYCDKEGEV ISKRRSEGGEWNRDYYIRQNVE 5' on Rat βMEPEPGLSEQUELSDLEQVSTASSFHSD		SSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRL
WKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQDQDRTDRSAPRSASQAEE EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYS HEHVDRYVHREHNNREESHSSNGHRHREPRHRTDMGRDQDHNECSKQRSRHK SKDRYCDKEGEVISKRRSEAGEWNRDVYIRQRat 5' on NVE βMQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRV VKEGCDIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPVDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSNLSIQLVAAEKLAQ QSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSYVLRat 5' + SH3 on NVE βMQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNVRYSAQEDDVPVGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLETQLDDACEHLGEFLESYWRATHPPNQPGSRPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' + SH3 on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPV4FAVRTNVRYSAAQEDDVPY POMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSRSVLADDTINHPAQLSKTSLAPIVVLVGSSKVLQALDFDMHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALPDFLKHRFEGRISTIRVTADISLAKRSVLNNPSKHAIIERSNTRSLAEVQSEIERIF EAASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPY PRLLSRTLATTSLPLSPTLASNSQGSQDQRTDRSAPRSAQAEEEPCLEPVKKSQH NVEGSEIERIF EAASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPY NVIEGGERPSVYLNVE 5' on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRA		IKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAY
EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYS HEHVDRYVPHREHNIREESHSSNGHRHREPRHRTRDMGRDQDHNECSSQRSRHK SKDRYCDK5GCVISKRSEAGEWNRDVYIRQRat 5' on NVE βMQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRV VKEGCDIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSYYLRat 5' + SH3 on NVE βMQCCGLVHRRRVRVSYGSADSYTSRPSDDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNVRYSAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQUVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPNVQPSNSTPQY NVIEGGERPSYYLNVE 5' + SH3 on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRL VQWAAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSNLPGRSVRFSSAJDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISTRVTADISLAKRSVLNPSSAJDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISTRVTADISLAKRSVLNPSKAIDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPYDVVFSMRPVVLVRSSKQAEEEFIE ELARTLQLVVLDADTINHPAQLSKTSLAPINYKKISARVQRGRSQAEEFPCLEPVKKSQH NVLSGTGRJSSELDQUFSDSKSSQGQQQRTDRSAPRSAQAEEEPCLEPVKKSQH NVQMVAAADKLAQCPPQESFDVILDENVLENSKLQHEQKEGCOIGFIPTPVKLENMRLQHEQRAK COMPORDUFORMED M		WKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEE
HEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHK SKDRYCDKEGEVISKRRSEAGEWNRDVYIRQRat 5' onMQCCGLVHRRRVRSYGSADSYTSRFSDSDSVLEEDREAVRREAERQAQAQLEK NVE βNVE βAKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWVIGRV VKEGCDIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTINTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ (CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPNVQPSNSTPQY NVIEGGERPSVYLRat 5' + SH3 on NVE βMQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNVRYSAQEDDVPVGMAISFEAKDFLHVKEKFNNDWVIGRL VKEGCEIGFIPSPSKLLSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTINTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLETQLDDACEHLGEFLESYWRATHPPNQPGSRPNVPSNSTPQY NVIEGGERPSYYLNVE 5' + SH3 on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGFYSSKSGGNSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKERMPFFKKTEHTPPDVDVPSMRPVVLQPSLAGVEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAHIERSNTRSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYKKISSFKVLQRLIKSRGKSQAKHL NVQMAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGQQRTDRSAPKSAQAEEPCLEPVKKSQH HNREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYD		EPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYS
SKDR YCDKEGE VISKRRSEAGEWNRDVYIRQRat 5' onMQCCGL VHRRRVRVSYGSADSYTSRPSDSDVSLEEDREA VRREAERQAQAQLEKNVE βAKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVLRat 5' + SH3MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEKon NVE βAKTKPVAFAVRTNVRYSAAQEDDVPVGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQEDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNL/VLDCETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDL/LEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDENRDSDPAYSH3 on Rat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRAKQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKPSANSVTSPHSKEKMPFFKKTEHTPPYDVVPSMRPVLUGPSLKGYEVTDMMQKALFDFLKHRFFERFISISTRVTADISLAKRSVLNPSKHAIERSNTRSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIUVVKISSPKVLQRLIKSRGKSQAKHLNVQWAAADKLAQCPPQESFDVILDENQLEDACEHLADVLEAYWKATHPSSNLPNPLLSTILTS		HEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDODHNECSKORSRHK
Rat 5' onMQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEKNVE βAKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVYLRat 5' + SH3on NVE βMQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEKAKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVE 5' +SH3 on Rat βRASDTSSIEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPYPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRAKQGKFYSSKSGGNSSSLSGDIVPSSRKSTPPSSAIDIDATGLAAEENDIPANHRSFKPSANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQKALFDFLKHRFEGRISITRVTADISLAKRSVLNPSKHAIIERSNTRSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIUVYVKISSPKVLQRLIKSRGSQAKHLNVUEGGERPSVRIPNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYRat βMEPEPGLSEDRETSRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPVNVE 5' on		SKDRYCDKEGEVISKRRSEAGEWNRDVYIRO
NVE βAKTKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRV VKEGCDIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLRat 5' + SH3 on NVE βMQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK AKTKPVAFAVRTNVRYSAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTINMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' + SH3 on Rat βRASDTSSIEDDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSLGDIVPSSRKSTPPSSADIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAILRESNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQERSPSAVGERSNGGNSSAGAGNASKSCARSVEFVAFAVETNLRYDGSEDDDPAY RAt βNVE 5' on Rat βMEPEPGLSEQUELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVETNLRYDGSEDDDSPYH RASDTSSIEDDRETSRRELERRAWDALQAARSKPVAFAVETNLRYDGSEDDDSPYH RASDTSSIEDDRETSRRELERRAWDALQAARSKPVAFAVETNLRYDGSEDDDSPYH RASDTSSIEDDRETSRRELERRAWDALQAARSKPVAFAVETNLRYDGSEDDDSPYH RASDTSSIEDRETSRRELERRAWDALQAARSKPVAFAVETNLRYDGSEDD	Rat 5' on	MOCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAEROAOAOLEK
TWE βMATRA WARNER DUBDEDMIGAT VERTER ALL NUMBERVKEGC DIGFIPTPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVVIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLRat 5' + SH3 on NVE βMQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK AKTKPVAFAVRTNVRYSAAQEDDVPVFGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERSVYLNVE 5' + SH3 on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENNRLQHEQRA KQGKFYSSKSGGNSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPK SANSVTSPHSKERKMPFFKKTEHTPYDVVPSMRPVVLVGPSLKGKEVTDMMQK ALFDFLKHRFEGRISTRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQDRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEFKEDYSHEHVDRYPHRE HNHRESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' on Rat βMEPEPGLSEQUIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRLVKEGCDIDGPTPVKLENMRLQHEQRAK GAAVSFEAKDFLHVKEKFNDDWWIGRDWURGRCVDRAF UND UNDENTYC </td <td>NVE ß</td> <td>AKTKPVAFAVRTNI RVDGSEDDDSPVHGAAVSEFAKDEI HVKEKENDDWWIGRV</td>	NVE ß	AKTKPVAFAVRTNI RVDGSEDDDSPVHGAAVSEFAKDEI HVKEKENDDWWIGRV
NEBSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLRat 5' + SH3 on NVE βMQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK AKTKPVAFAVRTNVRYSAQEDDVPVFGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKFKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' + MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY SH3 on Rat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPKLENMRLQHEQRA KQGKFYSSKSGGNSSSSIGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSFKP SANSVTSPHSKERMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISTRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIVVVKISPSVLQRLIKSRGKSQAKL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLAFWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEFKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWRNDVYIRQNVE 5' on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFTPTVKLENMRLQHEQRAK GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFTPTVKLENMRLQHEQRAY CASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPHY GAAVSFEAKDFLHVKKEFNDDWWIGRVVKEGCDIGFTPTVKLENMRLQHEQRAY CONDAWINGRVVKEGCDIGFTPTVKLENMR	ПЛЕР	VKEGCDIGEIPTPSKI KSI OOIGGTASGPGMPNSKPDVEOEDMVNOAOSPTNTSPS
KHSSISVDAEMOVELDDDQQSFISFINKLEPKSAUTVSSQUTATOLQAEKKUALFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDEMKHRFSGRVLIARVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQCSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQYNVIEGGERPSVYLRat 5' + SH3MQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEKon NVE βAKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPSRHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKGLFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIARVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLDCETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQVVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYSH3 on Rat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRAKQGKFYSSKSGGNSSSLGDIVPSSRKSTPPSADIDATGLDAEENDIPANHRSPKPSANSVTSPHSKEKRMPFFKKTEHTPPYDVVSMRPV1LVGPSLKGYEVTDMMQKALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSNLPNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSNLPNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYRat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVKEGCDIGFIPTYKLENMRLQHEQRAKCWEVPREPOLSEQDIELDSLEQVTASSFHSDIQRHYNDGREASRFIG		
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RVTSDISLAKRTNMSNPGRQTIMERTIKNKNTGLAEVQQEIERIFELARGCNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLRat 5' + SH3MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' + SH3 on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGONSSSLGDIVPSSRKSTPPSSADIDIATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIUVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRESRNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEEV USKRRSEAGEWNRDVYIRQNVE 5' on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPH GAAVSFEAKDPINPVIRQNVE 5' on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPH GAAVSFEAKDGCUM000000000000000000000000000000000000		LFKKQEQLPPYDVVPSMKPIVLVGPSLKGYEVIDMMQKALLDFMKHKFSGKVLIA
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CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLRat 5' + SH3MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK on NVE βAKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKGCDUGGTIFIPVKLENMRLQHEQRAK QAKSFEAKDFLHVKEKFNDDWWIGRVVKGCDUGFIPTVKLENMRLQHEQRAK QAKSFEAKDFLHVKEKFNDDWWIGRVVKGCDUGFDIPVKLENMRLQHEQRAK QAKSFEAKDFLHVKEKFNDDWWIGRVVKGCDUGFDIPVKLENMRLQHEQRAK QAKSFEAKDFLHVKEKFNDDWWIGRVVKGCDUGFDIPVKLENMRLQHEQRAK QAVSFEAKDFLHVKEKFNDDWWIGRVVKGCDUGFDDRYCKLEQKGCUGFIFIPVKLENMRLQHEQRAK QAVSFEAKDFLHVKEKFNDDWWIGRVVKGCDUMFNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDGLUGAUGOUNGEQUMF		CETVNHPIQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ
NVIEGGERPSVYLRat 5' + SH3MQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWVIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSADIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKGCDUGGTIPTYKLENMRLQHEQRAK COMENGENGENGDIGHIPTYKLENMRLQHEQRAK COMENGENGENGUNDVYIRQ		CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY
Rat 5' + SH3MQCCGLVHRRVRVSYGSADSYTSRPSDSDVSLEEDREAVREAERQAQAQLEK AKTKPVAFAVRTNVRYSAAQEDDVPVGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPAH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKGCCDIGFIPTPVKLENMRLQHEQRAK OKVSFGAKDFLHVKEKFNDDWWIGRVVKGCCDIGFIPTPVKLENMRLQHEQRAK OKVSFGAKDGLMBRAPLAPHNDBREDAUDAPSDDAUTSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPAH GAAVSFEAKDFLHVKEKFNDDWWIGRVVDRDEDAUEDDAUFDAUFDAUFDAUFDAU MPDAUSSPACHUPSDPAUHDSOPAUFDAUFDAUFDAUFDAUFDAUFDAUFDAUFDAUFDAUFD		NVIEGGERPSVYL
on NVE βAKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRA KOSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYCPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQ	Rat 5' + SH3	MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK
VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK COMEWG000000000000000000000000000000000000	on NVE β	AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL
RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKKGCDIGFIPTPVKLENMRLQHEQRAK GAAVSFEAKDFLHVKEKFNDDWWIGRVVFKEGCDIGFIPTPVKLENMRLQHEQRAK HANSFEAGEWNRDVYIRQ		VKEGCEIGFIPSPSKLKSLQQIGGTASGRGMRNSKRDVFQFDMVNQAQSPTNTSPS
LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' + SH3 on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK CAAVSFEAKDFLHVKKKFNDDWWIGRVVKEGCDIGFIPTVKLENMRLQHEQRAK NVEC 1 DW MEDAVCKEGCDIGFIPTVKLENMRLQHEQRAK		RHSSTSVDAENGVEYDDDQQSPTSPTNKTLPRSASGTTVSSQPGTATGTQGKPKKG
RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' on RasMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK COVERVERCEDVERDENDELDDUGDVCCTPUSSALDDISLEDVERCEDVERCEDVERCEDVERCEDDSPVH CAAVSFEAKDFLHVKEKFNDDWWIGRDVESALDDFNCALDARSPOSALDDSPVH CAAVSFEAKDFLHVKEKFNDDWWIGRDVESALDDFNCALDARSPOSALDDFNRDSDPAY		LFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALLDFMKHRFSGRVLIA
CETVNHPTQLAKTSLAPMIVYIKIAAPKVLQRLIKTRGKSQSRNLSIQLVAAEKLAQ CSEDMYDLVLEETQLDDACEHLGEFLESYWRATHPPNQPGSRPPNVQPSNSTPQY NVIEGGERPSVYLNVE 5' +MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYSH3 on Rat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNVRYSAAQEDDVPV PGMAISFEAKDFLHVKEKFNNDWVIGRLVKEGCEIGFIPSPVKLENMRLQHEQRA KQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKP SANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQK ALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIF ELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHL NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQNVE 5' on Rat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK GOVERDWUCCDWEDSUCTDDDA UTDD DVTCT DE DEDUCT 		RVTSDISLAKRTNMSNPGKQTIMERTKNKNTGLAEVQQEIERIFELARGLNLVVLD
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IOMALST LAKDTLINKD WHOKL VKLOCLIOTITST VKLERMIKLQILLQKAKQGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKPSANSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQKALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEVISKRRSEAGEWNRDVYIRQNVE 5' onRat βMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAKOKEVGGRGGGGGAGGAGLGDWBGSDWGTDRSGADDD A TEUP A VEDEPCI	SIIS on Rat p	DCMAISEEAKDELHVKEKENNDWWIGDI VKEGCEIGEIDSDVKI ENMPLOHEODA
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SANSVISPHSKEKKMPPFKKTEHTPFIDVVPSMRPVVLVOPSLKOTEVIDMMQKALFDFLKHRFEGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIFELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEVISKRRSEAGEWNRDVYIRQNVE 5' onRat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAKOCKEVAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAG		CANSUTSDUSKERDMDEERKTEHTDDVDV/DSMDDV/UVCDSLKCVEVTDMMOV
ALFDFLKHKFEGKISTIKVTADISLAKKSVLNNPSKHAIIEKSNTKSSLAEVQSEIEKIFELARTLQLVVLDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEVISKRRSEAGEWNRDVYIRQNVE 5' onRat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAKOCKEVAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAGAG		ALEDELKIDEECDIGTEDVTADIGLAKDGVI NNDGKIJAHEDGNTDGGLAEVOGEIEDIE
ELARTLQLVVLDADTINHPAQLSKTSLAPITVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEVISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYRat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAKOKEVSSAGCONSSSIECDRESS		ALFDFLKHKFEGKISTIKVI ADISLAKKSVLNNPSKHAIIEKSNI KSSLAEVQSEIEKIF
NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQHRSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEVISKRRSEAGEWNRDVYIRQNVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYRat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAKOCKEVESKOCONSSERCE CDWDSSDKCTDDSCA DDD A TICL DA EED DD A TICL DA EED DD A TICL DA EED DD A TICL DA DED DD A TICL DA DA DD A TICL DA DED DD A TICL DA DA D		ELARILQLVVLDADIINHPAQLSKISLAPIIVYVKISSPKVLQKLIKSKGKSQAKHL
NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQ NVE 5' on MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY Rat β RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK OCKEVASKAGCMSSSGLCDWBSSDKGTDDSCALDDALTGLALST		NVQMVAADKLAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLP
RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQ NVE 5' on MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY Rat β RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK OCKEVESKEGCONSSESSESSESSESSESSESSESSESSESSESSESSESSE		NPLLSRTLATSTLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQH
HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV ISKRRSEAGEWNRDVYIRQ NVE 5' on MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY Rat β RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK OCKEVASSASL CDWDSSDL CDWDSSDL ATCL DA EEDIDD A TCL DA A TCL D		RSSSATHQNHRSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHRE
ISKRRSEAGEWNRDVYIRQ NVE 5' on Rat β MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK OCKEVERSECONSESSECO		HNHREESHSSNGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEV
NVE 5' onMEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAYRat βRASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVHGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAKOCKEVSSKACCNSSSSLCDWDSSDKCTDDSSCAUDD A TECHDA DEDIDIDA NUDSDKCCU		ISKRRSEAGEWNRDVYIRQ
Rat β RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK OCKEVERRAGONESSELCENWESSENCETERSELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH	NVE 5' on	MEPEPGLSEQUIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY
GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLQHEQRAK	Rat β	RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPVH
	'	GAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPVKLENMRLOHEORAK
UUGKFYSSKSUGNSSSSLUDIVPSSKKSTPPSSAIDIDATULDAEENDIPANHRSPKPSA		OGKFYSSKSGGNSSSSLGDIVPSSRKSTPPSSAIDIDATGLDAEENDIPANHRSPKPSA

	NSVTSPHSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQKALF
	DFLKHRF
	EGRISITRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIFELARTLQLVV
	LDADTINHPAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADK
	LAQCPPQESFDVILDENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRTLATS
	TLPLSPTLASNSQGSQGDQRTDRSAPRSASQAEEEPCLEPVKKSQHRSSSATHQNH
	RSGTGRGLSRQETFDSETQESRDSAYVEPKEDYSHEHVDRYVPHREHNHREESHSS
	NGHRHREPRHRTRDMGRDQDHNECSKQRSRHKSKDRYCDKEGEVISKRRSEAGE
	WNRDVYIRQ
EdCa _V β 2 with	MEPEPGLSEQDIELDSLEQVSTASSFHSDIQRHYNDGREASRFIGADDFNRDSDPAY
NVE β	RASDTSSIEEDRETSRRELERRAWDALQAARSKPVAFAVRTNLRYDGSEDDDSPV
NTerm	HGAAVSFEAKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPSKLKSLQQVGPATG
	GRPVRGSSKTVFHFNDMVNQAQSPTNTSPSRHSSASVVDAENGMEYNEEEQHSPT
	SPTSKTSTLPRSASGNTVTSQSAPGQQGKSKKAFFKKQEQLPPYDVVPSMRPIVLV
	GPSLKGYEVTDMMQKALFDYMKHQFSGRVLISRVTSDISLAKRSNLANPSKRNIIE
	RSNSKNSGLAEVQQEIERIFELSRGLNLVVLDCDTVNHPTQLAKTSLAPLVVYVKIS
	APKVLQRLIKTRGKTQSRALNVQLVAAEKLAQCSEDLYDLILDETQLQDACHHLG
	EFLESYWRATHPPNQPGSRPPNMQQSTPQYNVIEAGERPSVYL
EdCa _v β 2 with	MWFGTKKSKDSERRKRQPIDVYREQALSVNPAYIWGDDLDSRKTSGTSSEYGEDD
CcCa _v β	IEQIRVQALEQLAAARVKPVAFAMRANYGYNGAEDDDSPIHGMALSFEPKDFLHI
NTerm	KEKFNNDWLIGRVVREGCDIGFIPSPSKLKSLQQVGPATGGRPVRGSSKTVFHFND
	MVNQAQSPTNTSPSRHSSASVVDAENGMEYNEEEQHSPTSPTSKTSTLPRSASGNT
	VTSQSAPGQQGKSKKAFFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQK
	ALFDYMKHQFSGRVLISRVTSDISLAKRSNLANPSKRNIIERSNSKNSGLAEVQQEI
	ERIFELSRGLNLVVLDCDTVNHPTQLAKTSLAPLVVYVKISAPKVLQRLIKTRGKT
	QSRALNVQLVAAEKLAQCSEDLYDLILDETQLQDACHHLGEFLESYWRATHPPNQ
	PGSRPPNMQQSTPQYNVIEAGERPSVYL
EdCa _v β 2 with	MVTASYNVPLDNTSATHSFNYPHAFLLTHSSCSYHSNEGFINSSTEVDIVDENDFKP
PpCa _v β	LFEGNSNEPHCQKKVISFSSLLDNVVAPIWYFFEMGDEFDSRKTSGTSSEYGEEDV
NTerm	EALRVQALEQLAAAASKPVAFAVRANYGYNGSEDEDCPVNGMAVSFEAKDCLHI
	KVKFNNDWWIGRVVKEGHDIGFIPSPSKLKSLQQVGPATGGRPVRGSSKTVFHFN
	DMVNQAQSPTNTSPSRHSSASVVDAENGMEYNEEEQHSPTSPTSKTSTLPRSASGN
	TVTSQSAPGQQGKSKKAFFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQ
	KALFDYMKHQFSGRVLISRVTSDISLAKRSNLANPSKRNIIERSNSKNSGLAEVQQE
	IERIFELSRGLNLVVLDCDTVNHPTQLAKTSLAPLVVYVKISAPKVLQRLIKTRGKT
	QSRALNVQLVAAEKLAQCSEDLYDLILDETQLQDACHHLGEFLESYWRATHPPNQ
	PGSRPPNMQQSTPQYNVIEAGERPSVYL
EdCa _V β 2 with	MQCCGLVHRRRVRVSYGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEK
Rat β NTerm	AKTKPVAFAVRTNVRYSAAQEDDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRL
	VKEGCEIGFIPSPSKLKSLQQVGPATGGRPVRGSSKTVFHFNDMVNQAQSPTNTSP
	SRHSSASVVDAENGMEYNEEEQHSPTSPTSKTSTLPRSASGNTVTSQSAPGQQGKS
	KKAFFKKQEQLPPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALFDYMKHQFSGR
	VLISRVTSDISLAKRSNLANPSKRNIIERSNSKNSGLAEVQQEIERIFELSRGLNLVVL
	DCDTVNHPTQLAKTSLAPLVVYVKISAPKVLQRLIKTRGKTQSRALNVQLVAAEK
	LAQCSEDLYDLILDETQLQDACHHLGEFLESYWRATHPPNQPGSRPPNMQQSTPQ
	YNVIEAGERPSVYL
EdCa _v β 2 with	MVQKSGMSRGPYPPSQEIPMEVFDPSPQGKYSKRKGRFKRSDGSTSSDTTSNSFVR
CxCa _v β	QGSAESYTSRPSDSDVSLEEDREALRKEAERQALAQLEKAKTKPVAFAVRTNVGY
NTerm	NPSPGDEVPVQGVAITFEPKDFLHIKEKYNNDWWIGRLVKEGCEVGFIPSPSKLKS
	LQQVGPATGGRPVRGSSKTVFHFNDMVNQAQSPTNTSPSRHSSASVVDAENGME
	YNEEEQHSPTSPTSKTSTLPRSASGNTVTSQSAPGQQGKSKKAFFKKQEQLPPYDV
	VPSMRPIVLVGPSLKGYEVTDMMQKALFDYMKHQFSGRVLISRVTSDISLAKRSN
	LANPSKRNIIERSNSKNSGLAEVQQEIERIFELSRGLNLVVLDCDTVNHPTQLAKTS

	LAPLVVYVKISAPKVLQRLIKTRGKTQSRALNVQLVAAEKLAQCSEDLYDLILDET
	QLQDACHHLGEFLESYWRATHPPNQPGSRPPNMQQSTPQYNVIEAGERPSVYL
EdCa _v β 2 with	MMHGSQTEPAISSMTSERNHKNLSHGSRTSINSQRSTNKKVNSHVSFDESTAAPSS
ChCa _v β	KKPGALSAAGGKKSVDDNFSSSVLQTVFALRWQKKAAQKKKKPDDFQQMYMHS
NTerm	MSGALGSIIGDEFDGRKTSGTSSEYGDGEDLEALRILALEKLQAARTRPVAFAVRA
	NYGYNGSEDDDSPVHGMAVSFEKDDCLHIKDKFNKDWWIGRVVKEGHNIGFVPS
	PSKLKSLQQVGPATGGRPVRGSSKTVFHFNDMVNQAQSPTNTSPSRHSSASVVDA
	ENGMEYNEEEQHSPTSPTSKTSTLPRSASGNTVTSQSAPGQQGKSKKAFFKKQEQL
	PPYDVVPSMRPIVLVGPSLKGYEVTDMMQKALFDYMKHQFSGRVLISRVTSDISL
	AKRSNLANPSKRNIIERSNSKNSGLAEVQQEIERIFELSRGLNLVVLDCDTVNHPTQ
	LAKTSLAPLVVYVKISAPKVLQRLIKTRGKTQSRALNVQLVAAEKLAQCSEDLYD
	LILDETQLQDACHHLGEFLESYWRATHPPNQPGSRPPNMQQSTPQYNVIEAGERPS
	VYL
EdCa _v β 2 with	MAQDFALSNRDIELDSLEHVSTGSSTPSEIQRWHMYSDRSGRVVCKDSEPAYRAS
EdCa _v β1	DTSSVDEDKETSRRELERRAWEALQAARSKPVAFAVRTNIAYEGSEDDDSPVHGA
NTerm	AVSFNVKDFLHVKEKFNDDWWIGRVVKEGCDIGFIPTPSKLKSLQQVGPATGGRP
	VRGSSKTVFHFNDMVNQAQSPTNTSPSRHSSASVVDAENGMEYNEEEQHSPTSPT
	SKTSTLPRSASGNTVTSQSAPGQQGKSKKAFFKKQEQLPPYDVVPSMRPIVLVGPS
	LKGYEVTDMMQKALFDYMKHQFSGRVLISRVTSDISLAKRSNLANPSKRNIIERSN
	SKNSGLAEVQQEIERIFELSRGLNLVVLDCDTVNHPTQLAKTSLAPLVVYVKISAP
	KVLQRLIKTRGKTQSRALNVQLVAAEKLAQCSEDLYDLILDETQLQDACHHLGEF
	LESYWRATHPPNQPGSRPPNMQQSTPQYNVIEAGERPSVYL