

1 Kinome scale profiling of venom effects on cancer cells reveals potential new 2 venom activities

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33Abstract

34The search for novel and relevant cancer therapeutics is continuous and ongoing. Cancer
35adaptations, resulting in therapeutic treatment failures, fuel this continuous necessity for new drugs
36to novel targets. Recently, researchers have started to investigate the effect of venoms and venom
37components on different types of cancer, investigating their mechanisms of action. Receptor
38tyrosine kinases (RTKs) comprise a family of highly conserved and functionally important druggable
39targets for cancer therapy. This research exploits the novelty of complex venom mixtures to affect
40phosphorylation of the epidermal growth factor receptor (EGFR) and related RTK family members,
41dually identifying new activities and unexplored avenues for future cancer and venom research. Six
42whole venoms from diverse species taxa, were evaluated for their ability to illicit changes in the
43phosphorylated expression of a panel of 49 commonly expressed RTKs. The triple negative breast
44cancer cell line MDA-MB-468 was treated with optimised venom doses, pre-determined by SDS
45PAGE and Western blot analysis. The phosphorylated expression levels of 49 RTKs in response to the
46venoms were assessed with the use of Human Phospho-RTK Arrays and analysed using ImageLab
475.2.1 analysis software (BioRad). Inhibition of EGFR phosphorylation occurred with treatment of
48venom from *Acanthoscurria geniculata* (Theraphosidae), *Heterometrus swammerdami*
49(Scorpionidae), *Crotalus durissus vegrandis* (Crotalidae) and *Naja naja* (Elapidae). Western green
50mamba *Dendroaspis viridis* venom increased EGFR phosphorylation. Eph, HGFR and HER were the
51most affected receptor families by venoms. Whilst the importance of these changes in terms of
52effect on MDA-MB-468 cells' long-term viability and functionality are still unclear, the findings
53present exciting opportunities for further investigation as potential drug targets in cancer and as
54tools to understand better how these pathways interact.

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57Keywords

58Breast Cancer, Venom, targeted therapy, Receptor Tyrosine Kinase, MDA-MB-468, Triple negative

59 1. Introduction

60 Venom systems present in a diverse range of animals, contain venom components known to
61target a range of biological pathways and tissue types accessible by the bloodstream (Fry *et al.*,
622009; Estevao-Costa *et al.*, 2018). For example, snake venom produces neurotoxic, haemotoxic and
63cytotoxic effects in humans and prey animals (Casewell *et al.*, 2014). To date, six FDA approved
64drugs have been derived from venoms (not including follow ups), with these currently providing
65treatment options for diabetes, chronic pain, hypertension and coagulation (Robinson *et al.*, 2017).
66Beyond this, many more drugs derived from venoms are in development or in clinical trials
67(Mohamed Abd El-Aziz *et al.*, 2019) and it is clear that there is potential for many more such
68discoveries. Currently very little is known about venom effects on receptor tyrosine kinase
69phosphorylation.

70 Venom peptides are highly selective and potent (Pennington, Czerwinski and Norton, 2017),
71thus offering a potential advantage over small molecule inhibitors leading to potentially fewer side
72effects (Craik *et al.*, 2013). In recent years cancer researchers have turned to venoms to look for
73drug leads following the need to overcome side effects and resistance in standard and targeted
74therapies (Thangam *et al.*, 2012; Ma, Mahadevappa and Kwok, 2017). Disintegrins are an example of
75abundant proteins in snake venom which acts as a potent inhibitors of platelet aggregation and cell
76adhesion (Arruda Macedo, Fox and de Souza Castro, 2015). This has also been shown to have an
77effect on cancer cells (Chakrabarty and Chanda, 2015). Haemotoxic and cytotoxic venom
78components have also been shown to degrade tumour tissue (Tasoulis and Isbister, 2017) and to

79have the potential to show clinically useful anti-metastatic and antiangiogenic properties (Kerkkamp
80*et al.*, 2018). Here for example, a range of scorpion venoms have been shown to affect Erk1/2 and
81STAT3 pathways and to cause DNA damage in colorectal and breast cancer lines in culture (Al-
82Asmari, Riyasdeen and Islam, 2018). Evidence for venoms affecting phosphorylation of receptor
83tyrosine kinases are limited to *Naja atra* cardiotoxin III blocking EGFR (Tsai *et al.*, 2016), insulin
84signalling within *Heloderma* and *Conus* venoms (Ahorukomeye *et al.*, 2019), neurotrophins (Katzir *et*
85*al.*, 2003).

86Here we have investigated the effect of a diverse range of venoms from spiders, snakes and
87scorpions on the activity of receptor tyrosine kinases from the Epidermal Growth Factor Receptor
88(EGFR) family and related families. The EGFR family of tyrosine kinase receptors are key regulators of
89cell growth, transformation and other cellular processes in some breast cancer subtypes (Jacot *et al.*,
902015). The EGFR family consists of EGFR (HER1,ErbB1), HER2(ErbB2), HER3(ErbB3) and HER4(ErbB4),
91with EGFR and HER2 considered to be relevant and attractive clinical targets in breast cancer drug
92discovery (Hsu and Hung, 2016). Existing anti-EGFR and HER2 therapies include monoclonal
93antibodies such as Trastuzumab, which targets the extracellular domain of HER2, or small molecule
94tyrosine kinase inhibitors such as Lapatinib which inhibits receptor phosphorylation by targeting the
95intracellular ATP binding site of both HER2 and EGFR (Zhang *et al.*, 2007; Rusnak and Gilmer, 2011).
96These treatments are however limited as Trastuzumab does not properly infiltrate solid tumours
97(Zhang *et al.*, 2007) and Lapatinib has toxicity issues (Rana and Sridhar, 2012). Resistance has also
98been reported with Lapatinib and other small molecule inhibitors (Escriva-de-Romaní *et al.*, 2018).
99Our assays have utilised the triple negative breast cancer cell line MDA-MB-468, an oestrogen-
100independent cell line originating from a pleural effusion that usually expresses more than 10^6 EGF
101receptors per cell (Zhang, Fidler and Price, 1991; Modjtahedi, Styles and Dean, 1993).

102 These analyses indicate that whole venoms have an effect on phosphorylation of EGFR family
103 members and related receptor tyrosine kinase which have the potential to block cancer related
104 pathways and thus could contain useful tools to understand these pathways better.

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106 **2. Materials and Methods**

107 **2.1 Venom extraction**

108 Venoms from the Brazilian whiteknee tarantula (*Acanthoscurria geniculata*), the Uracoan rattlesnake
109 (*Crotalus durissus vegrandis*), the Western green mamba (*Dendroaspis viridis*), the giant forest
110 scorpion (*Heterometrus swammerdami*), the Indian cobra (*Naja naja*) and the African Black Tail
111 Scorpion (*Parabuthus liosoma*) were supplied by Venomtech Ltd. They were collected using
112 Venomtech's optimised methodology to maintain maximum venom yield and quality. Snakes were
113 'milked' using a voluntary bite protocol, whilst invertebrates were milked using anaesthesia and mild
114 electrical stimulation. Following extraction, the protein concentration of the whole venoms were
115 determined by measuring absorbance at 280nm using a DS11 spectrophotometer (DeNovix, USA)
116 blanked against HPLC grade H₂O. Venoms were then freeze dried or frozen at -20°C until required.

117 **2.2 Mammalian cell culture**

118 MDA-MB-468 (ATCC, USA) were cultured in 25cm³ culture flasks and Dulbecco's modified Eagle's
119 medium (DMEM) (Gibco, UK). The DMEM media was supplemented with L-Glutamine (1%),
120 penicillin-streptomycin (1%) and Foetal Calf Serum (10%). Cells were incubated at 37°C, 95% air and
121 5% CO₂. This cell line was authenticated using STR profiling in March 2018 (100% match to the MDA-
122 MB-468 profile on the Cellosaurus database, ref CVCL_0419) and the work reported here was carried
123 out in the same year. Cell growth was maintained using standard sub-culturing procedures.

1242.3 Venom assay and cell lysis

125MDA-MB-468 cells were plated out in six well plates and grown to 90% confluency before being
126treated with a 1:50- 1:1 000 000 serial dilution of each whole venom in DMEM media. Cells were
127incubated with venom for two hours at 37°C, 5% CO₂. The media containing the venom was then
128replaced with fresh media and EGF was added to a final concentration of 1x10⁻⁷M to all wells except
129the negative control. After 5 mins cells were washed with 2mM EGTA/PBS pH 7.4 and lysed using a
130RIPA buffer cocktail containing protease inhibitor cocktail, phosphatase inhibitor cocktail and EDTA.
131Cell lysates were then transferred to micro centrifuge tubes and centrifuged at 13000 rpm, 4°C for
13210 mins. Once cell debris had pelleted, the supernatant was collected and mixed with 5x reducing
133sample buffer, heated to 100°C and stored at -20°C.

1342.4 SDS PAGE and Western Blotting

13520µl of each cell lysate were analysed on 9% and 12%, 0.75 mm polyacrylamide gels electrophoresed
136using a mini protein tetra cell (BioRad) and a Tris/Glycine/SDS buffer (0.025M Tris, 0.192M glycine,
1370.1% SDS, pH8.3) at 70V until samples entered the gel and then at 170V till the dye front reached the
138end of the gel. Gels were then either stained for one hour using Coomassie blue dye or transferred
139to nitrocellulose via semi-dry blotting using an Invitrogen semi-dry western blotter for 45-60 minutes
140at 15V.

141For Western blotting, the nitrocellulose membranes were incubated for one hour in blocking buffer
142(5% w/v Marvel non-fat milk powder solution in phosphate-buffered saline (PBS) 0.1% v/v
143Polyoxyethylenesorbitan monolaurate (Tween20)). Membranes were then washed 3 times for 10
144min in PBS Tween20 and incubated overnight using a mouse monoclonal PY20 antibody (Sigma, UK)
145at 1.5µg/ml. Anti-β actin antibody (mouse, monoclonal AC-15 clone. Sigma) was used at a
146concentration of 3.5µg/ml as a loading control. After washing with PBS blots were incubated in
147rabbit anti-mouse-HRP antibody 1/20,000 for 1h. Blots were washed again using PBS and Enhanced

148 Chemiluminescence (ECL) reagents were mixed in equal volumes and applied directly onto the blots.

149 ECL signals were developed using a Chemidoc (BioRad, UK).

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151 2.5 Human Phospho-RTK Array

152 MDA-MB-468 cells were grown in 25cm² flasks until 90% confluent. Cells were treated with A.

153 *geniculata*, *C. vegrandis*, *D. viridis*, *H. swammerdami*, *N. naja* or *P. liosoma* venoms for two hours at

154 dilutions of 1:100, 1:1000, 1:10 000, 1:50, 1:10 000, 1:150 respectively. Cell lysates were then

155 collected as described above and analysed according to the manufacturer's instructions using a

156 Human Phospho-RTK Array Kit (R&D Systems).

157 Kinome array images were analysed using the ImageLab 5.2.1 analysis software (BioRad, UK). Lanes

158 and pairs of dots were identified, allowing for the production of a pixel intensity from each duplicate

159 pair of receptor dots. A template showing the RTK location on the blot is located in Appendix A,

160 Table A.1). A fold change in intensity was created by dividing the intensity of each venom treated

161 receptor by the intensity generated from the positive control of each receptor (No venom, +EGF).

162 Changes in receptor phosphorylation were then displayed graphically as a fold-change in intensity,

163 relative to the positive control receptor intensity levels. RTK's displaying a two fold change were

164 considered to be affected by the venom treatment.

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166 3 Results and Discussion

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1683.1 Changes in receptor phosphorylation and expression profiles in response to whole venom

169The following optimised concentrations of venom were used (see Appendix B, Figure B.1) for these
170experiments 1/10,000 dilution (0.025mg/ml) of *N.naja* venom, 1/150 dilution (1.5mg/ml) of
171*P.liosoma* venom, 1/50 dilution (2mg/ml) of *H.swammerdami* venom, 1/10,000 dilution
172(0.025mg/ml) of *D.viridis* venom, 1/1,000 dilution (0.065mg/ml) of *C.durissus vegrandis* venom,
1731/100 dilution (2.5mg/ml) of *A.geniculata* venom.

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175Changes in the phosphorylation and/or expression of 49 members of the receptor tyrosine kinase
176(RTK) family, were analysed in response to two hour incubation with venom. The arrays assess the
177changes in the expression/phosphorylation of representative members from most of the diverse
178sub-families of RTKs. Two-fold changes in receptor expression/phosphorylation in response to the
179venom were considered biologically interesting and both increases and decreases were observed
180(Appendix C, Table C.1).

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182The majority of the tested RTKs decrease in response to *C.durissus vegrandis* venom (See Table D.1.,
183Appendix D). It is possible that *C.durissus vegrandis* does indeed have a pan kinome effect but
184further investigation would be required to confirm this. Even though protein levels in the Coomassie
185gel did not show a reduction from cytotoxicity, the comprehensive reduction in RTK signal could be
186due to proteolytic cleavage of the cell surface receptors but this is below the level detectable on the
187Coomassie gel. It is well known that Viperidae venoms contain more proteases than the other
188species tested. The majority of RTK's were also reduced in response to treatment with *P.liosoma*
189venom. However upon further follow up investigations with Coomassie gel analysis of the treated
190cell lysates produced for the kinome arrays, it was determined that the selected dose of *P.liosoma*
191venom appeared to have caused a large degree of cytotoxicity (Appendix E, Figure E.1). Due to these
192high levels of observed cytotoxicity, all changes in the expression/phosphorylation of the RTKs
193treated with this venom were deemed inconclusive and subsequently disregarded. There is still the

194possibility that *P. liosoma* venom may have an effect on some of the 49 members of the RTKs
195provided on the array membranes at an appropriately selected sub-lethal dose, but this cannot be
196confirmed from these results.

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198The consistent protein level in all other lysates supports the changes detected, further in-depth
199discussion of some of the observed changes in RTK sub-family members and the implications of
200these changes to cancer therapy will be further discussed.

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202Figures 1-3 display changes in phosphorylation of the RTKs in response to the venoms. Two-fold
203threshold in phosphorylation/expression limits were set to triage effects compared to 1×10^{-7} M EGF
204stimulated cell receptor levels. All receptor changes were displayed in a table for ease, with those
205over threshold highlighted (Appendix D, Table D.1).

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207The majority of the changes in phosphorylation levels were detected in the Ephrin and Epidermal
208growth Factor Receptor gene families. Although there are no previously published reports linking
209venoms to the Ephrin pathways, there is previous evidence of Chinese cobra cardiotoxin III from
210*Naja atra* venom reducing EGFR signalling (Tsai *et al.*, 2016).

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2123.2 All venoms tested affected ephrin receptors

213Eph receptors and their binding ligands, ephrins, constitute the largest sub-family of receptor
214tyrosine kinases. Eph receptors play a fundamental role in cell signalling pathways involved in animal
215development (Castaño, 2008). Binding of ephrins, to Eph receptors results in the bi-directional
216stimulation of the eph/ephrin signalling axis. Over-expression of ephrins and eph receptors can
217result in tumorigenesis, promoting tumour growth, survival, angiogenesis and metastasis (Surawska,
2182004; Pasquale, 2010). Eph receptors can act as both suppressors and promoters of tumours in
219different contexts (Genander and Frisen, 2010). Many of the family members are clinically relevant

220and tractable targets for intervention in human breast cancer (Brantley-Sieders *et al.*, 2011; Kaenel,
221Mosimann and Andres, 2012). Receptors of this subfamily are attractive targets for antiangiogenic
222therapy (Mosch *et al.*, 2010). This family's signalling activities in cancer appear to be complex
223(Pasquale, 2010) and therefore since some of the venoms target members of this subfamily, they
224could be used to understand these pathways further.

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249 **Figure 1: Kinome array analysis of MDA-MB-468 cells treated with *A.geniculata* and *C.durissus vegrandis* venom.**

250 Graphs display the fold-changes in combined receptor expression/phosphorylation in response to treatment with each
251 venom compared to levels in venom untreated cells

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Figure 2: Kinome array analysis of MDA-MB-468 cells treated with *D. viridis* and *H. swammerdami* venom.
Graphs display the fold-changes in combined receptor expression/phosphorylation in response to treatment with each venom compared to levels in venom untreated cells.

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359 **Figure 3: Kinome array analysis of MDA-MB-468 cells treated with *N.naja* venom.**

360 Graphs display the fold-changes in combined receptor expression/phosphorylation in response to treatment with each
361 venom compared to levels in venom untreated cells

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363 EphA1 over-expression has been identified in gastric cancer (Yuan, 2008), prostate cancer and a sub-
364 set of colon, liver, lung, melanoma and mammary carcinomas (Robinson, 1996; Kao, 2003; Herath,
365 2006). EphA2 receptor over-expression has been identified in oesophageal, gastric, prostate and
366 breast cancer (Easty *et al.*, 1999; Miyazaki *et al.*, 2003; Zelinski *et al.*, 2001; Yuan *et al.*, 2009;
367 Nakamura *et al.*, 2005; Xu *et al.*, 2005; Gokmen-Polar *et al.*, 2011; Petty *et al.*, 2012, Huang *et al.*,
368 2014, Tsouko *et al.*, 2015) as well as lung cancer, where high EphA2 levels predicts metastatic
369 outcome (Kinch, 2003). EphA3 mutations are the most commonly occurring Eph receptor change,
370 identified in lung, hepatocellular, colorectal, glioblastoma and melanoma (Bae *et al.*, 2009;
371 Balakrishnan, 2007). These mutations appear to confer impaired kinase function, suggesting that
372 EphA3 may function as a kinase-dependent tumour suppressor, which is disrupted by somatic cancer
373 cell mutations (Lisabeth *et al.*, 2012). High levels of EphA4 expression have been linked to poor
374 patient survival in gastric cancers (Miyazaki *et al.*, 2013), promotes cell proliferation and migration of
375 human glioma cells (Fukai *et al.*, 2008), promotes cell growth in human pancreatic ductal
376 adenocarcinoma (Iizumi, *et al.*, 2006) and increased levels of metastasis in colorectal cancer
377 (Oshima *et al.*, 2008). EphA5 receptor has been shown to be downregulated in breast cancer (Fu *et*
378 *al.*, 2010) and EphA6, whilst shown to be downregulated in colorectal and kidney cancer (Hafner *et*
379 *al.*, 2004), has been shown to be upregulated in breast cancer (Zhou *et al.*, 2018). Higher expression
380 of EphA7 is detected in breast and glioblastoma cancers (Brantley-Sieders, 2011; Wang *et al.*, 2008)
381 and a reduced expression level in colorectal and prostate cancer (Wang *et al.*, 2005; Guan *et al.*,

3822009). EphA10 receptor has been shown to be upregulated in breast cancer including triple negative
383types, prostate and colorectal cancer (Nagano, 2014a and 2014b; Li, 2017).

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385Reductions in EphA2 occurred in response to *N.naja* venom (Figure 3), EphA6 in response to
386*A.geniculata* (Figure 1a) and *D.viridis* (Figure 2a) venoms, and EphA7 in response to *A.geniculata*
387venom. Over-expressions of EphA1 and A2 have been identified in a variety of cancers, including
388breast cancer, making *N.naja* venom attractive for further investigation. Whilst EphA4 receptor does
389not appear to be commonly upregulated in breast cancer, its upregulation in gastric, pancreatic,
390colorectal and glioma cancers are indicative of metastasis and poor patient prognosis. *A.geniculata*
391and *D.viridis* venoms would however be interesting to follow up for down-regulation of EphA6,
392which has been shown to be over-expressed in breast cancer, where it is indicative of poor patient
393prognosis (Zhou *et al.*, 2018). Similarly *A.geniculata* venom shows potential for containing
394interesting targeting molecules for EphA7 receptor, which has also been shown to be overexpressed
395in breast cancer and glioblastoma (Brantley-Sieders, 2011; Wang, 2008). The search for novel targets
396for triple negative breast cancer makes EphA10 a viable target for novel targeted therapies, several
397venoms were close to threshold and related species might contain useful molecules.

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399Loss of EphB1 receptor tyrosine kinase has been linked to the progression of aggressive cancer types
400including acute myeloid leukaemia (Kampen *et al.*, 2015), gastric, colorectal and ovarian cancer
401(Sheng *et al.*, 2007; Wang *et al.*, 2013) and renal cell carcinoma (Zhou *et al.*, 2014). Both
402upregulations and downregulations in the expression of EphB2 have been linked to the progression
403of cancer. EphB2 has been shown to be over-expressed in highly aggressive breast cancer types,
404where it has been shown to regulate multiple functions including autophagy, apoptosis and invasion
405(Chukkapalli *et al.*, 2014) and to result in poor survival in patients with ovarian cancers that present
406with high levels of EphB2 (Wu *et al.*, 2006). Whilst reduced EphB2 expression has been linked to liver
407metastasis in colorectal cancer (Oshima *et al.*, 2008). Like EphB2, EphB3 has been found to be both

408upregulated and downregulated in the progression of cancer. EphB3 has been shown to be both up
409and downregulated in non-small cell lung cancers (Li *et al.*, 2012; Ji *et al.*, 2011). Over-expression of
410EphB3 has been linked to the suppression of colon cancer tumour growth (Chiu *et al.*, 2009) and
411alternatively has been linked to stimulation of cell migration and metastasis in papillary thyroid
412cancer (Li *et al.*, 2017). EphB4 receptor increases and decreases have both been linked to breast
413cancer progression (Xiao *et al.*, 2012). EphB4 has been shown to suppress breast cancer
414tumorigenicity through an Abl/crk pathway (Noren *et al.*, 2006) and to act as a survival factor in
415breast cancers (Kumar *et al.*, 2006). The extracellular domain of EphB4 has also been shown to
416induce angiogenic responses in endothelial cells and its expression on the surface of breast cancer
417cells has been shown to promote angiogenesis by activating EphB2 reverse signalling, increasing
418tumour growth (Noren *et al.*, 2004; Noren *et al.*, 2007). EphB4 has been shown to be expressed in
419other cancers, with its upregulation shown in colon cancer (Stephenson, *et al.*, 2001), bladder cancer
420(Xia *et al.*, 2006) and ovarian cancer (Kumar *et al.*, 2007). Finally, the expression levels of EphB6 in
421cancer cells has been linked to their progression and development, with losses in EphB6 expression
422often indicative of a more aggressive cancer type. Downregulations in EphB6 receptor have been
423seen in breast cancer cells, where it has been found to interact with c-Cbl to function as a tumour
424suppressor and to prevent tumour cell invasiveness (Fox & Kandpal, 2009; Truitt *et al.*, 2010; Fox &
425Kandpal, 2006; Fox & Kandpal, 2004). EphB6 expression has been shown to partially suppress
426epithelial-to-mesenchymal transition in triple negative breast cancer cells and to reduce tumour
427drug-resistance to DNA-damaging drugs, resulting in better chances for recurrence-free survival in
428patients with higher EphB6 expressing tumours (Toosi *et al.*, 2018). Silencing or mutations of EphB6
429expression in early stage non-small cell lung cancer has been found to be associated with the
430development of distant metastases and a more aggressive cancer type. It is thought, like with breast
431cancer, that EphB6 confers tumour suppression in NSCLCs (Yu *et al.*, 2010; Bulk *et al.*, 2012).
432Reduced gene expression of EphB6 in neuroblastoma, melanoma and prostate cancer are indicative
433of poor patient prognosis, amongst other cancer types (Tang *et al.*, 2000; Tang *et al.*, 2004;

434Mohamed *et al.*, 2015). Alternatively, EphB6 receptor over-expression in colorectal cancer has been
435linked to the promotion of tumour cell proliferation, migration and invasion (Xu *et al.*, 2016).

436

437EphB type receptors EphB4 and B6 were reduced following *A.geniculata* venom treatment (Figure
4381a). Greater than 2-fold increases in EphB1 and B3 were observed in response to treatment with
439*H.swammerdami* venom (Figure 2b). Losses of EphB1 receptor have been shown in literature to be
440indicative of highly aggressive cancer types and poor patient prognosis. *H.swammerdami* venom is
441likely to contain possible therapeutic tools for this target. Treatment with this venom resulted in a 2-
442fold increase in EphB1 combined expression/phosphorylation levels, which could be useful for
443restoring EphB1 expression levels in cancers where, EphB1 acts as a tumour suppressor and had
444been downregulated. Both up and downregulations in EphB2 expression levels have been observed
445in cancer. Dosing with *H.swammerdami* venom resulted in a greater than 2-fold increase in the
446combined expression/phosphorylation of EphB3. A component from this could have potentially
447interesting implications for the treatment of cancers where EphB3 is a known tumour suppressor
448and has been downregulated in expression to circumvent this, such as has been shown to be the
449case in colon cancer tumours (Chiu *et al.*, 2009). Both EphB4 and EphB6 receptors were reduced in
450response to treatment with *A.geniculata* venom (Figure 1a). Whilst both receptors have been shown
451to be up and downregulated in cancer types, EphB4 upregulations are more commonly implicated in
452poor cancer prognosis, whilst EphB6 downregulations are more indicative of poor patient outcome.
453Treatment with both these venoms resulted in downregulations in both receptors
454expression/phosphorylation levels. These changes could prove beneficial for the treatment of ErbB4
455over-expressing cancers, including breast, bladder, ovarian and colon cancer. Whilst EphB6
456downregulations are less likely to be useful in a therapeutic capacity for the treatment of cancer, as
457loss of EphB6 expression appears more common in tumorigenesis, there are cases of cancer that do
458appear to express over-expression of EphB6, such as colorectal cancer. Currently in clinical trials are

459cancer drugs that target the kinase activity of EphA2 and EphB4 but there is still a lot to learn about
460this receptor network (Buckens *et al.*, 2020).

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462**3.3 Effects of venoms on EGFR family member phosphorylation levels**

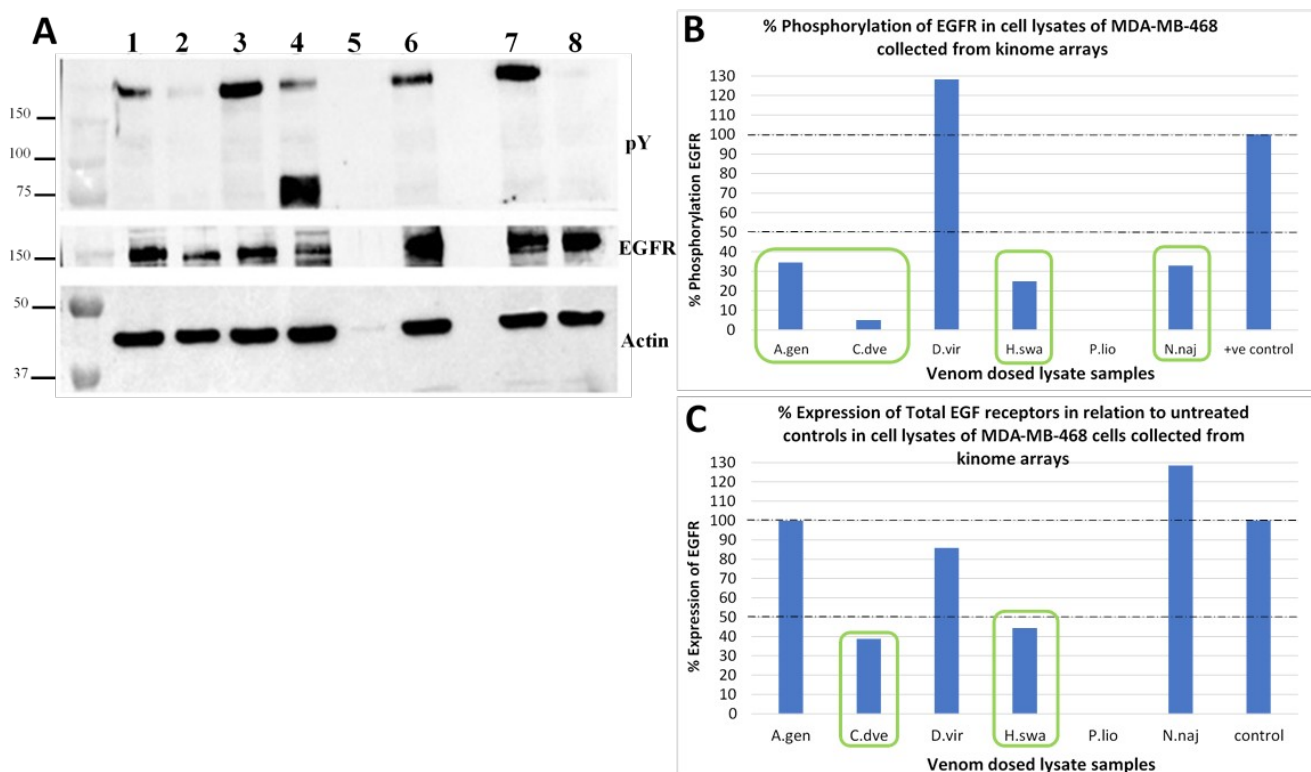
463Some, but not all, of the investigated venoms reduced detectable phosphorylation above threshold
464in EGFR family members. Interestingly, from the changes observed in the EGFR family members,
465there appears to be both selective and multiple targeting of like-receptor types. Selectivity is
466interesting from complex mixtures and hints at a single active component.

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468No significant reductions were seen in EGFR expression/phosphorylation in response to venom using
469the kinome arrays. However due to the over-expression of EGFR in the MDA-MB-468 cells used as a
470model for these experiments, it was considered possible that changes may be occurring but are
471undetectable due to saturation of the EGFR antibody binding capacity of the blots (see the EGFR dots
472in Appendix C, Figure C.1). Follow up Western blot analysis was undertaken on lysates previously
473produced for kinome array analysis to determine if changes to EGFR expression or phosphorylation
474could be observed using an alternative/less sensitive method (Figure 4a). Anti- β actin analysis
475confirmed that all samples were loaded with a similar amount of total protein, with the exception of
476the *P. liosoma* treated cell lysate, previously shown in Coomassie gel analysis to be lacking protein
477due to toxicity (see Appendix E, Figure E.1). Western blot analysis of EGFR phosphorylation (pY) and
478expression levels (EGFR) showed that there were detectable differences in phosphorylation in
479response to the different venoms, previously undiscernible in kinome arrays because of
480oversaturation (Appendix C, Figure C.1). Thus the differences are likely due to the degree of
481sensitivity of the two analyses. Kinome arrays are highly sensitive to low levels of receptors or small
482changes in their expression level. MDA-MB-468 cells express EGFR at such a high level that there is a
483very strong probability that even in low levels (like with the *P. liosoma* lysate) there was enough
484receptor present to saturate the preloaded antibody available on the blot for binding.

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486 Figures 4b and 4c display the percentage phosphorylation and percentage receptor expression
487 respectively and reveal that reductions in EGFR receptor phosphorylation levels of nearly 70%
488 occurred in response to treatment with both *A.geniculata* and *N.naja* venom. A combination of
489 changes in the overall expression and phosphorylation level of EGFR were seen in response to
490 treatment with *C.durissus vegrandis* venom, with calculated reduction in expression of 60% and
491 reductions in the detectible phosphorylation levels of nearly 95%. EGFR expression and
492 phosphorylation levels post-dosing with *H.swammerdami* venom revealed that there appears to be
493 EGFR breakdown in response to treatment. A detectable phosphorylated band of around 75k Da was
494 observed when looking at phosphorylation levels of EGFR on the Western blot (Figure 4a), with
495 reductions in detectible EGFR phosphorylation of 75% also observed. Overall EGFR expression levels



496

497

498 **Figure 4: Western Blot analysis of EGFR phosphorylation and expression levels in MDA-MB-468 cells post whole venom**
499 **treatment.**

500 Lysates produced for kinome array analysis were analysed via western blot to determine changes in expression (EGFR) and
501 phosphorylation (pY). Anti- β actin was used as a loading control to validate any observable changes. All pY and EGFR bands
502 were normalised against actin bands before % phosphorylation was calculated relative to the +ve control band for each
503 blot.

5041: *A.geniculata*, 2: *C.durissus vegrandis*, 3: *D.viridis*, 4: *H.swammerdami*, 5: *P.liosoma*, 6: *N.naja*, 7: +EGF only (+ve Control),
5058: -Venom, -EGF (-ve Control)
506
507

508are also considerably lower compared to the untreated EGFR expression level controls, with around
50955% reductions in total EGFR protein. There appears to be a slight EGFR expression reduction of 15%
510in response to *D.viridis* treatment, however despite this, treatment with this venom still appears to
511have resulted in nearly a 30% increase in EGFR phosphorylation levels.

512

513Reductions in EGFR expression or phosphorylation in response to treatment with four of the
514selected venoms, including two distinctly diverse snake species, one scorpion and a theraphosid
515venom warrants further investigation. EGFR over-expression and signalling have been shown to be
516important in the development, progression and metastasis of a large number of cancer types
517including triple-negative breast cancer (Foley *et al.*, 2010; Ueno *et al.*, 2011; Davis, 2014; Park, 2014;
518Nakai, 2016; Ali, 2017; Liang, 2017), colorectal cancer (Koustas, 2017; Zhao *et al.*, 2017; Huang *et al.*,
5192017; Huang *et al.*, 2018) and lung cancer (Liu *et al.*, 2017; Nukaga *et al.*, 2017; Singh, 2018)
520amongst many others. EGFR is now well established as a target for treatment in a wide variety of
521cancers, with high-level EGFR in primary tumours correlating with highly aggressive basal-like
522phenotypes and poor patient prognosis. Due to its over-expression in many cancer types, the
523inhibition of EGFR phosphorylation has been shown to be a successful strategy in the fight against
524cancer (Ono and Kuwano, 2006). However, development of resistance to current cancer therapies
525through further EGFR mutation or EGFR-pathway circumvention is a common occurrence
526(Pietrantonio *et al.*, 2017; Lim, 2018; Liu, 2018; Yu, 2018), often linked to patient relapse. Reduction
527in EGFR expression and phosphorylation levels seen in response to *C.durissus vegrandis*, *N.naja* as
528well as scorpion *H.swammerdami* and theraphosid *A.geniculata* venoms could open up a large pool
529of venom-derived biological molecules, from a large diverse population of species, which may

530possess novel mechanisms and binding sites for the targeted suppression of EGFR and treatment of
531EGFR-expressing cancers where prior treatment has failed due to therapy resistance.

532

533HER2 over-expression has been shown to be linked to the induction and progression of a variety of
534cancer types including, prostate (Day *et al.*, 2017), colon and colorectal (Takegawa *et al.*, 2017;
535Pirpour Tazehkand *et al.*, 2018; Siena *et al.*, 2018), gastric and oesophageal (Gerson *et al.*, 2017; Wu
536*et al.*, 2017), ovarian (Luo *et al.*, 2018) and predominantly occurring in the HER2+ breast cancer
537subtypes (Baselga *et al.*, 2017; Loibl & Gianni, 2017; Pondé, 2018). A two-fold reduction was
538observed in HER2 phosphorylation in response to treatment with *N.naja* (Figure 3) and
539*H.swammerdami* (Figure 2) venoms. Whilst prognosis for patients presenting with HER2-positive
540breast cancers has greatly improved thanks to advances in targeted therapies, resistance through
541HER3 up-regulation is a common problem. Oncogenic HER3 mutations have emerged as new
542therapeutic targets for the treatment of breast, ovarian, lung, prostate and other cancer subtypes
543(Jaiswal *et al.*, 2013; Schardt *et al.*, 2017). Targeting of HER3 has also been shown to sensitise head
544and neck squamous cell carcinomas by increasing tumour sensitivities to Cetuximab, reducing HER3
545activity and preventing HER2/HER3 dimerisation occurrence (Wang *et al.*, 2017). HER3 has been
546shown to play fundamental roles in cancer, both independently and in conjunction with other RTKs
547to circumvent therapeutic suppression, making it, like other ErbB receptor kinases a key target for
548therapeutic development. Reductions in combined HER3 phosphorylation/expression levels were
549observed in response to *A.geniculata* (Figure 1a) and *N.naja* (Figure 3), suggesting that these venoms
550could contain useful components for the treatment of HER3 over-expressing cancers. Activating
551mutations in HER3 have been identified in both HER2+ and ER+ breast cancer types, with HER2 and
552HER3 co-expression in breast cancer commonly observed (Mishra, 2018; Mishra, 2018). Studies have
553shown upregulation in HER3 expression by HER2 as a mechanism involved in therapy-resistance
554(Yang, 2017; Li, 2018; Lyu, 2018). Treatment with *N.naja* venoms resulted in the suppression of both
555HER2 and HER3, suggesting the propensity for these venoms to contain useful components effective

556against HER2/HER3 co-expressing cancers and HER2+ breast cancer subtypes which have
557upregulated HER3 overcoming therapeutic suppression.

558

559*H.swammerdami* venom produced a two-fold increase in HER4 phosphorylation. Given that both up-
560regulations and down-regulations in HER4 expression and signalling have been linked to the
561development and progression of cancer. The observed increase in expression of HER4 following
562treatment with *H.swammerdami* venom could have useful implications in for finding compounds to
563restore normal receptor levels. Cancers known to down-regulate HER 4 expression include renal
564(Thomasson *et al.*, 2004), papillary carcinoma (Kato *et al.*, 2004) high-grade gliomas (Andersson *et*
565*al.*, 2004) and breast cancer (Wang *et al.*, 2016). HER4 expression levels have been shown to be
566both down- and up-regulated in triple-negative and non-triple-negative breast cancer types
567respectively (Ansarin *et al.*, 2018).

568

569Pan-HER treatments, targeting EGFR, HER2 and HER3 simultaneously have been developed in recent
570years in an attempt to overcome the development of resistance to antibody-based therapies
571through target circumventing (Iida *et al.*, 2016) and small molecules tyrosine kinase inhibitors
572(Geuna *et al.*, 2012; Solca *et al.*, 2012; Mancheril, Aubrey Waddell & Solimando, 2014). Aptamer
573based therapies that also target the three receptors in breast cancer are also being used in an
574attempt to eliminated the problem of resistance development and therapy failure (Yu *et al.*, 2018).
575Treatment with *N.naja* venom displayed this same Pan-HER targeting ability, causing reductions in
576the combined phosphorylation/expression levels of EGFR, HER2 and HER3. *A.geniculata* venom,
577whilst not targeting all HER receptors showed dual targeting of EGFR and HER3.

578

579Whilst all other tested venoms resulted in a change in at least one of the ErbB receptor family
580members, *D.viridis* venom had no detectible effects on the members of this receptor sub-family,

581 thus the effects observed are likely to be specific responses to the venoms. HER3 and HER4
582 receptors have been detected at the neuromuscular junction and in association with nicotinic
583 acetylcholine receptors (Zhu *et al.*, 1995), a known venom target, thus this may explain the
584 evolutionary targeting of venom components to these receptors.

585

586 **Other effects of whole venoms on receptor tyrosine kinases**

587 FGFR1 phosphorylation level was dramatically downregulated in cells dosed with *A.geniculata*
588 venom, with a lesser effect seen on FGFR2 (Figure 1). The amplification of FGFR1 is linked to 21% of
589 lung adenocarcinomas (Dutt *et al.*, 2011), as well as being observed in prostate (Devillard *et al.*,
590 2006), ovarian (Cole *et al.*, 2010), lung (Jiang *et al.*, 2015; Heist *et al.*, 2012) and oral squamous cell
591 carcinomas (Freier *et al.*, 2007). FGFR1 upregulation has been found to occur in 10% of cases in
592 oestrogen-dependent breast cancer (Gru & Allred, 2012), where it is linked to the promotion of cell
593 proliferation. Gene amplification of FGFR1 has been shown to occur in breast cancer (Turner *et al.*,
594 2010). 12% of endometrial cancers have been identified as positive for FGFR2 gene mutations (Dutt
595 *et al.*, 2008) as well as cases of lung squamous cell and cervical cancers (Liang *et al.*, 2013). FGFR2
596 gene amplifications or missense mutations are more commonly occurring than FGFR1 mutations in
597 cancer, with amplifications found in 10% of gastric cancers (Kato & Kato, 2009) and 2% of breast
598 cancers (Heiskanen *et al.*, 2001; Bai *et al.*, 2010). Even though the cells were dosed with whole
599 venom it suggests further study is warranted on the components responsible for the effect of
600 Theraphosidae venoms on FGF receptors. Other effects produced by *A.geniculata* venom include
601 reductions in TrkA, TrkC, Tie2 and HGFR.

602 Neurotrophin receptor signalling through tropomyosin receptors kinases (Trk) A, B and C has been
603 linked to the development of certain types of cancer. Whilst rare in most cancers, Trk fusions with
604 other proteins are well-established oncogenic-driver events in papillary thyroid carcinoma,
605 glioblastomas and secretory breast carcinomas. As well as Trk fusions, amplifications and alternative
606 splicing events have been described as drivers in cancer pathogenesis (Lange and Lo, 2018). Trk A

607over-expression has been linked to enhanced growth and metastatic propensity of breast cancer
608cells (Lagadec *et al.*, 2009; Demont *et al.*, 2012), with downregulation of Trk A expression by small
609interference RNAs (siRNAs) shown to abolish metastatic potential and increase chemosensitivity in
610them (Zhang, 2015). In neuroblastoma tumours, variable expression of Trk B in conjunction with
611brain-derived neurotrophic factor (BDNF) are indicative of poor patient prognosis, whilst high-level
612expression of Trk A and Trk C are associated with a good prognosis (Lucarelli *et al.*, 1997; Yamashiro
613*et al.*, 1997; Sugimoto *et al.*, 2001; Thiele & McKee, 2009; Tanaka *et al.*, 2014). Trk B over-expression
614has also been identified in highly aggressive metastatic human pancreatic cancers (Sclabas *et al.*,
6152005). Crosstalk between EGFR and Trk B has been shown to enhance cell migration and
616proliferation in ovarian cancer cells (Qiu *et al.*, 2006), whilst Trk B has been found to be a key
617regulator of PI3K and JAK/STAT signalling pathway activated metastasis and epithelial-mesenchymal
618transition in breast cancer cells (Kim *et al.*, 2015). TrkB forms a complex with EGFR and Sortilin in
619exosomes and Sortilin is also deregulated in cancer (Wilson *et al.*, 2016).

620

621Neurotrophin effects were expected from *N. naja* venom as NGF has been identified in this species
622(Hogue-Angeletti *et al.*, 1976) and other cobras *Naja kaouthia* (Katzir *et al.*, 2003) and *Naja atra* (Lu
623*et al.*, 2017). The published sequence of *Naja naja* venom NGF from only differs in two amino acids
624at the C terminal from the other two Aspartate (D) instead of from Glutamate (E) at position 103 and
625Threonine from Lysine at position 114 (Appendix F, Figure F.1). Although unlikely, these mutations
626may have an effect on trk phosphorylation especially if mutations in these RTK's are present in the
627MDA-MB-468 cells, but this requires further investigation.

628

629*Dendroaspis viridis* venom has a dramatic effect on the insulin receptor, increasing total
630phosphorylation 4.5 fold from control. Diverse venoms from Cone snails (*Conus spp.*) have utilised
631insulin signalling in prey capture (Ahorukomeye *et al.*, 2019) and famously a glucagon like peptide
632has been clinically utilised from *Heloderma suspectum* (Yap & Misuan, 2019). Therefore, this is

633possibly a newly discovered mechanism in the mamba *Dendroaspis viridis* which warrants further
634investigation.

635*Dendroaspis viridis* venom also had a dramatic effect on RET (REarranged during Transfection) proto-
636oncogene (c RET). Gain-of-function mutations and upregulation in the expression of c-RET receptor
637tyrosine kinase have been linked to the development of several cancer types. C-Ret expression is
638often observed in oestrogen receptor positive (ER+) breast cancer subtypes, where RET expression is
639induced by oestrogens and RET signalling enhances oestrogen-driven proliferation of the breast
640cancer cells. RET expression has been detected in primary breast cancer samples, with higher RET
641expression levels identified in ER+ tumours (Boulay *et al.*, 2008; Morandi *et al.*, 2011). RET mutations
642in the form of chromosomal rearrangements (inversion of balanced-translocation) involving the RET
643catalytic domain and leading to the creation of fusion RET/PTC oncogenes have been linked to
644papillary thyroid carcinoma (PTC) development (Mologni, 2011). Gain-of-function mutations in RET
645have also been linked to the development of medullary thyroid carcinoma (MTC) (Hedayati *et al.*,
6462016, Carlomagno, 2012; Phay and Shah, 2010). Both small molecule (Andreucci, 2016) and
647antibody-drug conjugate (Nguyen *et al.*, 2015) therapies have been developed as potential therapies
648for the treatment of RET over-expressing breast cancer, with treatments proving effective against
649these RET over-expressing cancers. However, despite the evidence for RET as an oncogene
650promoting cancer development in thyroid cancer and pheochromocytoma, RET has been identified
651to potentially have a tumour suppressive role in colon cancer. RET methylation was found in 27% of
652colon adenomas and 63% of colorectal cancers, where these aberrant methylation events were
653found to correlate with decreased RET expression. Subsequent restoration of RET expression in
654these instances was found to result in apoptosis of colorectal cancer cells (Luo *et al.*, 2013). The
655other major effect of *D.viridis* venom was the increase in hepatocyte growth factor receptor (HGF R/
656c-MET). C-MET receptor tyrosine kinase has been identified as a key player in many cancers including
657breast (Yan *et al.*, 2015), lung (Zucali *et al.*, 2008), melanoma (Cheng *et al.*, 2017), myeloma,
658(Moschetta *et al.*, 2013) adrenocortical carcinoma (Phan *et al.*, 2015), pancreatic cancer (Brandes *et*

659*al.*, 2015) and gastric cancer (Ha *et al.*, 2013), with its over-expression indicative of poor patient
660prognosis and highly invasive tumour types (Cazet *et al.*, 2010; Goetsch *et al.*, 2013; Ho-Yen *et al.*,
6612014; Ho-Yen *et al.*, 2015; Yan *et al.*, 2015; Zhang *et al.*, 2018). Within breast cancer subtypes high
662levels of c-MET protein in hormone-receptor (HR)+ breast cancers and phosphor-c-MET in HER2+
663breast cancers were indicative of worse relapse-free survival and overall survival rates in patients.
664High levels of c-MET and phosphor-c-MET were identified in all breast cancer types and were
665indicative of poor patient prognosis (Raghav *et al.*, 2012), with c-MET over-expressions also having
666been identified in triple-negative breast cancer cell lines, MDA-MB-468, HCC-1395, and MDA-MB-
667231, where it has been linked to EGFR-therapy resistance (Sohn *et al.*, 2014). Thus even though the
668c-MET is over expressed in this cell line, it is not fully phosphorylated as further phosphorylation was
669stimulated by *D.viridis* venom. *A.geniculata* and *N.naja* venoms are expected to contain useful
670signalling molecules due to the down regulation detected.

671

672Greater than two-fold reductions in the expression/phosphorylation were observed in Tie-2 receptor
673in response to all venoms, apart from *D.viridis*, (Figure 2) with the greatest specific reduction
674observed with *H.swammerdami* (Figure 2b) venom. Interestingly, no changes were observed in Tie-1
675receptor in response to treatment with any of the 5 selected venoms. Given Tie-1 is an orphan
676receptor and depends on dimerisation with Tie-2 to promote its activation (Savant *et al.*, 2015;
677Mueller & Kontos, 2016), it is possible that its expression and activity levels were unaffected by
678treatment with the venoms as there were no compatible binding molecules. Tie-2 mutation and
679upregulation has been linked to the development and progression of cancer, with increased
680expressions promoting the onset of angiogenesis in tumour microenvironments. Decreases in the
681expression or activation of these receptors in response to venoms, may prove beneficial in over-
682expressing tumour types, by delaying the triggering of angiogenesis. The lack of reduction in Tie-1
683receptor expression/activity may also be beneficial, as Tie-1 is thought to play a role as a tumour

684 suppressor in Tie-2 over-expressing cancers cells, by reducing Tie-2 signalling activity upon their
685 dimerisation together (Singh *et al.*, 2012).

686

687 Proto-oncogene tyrosine-protein kinase (Mer) receptor is overexpressed in many human cancers,
688 including various leukaemias and numerous solid tumours, including breast cancer (Linger *et al.*,
689 2010). Mer upregulation has been linked to increased cancer cell aggression, where like Axl, it has
690 been found over-expressed in metastatic breast cancer cells, relative to non-metastatic breast
691 cancer cells (Tavazoie *et al.*, 2008; Linger *et al.*, 2010). Frequent over-expression of Mer receptor has
692 been found to occur in human non-small cell lung cancer (NSCLC), where it has been shown to
693 attribute to erlotinib small molecule resistance, in EGFR mutated cancer types (Xie *et al.*, 2015). A
694 study by Linger *et al.*, (2013), evaluating 88 human NSCLC tumours found that Mer and Axl receptor
695 tyrosine kinases were over-expressed in 69% and 93% of the tumours tested respectively, when
696 compared to the levels of these receptors in normal surrounding lung tissue. The study also found
697 that Mer and Axl were frequently over-expressed and activated in NSCLC cell lines. They showed that
698 inhibition of Axl and Mer receptor activities promoted apoptosis, prevented proliferation and
699 enhanced the chemosensitivity of the cells (Linger *et al.*, 2013). A similar study in astrocytoma found
700 that inhibition of these receptors resulted in increased apoptosis and chemosensitivity (Keating *et*
701 *al.*, 2010). The two arachnid venoms tested in this study both reduced Mer phosphorylation levels
702 and thus could contain useful components for cancer research.

703

704 **Conclusion**

705 This study provides the first kinome scale investigation of the effects of venoms on cancer cells *in-*
706 *vitro*. The preliminary evidence identifies many previously unknown effects of venoms on receptor
707 tyrosine kinases and demonstrates the effects reported from other venoms on RTK's maybe
708 widespread throughout venomous taxa. Further work is required on fractionated venoms to identify
709 the active components responsible for these effects, to understand their evolutionary origin and

710therapeutic potential. It is clear through evolution that there is no selection pressure for venoms to
711affect cancer cells, however through this research we may uncover a greater understanding of the
712signalling pathways of venom components and their potential for therapeutic utility.

713

714**Additional information:**

715**Authorship**

716Danielle McCullough, Cristina Atofanei and Emily Knight: Investigation, Carol M Trim and Steven A
717Trim: Conceptualization, Methodology and Supervision. All authors contributed to writing original
718draft preparation, review and editing.

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724**Competing interests**

725There are no competing interests

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1304**Appendix A**

Coordinate	Receptor Family	RTK/Control		Coordinate	Receptor Family	RTK/Control
A1, A2	Reference Spots	-----		D1, D2	Tie	Tie-2
A23, A24	Reference Spots	-----		D3, D4	NGF R	Trk A
B1, B2	EGF R	EGF R		D5, D6	NGF R	Trk B
B3, B4	EGF R	ErbB2		D7, D8	NGF R	Trk C
B5, B6	EGF R	ErbB3		D9, D10	VEGF R	VEGF R1
B7, B8	EGF R	ErbB4		D11, D12	VEGF R	VEGF R2
B9, B10	FGF R	FGF R1		D13, D14	VEGF R	VEGF R3
B11, B12	FGF R	FGF R2a		D15, D16	MuSK	MuSK
B13, B14	FGF R	FGF R3		D17, D18	Eph R	Eph A1
B15, B16	FGF R	FGF R4		D19, D20	Eph R	Eph A2
B17, B18	Insulin R	Insulin R		D21, D22	Eph R	Eph A3
B19, B20	Insulin R	IGF-IR		D23, D24	Eph R	Eph A4
B21, B22	Axl	Axl		E1, E2	Eph R	Eph A6
B23, B24	Axl	Dtk		E3, E4	Eph R	Eph A7
C1, C2	Axl	Mer		E5, E6	Eph R	Eph B1
C3, C4	HGF R	HGF R		E7, E8	Eph R	Eph B2
C5, C6	HGF R	MSP R		E9, E10	Eph R	Eph B4
C7, C8	PDGF R	PDGF R α		E11, E12	Eph R	Eph B6
C9, C10	PDGF R	PDGF R β		E13, E14	Insulin R	ALK

C11, C12	PDGF R	SCF R		E15, E16	-----	DDR1
C13, C14	PDGF R	Flt-3		E17, E18	-----	DDR2
C15, C16	PDGF R	M-CSF R		E19, E20	Eph R	Eph A5
C17, C18	Ret	c-RET		E21, E22	Eph R	Eph A10
C19, C20	ROR	ROR1		F1, F2	Reference Spots	-----
C21, C22	ROR	ROR2		F5, F6	Eph R	EphB3
C23, C24	Tie	Tie-1		F7, F8	-----	RYK
				F23, F24	Control (-)	PBS

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1306 **Table A.1 Human p-RTKs.**

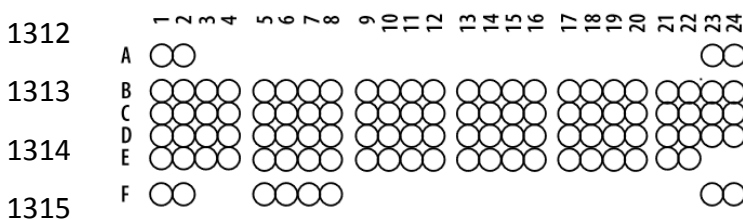
1307 The table displays a list of each RTK probed for on the kinome array membranes, the sub-family of RTKs they belong to, and
 1308 their relevant coordinate location on each blot.

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Human Phospho-RTK Array Coordinates

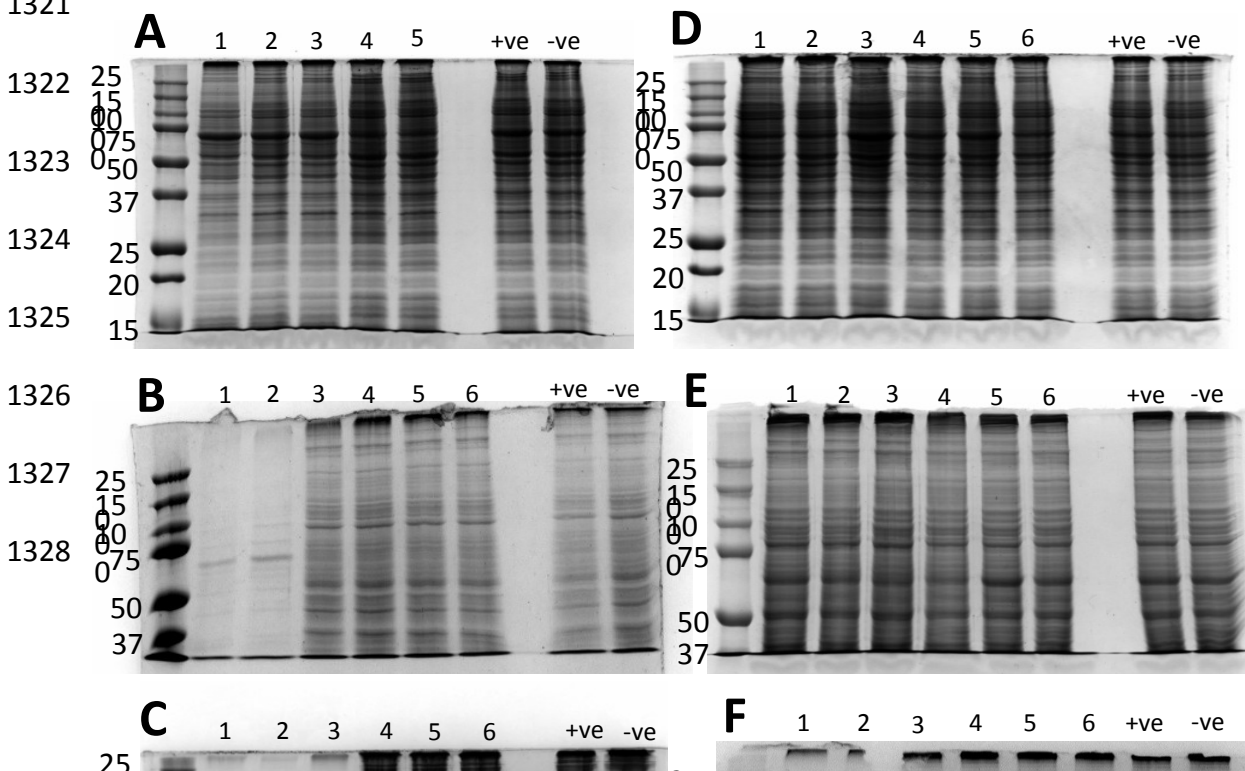


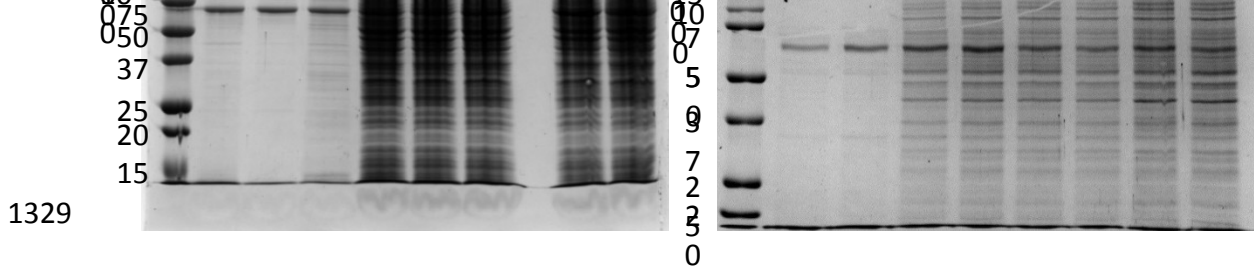
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Appendix B - Venom

1317 The following SDS PAGE gels (Appendix B figure B.1) were used to optimise the concentrations of
 1318 venom used to treat the cells in the kinome blots and Western blots of EGFR. The gels show the
 1319 effect of the venoms on the whole proteome and which concentration the venoms become toxic to
 1320 the cells reducing the protein available.

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1335 **Figure B1: Coomassie Gel Analysis of Venom Toxicities**

1336 **A.** MDA-MB-468 cell lysates from cells treated with a serial dilution of whole *A.geniculata* venom lanes 1-5 (1:1/50, 1337 2:1/100, 3:1/1000, 4:1/10,000, 5:1/100,000, respectively). **B.** MDA-MB-468 lysates from cells treated with a serial dilution 1338 of whole *D.viridis* venom lanes 1-6 (1:1/50, 2:1/100, 3:1/1000, 4:1/10,000, 5:1/100,000, 6:1/1,000,000 respectively). **C.** 1339 MDA-MB-468 lysates from cells treated with a serial dilution of whole *N.naja* venom 1-6 (1:1/50, 2:1/100, 3:1/1000, 1340 4:1/10,000, 5:1/100,000, 6:1/1,000,000 respectively). **D.** MDA-MB-468 lysates from cells treated with a serial dilution of 1341 whole *C.durissus vegrandis* venom 1-6 (1:1/50, 2:1/100, 3:1/1000, 4:1/10,000, 5:1/100,000, 6:1/1,000,000 respectively). **E.** 1342 Displays the Coomassie gel analyses of MDA-MB-468 lysates from cells treated with a serial dilution of whole 1343 *H.swammerdami* venom 1-6 (1:1/50, 2:1/100, 3:1/1000, 4:1/10,000, 5:1/100,000, 6:1/1,000,000 respectively). **F.** MDA- 1344 MB-468 lysates from cells treated with a serial dilution of whole *P.liosoma* venom lanes 1-6 (1:1/50, 2:1/100, 3:1/1000, 1345 4:1/10,000, 5:1/100,000, 6:1/1,000,000 respectively). All positive controls were produced from MDA-MB-468 cells treated 1346 with 1×10^{-7} M EGF (No venom, +EGF). All negative controls were produced from untreated MDA-MB-468 cells (No venom, - 1347 EGF).

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1349 **Appendix C**

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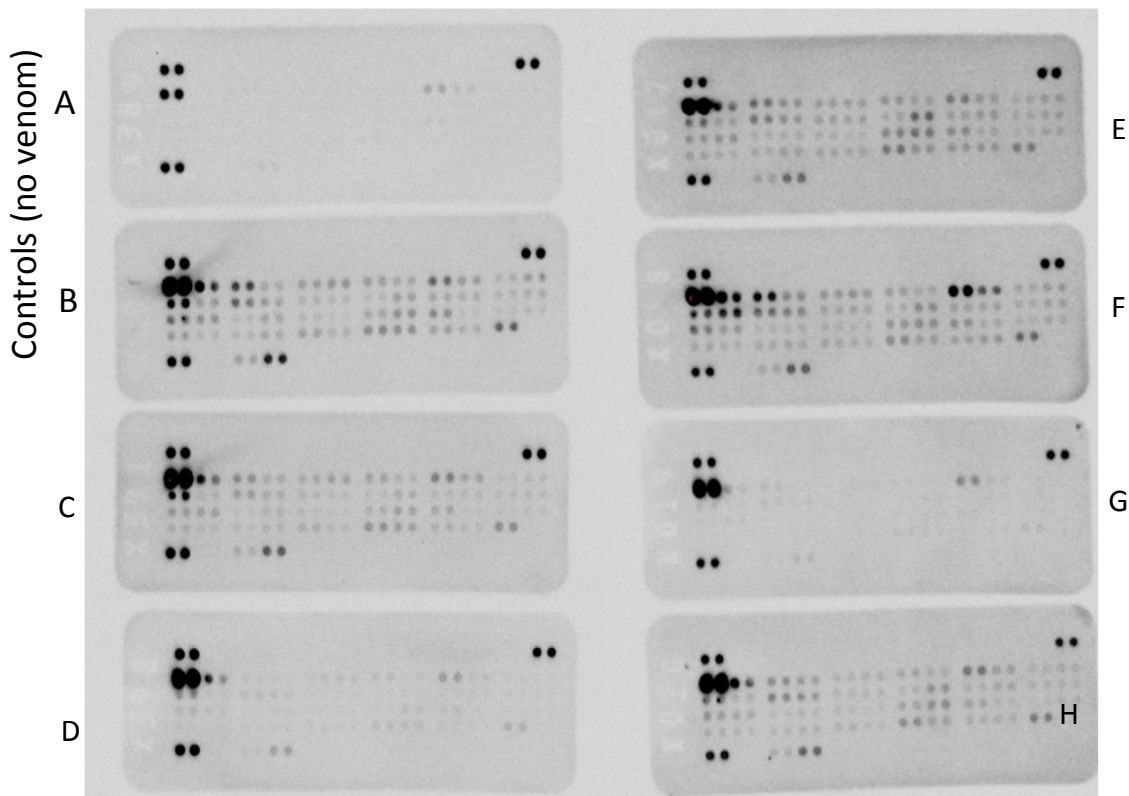
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1368 Figure C.1: Kinome array analyses of MDA-MB-468 cells treated with whole venoms

1369 The kinome arrays show changes in the expression and activity of 47 receptor tyrosine kinases in MDA-MB-468 cells in
 1370 response to the application of the six venoms of interest. All cells were treated with the venoms for two hours and
 1371 subsequently stimulated with 1x10⁻⁷M EGF for five minutes except for the positive and negative controls **A.** Receptor
 1372 expression and activity levels in untreated MDA-MB-468 cells which have not been stimulated with 1x10⁻⁷M EGF (Negative
 1373 control). **B.** Receptor expression and activity levels in untreated MDA-MB-468 cells which have been stimulated with 1x10⁻⁷M
 1374 EGF for five minutes (positive control). **C.** Receptor expression and activity levels of MDA-MB-468 cells which have been
 1375 treated with a 1/10,000 dilution (0.025mg/ml) of *N.naja* venom. **D.** Receptor expression and activity levels of MDA-MB-468
 1376 cells which have been treated with a 1/150 dilution (1.5mg/ml) of *P.liosoma* venom. **E.** Receptor expression and activity
 1377 levels of MDA-MB-468 cells which have been treated with a 1/50 dilution (2mg/ml) of *H.swammerdami* venom. **F.** receptor
 1378 expression and activity levels of MDA-MB-468 cells which have been treated with a 1/10,000 dilution (0.025mg/ml) of
 1379 *D.viridis* venom. **G.** Receptor expression and activity levels of MDA-MB-468 cells which have been treated with a 1/1,000
 1380 dilution (0.065mg/ml) of *C.durissus vegrandis* venom. **H** Receptor expression and activity levels of MDA-MB-468 cells
 1381 which have been treated with a 1/100 dilution (2.5mg/ml) of *A.geniculata* venom.

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1388 Appendix D

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	<i>A. gen</i>	<i>C. dve</i>	<i>D. vir</i>	<i>H. swa</i>	<i>N. naj</i>
EGFR	X	X	X	X	X
HER2	X	√	X	√	√
HER3	√	√	X	X	√
HER4	X	√	X	√	X
FGF R1	√	√	X	X	√
FGF R2 alpha	√	√	X	X	X
FGF R3	X	√	X	X	X
FGF R4	X	√	X	X	X
Insulin R	X	X	√	X	X
IGF-I R	X	√	X	X	X
Axl	X	√	X	X	X
Dtk	√	X	X	X	√
Mer	√	√	√	√	X
HGF R	√	√	√	X	√
MSP R	X	√	X	X	√
PDGF R alpha	X	√	X	X	X
PDGF R beta	X	√	X	X	X
SCF R	X	√	X	X	X
Flt-3	X	√	X	X	X
M-CSF R	X	√	X	√	X
c-RET	X	√	√	X	X
ROR1	X	√	X	X	√
ROR2	X	√	X	X	X
Tie-1	X	X	X	X	X
Tie-2	√	√	X	√	√
Trk A	√	√	X	X	√

Trk B	X	√	X	X	√
Trk C	√	√	X	X	X
VEGF R1	X	√	X	X	X
VEGF R2	X	√	X	X	X
VEGF R3	X	√	X	X	X
MuSK	X	√	X	X	X
Eph A1	X	√	X	X	X
Eph A2	X	√	X	X	√
Eph A3	X	√	X	X	X
Eph A4	X	√	X	X	X
Eph A5	X	√	X	X	X
Eph A6	√	√	√	X	X
Eph A7	√	√	X	X	X
Eph A10	X	√	X	X	X
Eph B1	X	√	X	√	X
Eph B3	X	√	X	√	X
Eph B2	X	√	X	X	X
Eph B4	√	√	X	X	X
Eph B6	√	√	X	X	X
ALK	X	√	X	X	X
DDR1	X	√	X	X	X
DDR2	√	√	X	X	X
RYK	√	√	X	X	X

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1391**Table D.1: Changes in RTK expression/phosphorylation state in response to treatment with whole venoms.**

1392The table displays 2-fold or greater reductions or increases in the combined phosphorylation/expression profile of each of
139349 receptor tyrosine kinases in response to 5 whole venom treatments. Greater than 2-fold upregulations in green, greater
1394than 2-fold downregulation in red.

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1399Appendix E

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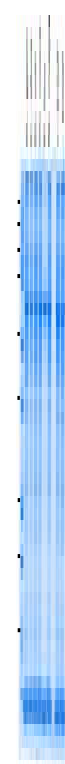
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1461 Appendix F

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P61898 NGFV_NAJAT      1  EDHPVHNLGEHSVCDSVSAWVTKTTATDIKGNTVTVMENVNLDNKVYKEYFFETKCKNPN      60
P61899 NGFV_NAJKA      1  EDHPVHNLGEHSVCDSVSAWVTKTTATDIKGNTVTVMENVNLDNKVYKEYFFETKCKNPN      60
P01140 NGFV_NAJNA      1  EDHPVHNLGEHSVCDSVSAWVTKTTATDIKGNTVTVMENVNLDNKVYKEYFFETKCKNPN      60
*****

P61898 NGFV_NAJAT      61  PEPGCRGIDSSHWSYCTETDTFIKALTMEGNQASWRFIRIETACVCVITKKGKGN      116
P61899 NGFV_NAJKA      61  PEPGCRGIDSSHWSYCTETDTFIKALTMEGNQASWRFIRIETACVCVITKKGKGN      116
P01140 NGFV_NAJNA      61  PEPGCRGIDSSHWSYCTETDTFIKALTMEGNQASWRFIRIDTACVCVITKKTGN      116
*****;*****.***
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1468 **Figure F.1 Alignment of cobra Nerve Growth Factors (NGF).** Although other neurotrophins are present in elapid snakes

1469 this alignment focuses on those of the same size across the species relevant to this manuscript.

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