COVID 19 IS SNAKE VENOM PROOF

PRESENTED BY DR BRYAN ARDIS

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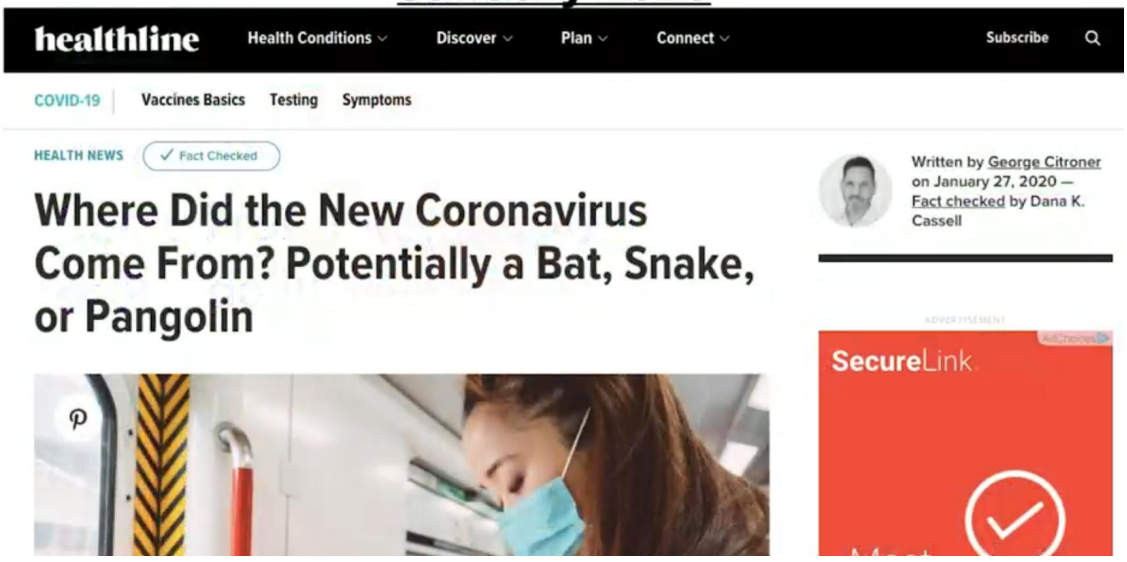

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The new coronavirus was first detected in Wuhan, China. Getty Images

- Coronaviruses are named for their crown-like shape, and were first identified in the mid-1960s. The virus typically causes respiratory illnesses like the common cold.
- A new study found the virus may have originated in bats and then spread to humans via a snake or pangolin.
- Seven coronaviruses are known to infect humans.

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Shen Yongyi, a professor with the university and member of the research team, told the Xinhua news service that although previous research found the novel coronavirus originated in bats, the animals hibernate in winter, making it unlikely that they caused the current outbreak.

However, the actual study hasn't been published. So far, the university has only issued a press release.

January 2020

Snakes could be the source of the Wuhan coronavirus outbreak

THE CONVERSATION

By Haitao Guo, Guangxiang "George" Luo and Shou-Jiang Gao, The Conversation

Updated 2041 GMT (0441 HKT) January 24, 2020

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(CNN) — Snakes -- the Chinese krait and the Chinese cobra -- may be the original source of the newly discovered coronavirus that has triggered an outbreak of a deadly infectious respiratory illness in China this winter.

The many-banded krait (Bungarus multicinctus), also known as the Taiwanese krait or the Chinese krait, is a highly venomous species of elapid snake found in much of central and southern China and Southeast Asia.

Related Article: Wuhan coronavirus death toll rises, as city imposes transport lackdown

The illness was first reported in late December 2019 in Wuhan, a major city in central China, and has been rapidly spreading. Since then, sick travelers from Wuhan have infected people in China and other countries, including the United States.

Using samples of the virus isolated from patients, scientists in China have determined the

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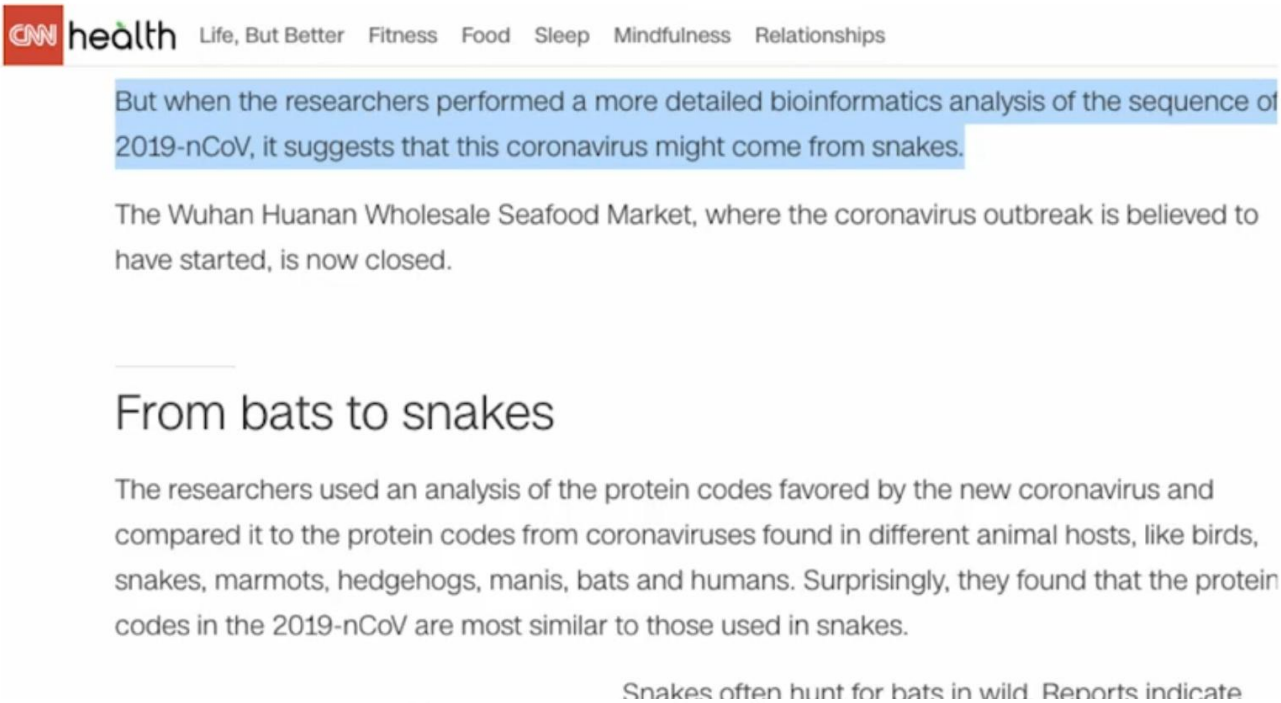

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But when the researchers performed a more detailed bioinformatics analysis of the sequence of 2019-nCoV, it suggests that this coronavirus might come from snakes.

The Wuhan Huanan Wholesale Seafood Market, where the coronavirus outbreak is believed to have started, is now closed.

From bats to snakes

The researchers used an analysis of the protein codes favored by the new coronavirus and compared it to the protein codes from coronaviruses found in different animal hosts, like birds, snakes, marmots, hedgehogs, manis, bats and humans. Surprisingly, they found that the protein codes in the 2019-nCoV are most similar to those used in snakes.

Snakes often hunt for bats in wild. Reports indicate

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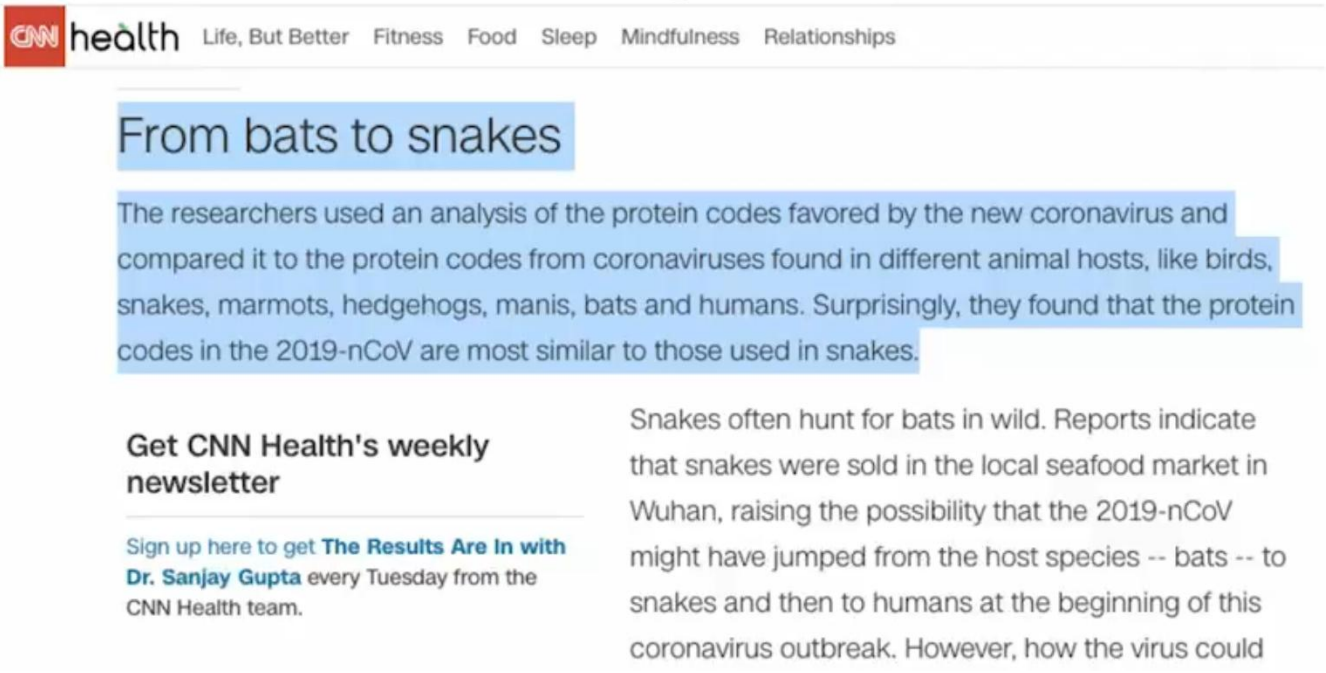

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From bats to snakes

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Snakes often hunt for bats in wild. Reports indicate that snakes were sold in the local seafood market in Wuhan, raising the possibility that the 2019-nCoV might have jumped from the host species -- bats -- to snakes and then to humans at the beginning of this coronavirus outbreak. However, how the virus could

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No, snakes probably aren't the source of that new coronavirus in China

New research pinpoints the reptiles, but virus researchers aren't convinced

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Wei Ji, a microbiologist at Peking University Health Science Center School of Basic Medical Sciences in Beijing, and his colleagues analyzed codons used by 2019-nCoV. Codons, which are trios of DNA or RNA that dictate amino acids in a protein, tend to be similar between a virus and the animal it infects. The team compared 2019-nCoV's codons with those in potential animal reservoirs, including humans, chickens, bats, hedgehogs, pangolins and two snake species.

Based on similarities between the virus's codons and those of its potential animal hosts, "snake is the most probable wildlife animal reservoir for the 2019-nCoV," the researchers write. Wei and his team suggest a virus from the many-banded krait (*Bungarus multicinctus*) or Chinese cobra (*Naja atra*) may have combined with a bat virus and sparked the new outbreak.

But "coronaviruses tend to be found in mammals," says David Robertson, a virologist at the University of Glasgow in Scotland. So it's improbable the new virus came from snakes, he says.

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"recombination" of a viral protein that recognizes and binds to receptors on host cells. Such recognition is key to allowing viruses to enter host cells, which can lead to infection and disease.

Finally, the team uncovered evidence that the 2019-nCoV likely resided in snakes before being transmitted to humans. Recombination within the viral receptor-binding protein may have allowed for cross-species transmission from snake to humans.

"Results derived from our evolutionary analysis suggest for the first time that snake is the most probable wildlife animal reservoir for the 2019-nCoV," the authors wrote. "New information obtained from our evolutionary analysis is highly significant for effective control of the outbreak caused by the 2019-nCoV-induced pneumonia."

An accompanying editorial notes that although the ultimate control of emerging viral infections requires the discovery and development of effective vaccines and/or antiviral drugs, currently licensed antiviral drugs should be tested against the 2019-nCoV.

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RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Cross-species transmission of the newly identified coronavirus 2019-nCoV

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Abstract

The current outbreak of viral pneumonia in the city of Wuhan, China, was caused by a novel coronavirus designated 2019-nCoV by the World Health Organization, as determined by sequencing the viral RNA genome. Many initial patients were exposed to wildlife animals at the Huanan seafood wholesale market, where poultry, snake, bats, and other farm animals were also sold. To investigate possible virus

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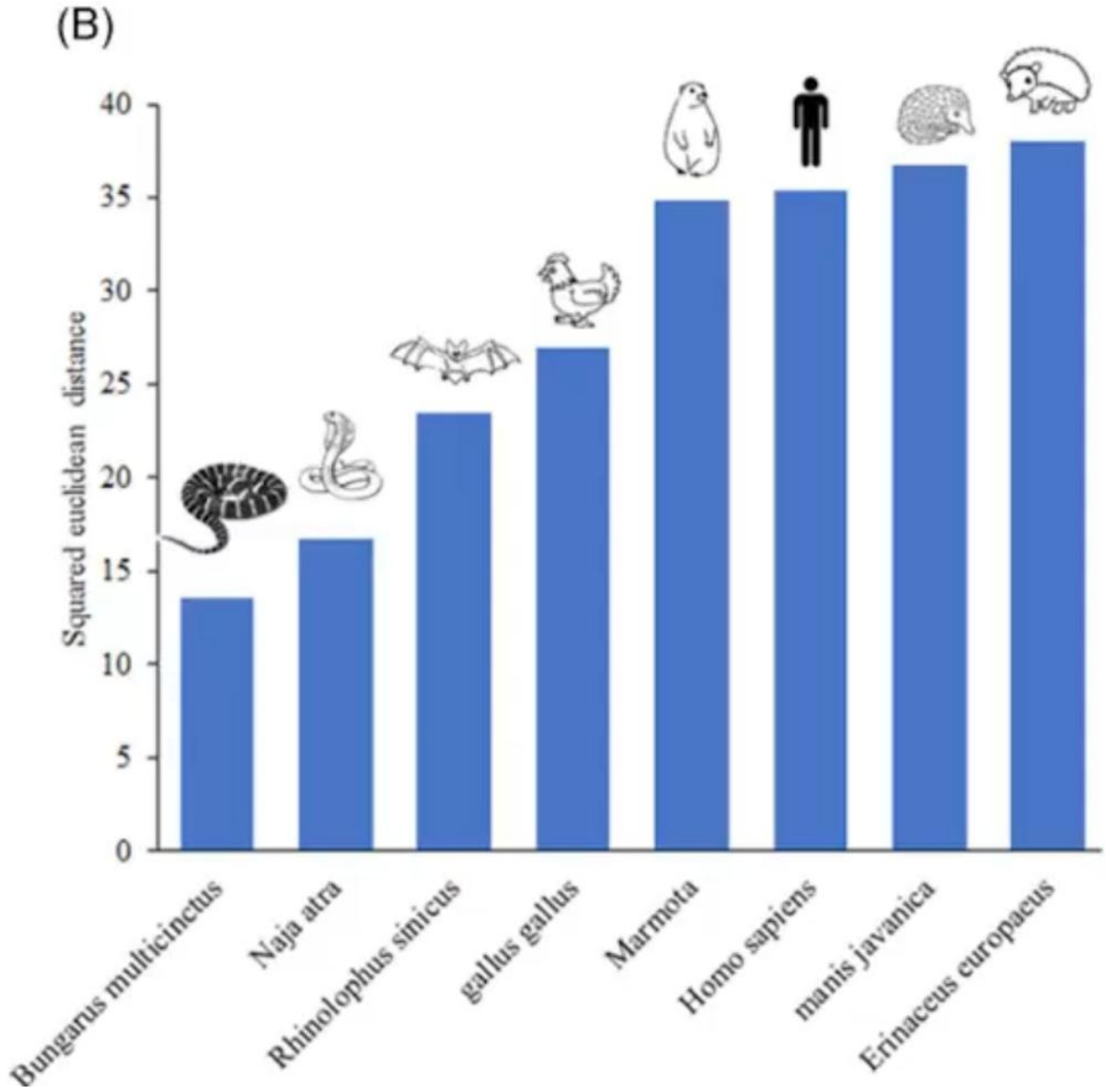
virus,[21] hepatitis B virus,[22] hepatitis C virus,[23] and classical swine fever virus.[18] Similarity plot analysis of the 2019-nCoV revealed that homologous recombination may occurred between Clade A strains (bat-coronaviruses) and the origin-unknown isolates, located within the spike glycoprotein that recognizes cell surface receptor (Figure 2). These characteristics indicate that cross-species transmission may be caused by homologous recombination.

3.3 | Relative synonymous codon usage analysis

As parasitic microorganism, virus codon usage pattern resembles its host to some extent. The RSCU bias shows that the 2019-nCoV, bat-SL-CoVZC45, and snakes from China have similar synonymous codon usage bias (Figure 3A, Table 1). The squared euclidean distance indicates that the 2019-nCoV and snakes from China have the highest similarity in synonymous codon usage bias compared to those of bat, bird, Marmota, human, Manis, and hedgehog and (Figure 3B). Two types of snakes, containing *B. multicinctus* (many-banded krait) and *N. atra* (Chinese cobra) were used for RSCU analysis. Squared Euclidean distance between the 2019-nCoV and *B. multicinctus* is 13.54. The distance between the 2019-nCoV and another snake *N. atra* is 16.69. The distance between the 2019-nCoV and Rhinolophus sinicus is 23.46. However, the distance between the 2019-nCoV and other animals is greater than 26, specifically 26.93 for bird, 34.79 for Marmota, 35.36 for human, 36.71 for Manis, and 37.96 for hedgehog. These data suggest that the 2019-nCoV might more effectively use snake's translation machinery than that of other animals.

Two types of snakes are common in Southeastern China including the city of Wuhan (Figure 4). Geographical distributions of *B. multicinctus* include Taiwan, the Central and Southern China, Hong Kong, Myanmar (Burma), Laos, and Northern Vietnam.[24] *N. atra* is found in Southeastern China, Hong Kong, Northern Laos, Northern Vietnam, and Taiwan.[25] Snakes were also sold at the



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other mammals.[27] Bootscanning plot analysis (data not shown) suggested that the major parents of the 2019-nCoV originated from Clade A (bat-SL-CoVZC45 and bat-SL-CoVZXC21) but formed a monophyletic cluster different from them. Overall, the ancestral origin of the 2019-nCoV was more likely from divergent host species rather than SARS-CoV.

The host range of some animal coronaviruses was promiscuous.[7] They caught our attention only when they caused human diseases

In summary, results derived from our evolutionary analysis suggest that 2019-nCoV has most similar genetic information with bat coronovirus and has most similar codon usage bias with snake. Additionally, a homologous recombination may occured within the viral receptor-binding spike glycoprotein, which may determine cross-species transmission. These novel findings warrant future investigation to experimentally determine if

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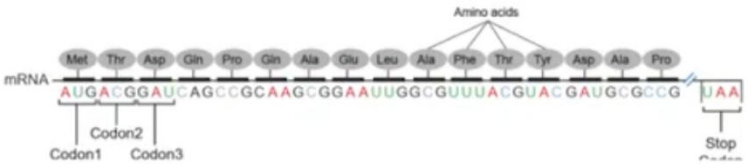
Codon

A codon is a trinucleotide sequence of DNA or RNA that corresponds to a specific amino acid. The genetic code describes the relationship between the sequence of DNA bases (A, C, G, and T) in a gene and the corresponding protein sequence that it encodes. The cell reads the sequence of the gene in groups of three bases. There are 64 different codons: 61 specify amino acids while the remaining three are used as stop signals.

Illustration



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Codon usage bias

Sujatha Thankeswaran Parvathy [1], Varatharajalu Udayasuriyan [2], Vijaipal Bhadana [3]

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Abstract

Codon usage bias is the preferential or non-random use of synonymous codons, a ubiquitous phenomenon observed in bacteria, plants and animals. Different species have consistent and characteristic codon biases. Codon bias varies not only with species, family or group within kingdom, but also between the genes within an organism. Codon usage bias has evolved through mutation, natural selection, and genetic drift in various organisms. Genome composition, GC content, expression level and length of genes, position and context of codons in the genes, recombination rates, mRNA folding, and tRNA abundance and interactions are some factors influencing codon bias. The factors shaping codon bias may also be involved in evolution of the universal genetic code. Codon-usage bias is critical factor determining gene expression and cellular function by influencing diverse processes such as RNA processing, protein translation and protein folding. Codon usage bias reflects the origin, mutation patterns and evolution of the species or genes. Investigations of codon bias patterns in genomes can reveal phylogenetic relationships between organisms, horizontal gene transfers, molecular evolution of genes and identify selective forces that drive their evolution. Most important application of codon bias analysis is in the design of transgenes, to increase gene expression levels through codon optimization, for development of

Phospholipase enzymes as potential biomarker for SARS CoV-2 virus

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Abstract-

Severe acute respiratory syndrome corona virus 2 (SARS CoV-2) is the responsible pathogenic RNA virus which is responsible for current ongoing pandemic covid 19. This review provides an updated summary of the current knowledge of phospholipase enzymes and its role on SARS CoV-2 virus, discussing the reported evidence as a potential bio marker and future directions that could be used to develop PLAs as a therapeutic target for covid 19 pandemic.

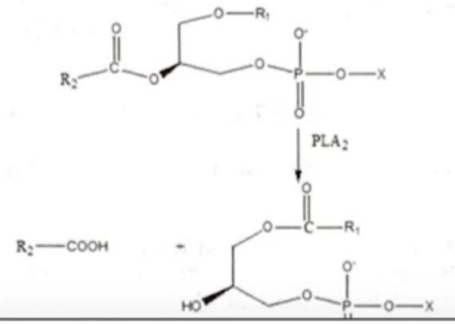
Index terms- bio marker, covid 19, LpPLA2, SARS CoV-2, sPLA2, therapeutic target

6. AdPLA2 - adipose PLA2

Among them, sPLA2 is the first discovered group of PLA2 enzymes, which was discovered as a component of cobra venom [22]. PLA2 has been identified as one of the main components of animal venom. Elapidae and Viperidae family snakes having sPLA2 group IA, IIA or IIB as the main component in snake venom [23]. Snake venom PLA2s induce pathophysiological alterations in the victim by hydrolyzing phospholipids in membranes [23].

Among all existing isoforms of phospholipase enzymes, sPLA2 mainly play a major role in developing drug target as inhibitors since it involves in many inflammatory conditions [24].

Studies about this sPLA2 enzyme and its function, hold great importance since PLA2 catalyzes the release of arachidonic acid, which is believed to be the rate-limiting event in the generation of pro-inflammatory lipid mediators (prostaglandins, leukotrienes, lipoxins) and platelet-activating factor [25]. Release of these mediators initiates the pain, swelling, and other unpleasant symptoms we experience as part of an inflammatory response [26].



*HYDROLYZING, THE BREAKING DOWN OF THE CELL STRUCTURE IN ORGANS

7.3 ROLE OF PLA2 IN LUNG INFECTIONS AND RELATED RESPIRATORY PROBLEMS

There are some evidence that elevated level of PLA2 is patients with lung infections and respiratory problems. Pulmonary surfactant is important to maintain alveolar stability by lowering surface tension along the alveolar epithelium. Destruction of this surface tension will results in lung injury (Acute Respiratory distress Syndrome ARDS) [44].

sPLA2 enzyme leads to hydrolyze phospholipid surfactant and destruction of surface tension. It had been found that inhibition of sPLA2 activity play a protective role in lung injury by maintaining surfactant integrity [45]. It was also reported that various sPLA2 isoforms are produced in lungs by macrophages and epithelial cells [46].

Using multicenter translational study including several pediatric and neonatal intensive care units suggested that sPLA2 might be the main cross road between inflammation and surfactant dysfunction in lungs [47].

Moreover it had been suggested that sPLA2 V and X participated to the lung injury by lipid mediator production and surfactant hydrolysis [48].There are patients with severe asthma showed increasing sPLA2 activity [49].

http://dx.doi.org/10.29322/IJSRP.11.01.2021.p10919 www.ijsrp.org

While both men and women have the same prevalence to SARS CoV-2 without any gender discrimination, men is more susceptible to face more complications and death [55]. Study [49] was evidenced the inverse correlation of sPLA2 activity with vitamin c concentration in covid 19 patients. Interestingly the vitamin C concentration in plasma is lower in males than females [49]. It also links with the severity of covid 19 in males with the correlation of increasing sPLA2 activity and the decrease in vitamin C content.

$LpPLA_2$ is a member of the GVII family of PLA_2 enzymes. This enzyme was named for its ability to cleave the acetyl group from the *sn*-2 position of PAF, as well as its association with lipoproteins [57] . It was well established that increasing LPPLA2 is a reliable marker for the risk of cardiovascular events. It had been evidenced that LpPLA2 level upregulation is mainly found in non-hospitalized covid 19 patients. This abnormal increase LpPLA2 was observed in covid 19 re-positive patients as well [58], [59], [60]. Those patients are not showed promising symptoms of pneumonia, however sometimes they first experienced cardiovascular symptoms [61]. The limited medical care of these patients may follow up cardiovascular diseases.

Another study was revealed that Increasing rates of LpPLA2 were positively correlated with not only viral loads in patients with COVID-19 but also severity of pneumonia in non-COVID-19 patients. Therefore it could be suggested that increased levels of Lp-PLA2 in plasma could provide insights to higher mortality was seen in patients underlying comorbidities (e.g. hypertension, diabetes mellitus, cardiovascular disease) [62].

Moreover proteomics studies of covid 19 infected host cell showed a potential link with inflammatory response supported by increasing of PLA2 at 24h after virus infection [63].

Above studies revealed the contribution of phospholipase enzymes to SARS CoV-2 into some extent. However, it would be further investigated beyond the current understanding.

August 2021

Like Venom Coursing Through the Body: Researchers Identify Mechanism Driving COVID-19 Mortality

Researchers have identified what may be the key molecular mechanism responsible for COVID-19 mortality – an enzyme related to neurotoxins found in rattlesnake venom.

Collaboration Amid Chaos

"The idea to identify a potential prognostic factor in COVID-19 patients originated from Dr. Chilton," Del Poeta said. "He first contacted us last fall with the idea to analyze lipids and metabolites in blood samples of COVID-19 patients."

Del Poeta and his team collected stored plasma samples and went to work analyzing medical charts and tracking down critical clinical data from 127 patients hospitalized at Stony Brook University Hospital between January and July 2020. A second, independent cohort included a mix of 154 patient samples collected from Stony Brook and Banner University Medical Center in Tucson between January and November 2020.

"These are small cohorts, admittedly, but it was a heroic effort to get them and all associated clinical parameters from each patient under these circumstances," Chilton said. "As opposed to most studies that are well planned out over the course of years, this was happening in real time on the ICU floor."

The research team was able to analyze thousands of patient data points using machine learning algorithms. Beyond traditional risk factors such as age, body mass index and preexisting conditions, the team also focused on biochemical enzymes, as well as patients' levels of lipid metabolites.

Researchers from the University of Arizona, in collaboration with Stony Brook University and Wake Forest School of Medicine, analyzed blood samples from two COVID-19 patient cohorts and found that circulation of the enzyme – secreted phospholipase A2 group IIA, or sPLA2-IIA, – may be the most important factor in predicting which patients with severe COVID-19 eventually succumb to the virus.

The sPLA2-IIA enzyme, which has similarities to an active enzyme in rattlesnake venom, is found in low concentrations in healthy individuals and has long been known to play a critical role in defense against bacterial infections, destroying microbial cell membranes.

When the activated enzyme circulates at high levels, it has the capacity to "shred" the membranes of vital organs, said **Floyd (Ski) Chilton**, senior author on the paper and director of the UArizona Precision Nutrition and Wellness Initiative in the university's **College of Agriculture and Life Sciences** (https://cals.arizona.edu/).

"It's a bell-shaped curve of disease resistance versus host tolerance," said Chilton, a member of the university's **BIO5 Institute**(https:// other words, this enzyme is trying to kill the virus, but at a certain point it is released in such high amounts that things head in a really bad direction, destroying the patient's cell membranes and thereby contributing to multiple organ failure and death."

An Enzyme with a Bite

The role of the sPLA2-IIA enzyme has been the subject of study for half of a century and it is "possibly the most examined member of the phospholipase family," Chilton explained.

Charles McCall, lead researcher from the Wake Forest School of Medicine on the study, refers to the enzyme as a "shredder" for its known prevalence in severe inflammation events, such as bacterial sepsis, as well as hemorrhagic and cardiac shock.

Previous research has shown how the enzyme destroys microbial cell membranes in bacterial infections, as well as its similar genetic ancestry with a key enzyme found in snake venom.

The protein "shares a high sequence homology to the active enzyme in rattlesnake venom and, like venom coursing through the body, it has the capacity to bind to receptors at neuromuscular junctions and potentially disable the function of these muscles," Chilton said.

"Roughly a third of people develop long COVID, and many of them were active individuals who now can't walk 100 yards," Chilton said. "The question we are investigating now is: If this enzyme is still relatively high and active, could it be responsible for part of the long COVID outcomes that we're seeing?"

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The Indian cobra reference genome and transcriptome enables comprehensive identification of venom toxins

Kushal Suryamohan, Sajesh P. Krishnankutty, ... Somasekar Seshagiri ✉ + Show authors

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Abstract

The Indian cobra reference genome and transcriptome enables comprehensive identification of venom toxins

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Abstract

Snakebite envenoming is a serious and neglected tropical disease that kills ~100,000 people annually. High-quality, genome-enabled comprehensive characterization of toxin genes will facilitate development of effective humanized recombinant antivenom. We report a de novo near-chromosomal genome assembly of *Naja naja*, the Indian cobra, a highly venomous, medically important snake. Our assembly has a scaffold N50 of 223.35 Mb, with 19 scaffolds containing 95% of the genome. Of the 23,248 predicted protein-coding genes, 12,346 venom-gland-expressed genes constitute the 'venom-ome' and this included 139 genes from 33 toxin families. Among the 139 toxin genes were 19 'venom-ome-specific toxins' (VSTs) that showed venom-gland-specific expression, and these probably encode the minimal core venom

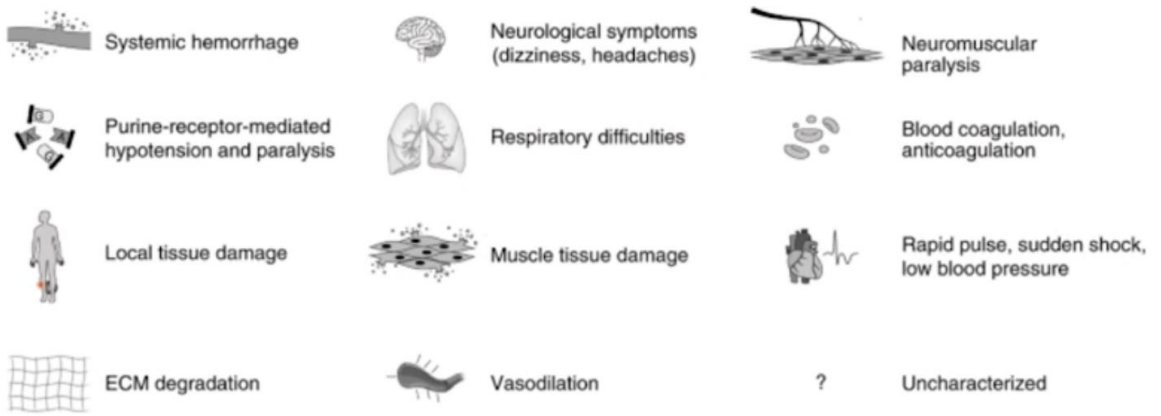
19 GENE TOXINS FROM KING COBRAS IN COVID 19

January 2020

The Indian cobra reference genome and transcriptome enables comprehensive identification of venom toxins

Overall, we found evidence for expression of 12,346 genes that constitute the venom-ome, and this included 139 toxin genes of which 19 were designated as VSTs based on their venom-gland-specific expression. Additionally, well-known modulators of venom function such as CVF, coagulation factors, protein disulfide isomerases, natriuretic peptides, hyaluronidases, PLA2s, phospholipase B-like genes, LAAO, vascular endothelial growth factor (VEGF) and 5′ nucleotidases were also found to be highly expressed in the venom gland. It is likely that these genes, together with the 19 VSTs, form the core toxic effector components of the venom and induce a wide range of symptoms including cardiovascular dysfunction, muscular paralysis, nausea, blurred vision and systemic effects such as hemorrhage[6] (Fig. 6). We propose that neutralization of these core venom effectors using antibodies would be an effective therapeutic strategy. Furthermore, given the variation in venom composition, cataloging the venom gland gene repertoire and its variation (Extended Data Fig. 10 and Supplementary Note), both within and across different snake species, will be important for developing a broadly efficacious antivenom[74,75].

The Indian cobra reference genome and transcriptome enables comprehensive identification of venor



The 19 VSTs, accessory venom proteins (AVPs) and their primary physiological targets. ECM, extracellular matrix; PDIs, protein disulfide isomerases. See Supplementary Table 6b (column L) for VST and AVP gene names.

February 2015: Acute Kidney Injury

(Fig. 1B). Since the toxic substances are circulated throughout the body with blood flow and whole blood samples of higher organism are filtered in the kidney. So kidney injury is among the common and most serious symptoms of cobra envenoming. The result of the present observations (Fig. 1B) were in agreement with findings reported by Amany et al. [15] which indicated that inflammatory cellular infiltration, vacuolation in the tubule and shrinkage of glomeruli in most cases in renal structure of envenoming mice injected with 1/2 LD_{50} *N. haje* venom.

KIDNEY FAILURE SIDE EFFECT OF REMDESIVIR

Ethics declarations

Competing interests

A. G. received payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation and from the Ben C. Martin Law Firm for work related to the Cook inferior vena cava filter litigation; received consulting fees from Edward Lifesciences; and holds equity in the healthcare telecardiology startup Heartbeat Health. B. B. reports being a consulting expert, on behalf of the plaintiff, for litigation related to a specific type of inferior vena cava filter. A. J. K. reports institutional funding to Columbia University and/or the Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, Philips, and ReCor Medical. J. M. B. reports an honorarium for participation on a grants review panel for Gilead Biosciences. D. A. is founder, director, and chair of the advisory board of Forkhead Therapeutics. H. M. K. works under contract with the Centers for Medicare & Medicaid Services to support quality measurement programs; was a recipient of a research grant, through Yale University, from Medtronic and the US Food and Drug Administration to develop methods for post-market surveillance of medical devices; was a recipient of a research grant with Medtronic and is the recipient of a research grant

The Indian cobra reference genome and transcriptome enables comprehensive identification of venom toxins

Ethics declarations

Competing interests

Employees of Genentech hold Roche shares/options, and employees of MedGenome hold MedGenome shares/options.

Additional information

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August 2011

NEWS

Gilead Sciences to purchase biologics process research and clinical manufacturing facility from Genentech

By Gilead Sciences Inc

8 August 2011

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Remember, sPLA2 in COVID-19 Patients was first discovered in Cobra Venom

6. AdPLA2 - adipose PLA2

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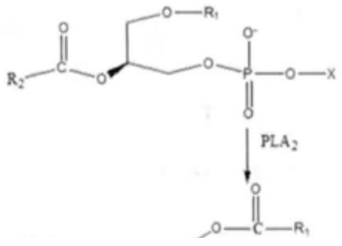


August 2011

Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the company has signed a definitive agreement under which Gilead will purchase a clinical biologics manufacturing facility and certain process development assets located in Oceanside, California from Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY). The agreement covers Genentech's Oceanside Clinical Plant (OCP), a 70,000 square-foot facility at 4049 Avenida de la Plata, as well as certain other process development assets. Gilead will hire certain of Genentech's biologics manufacturing specialists and process development scientists familiar with the facilities to assist with Gilead's operations. Genentech will continue to operate and maintain ownership of the Oceanside Commercial Manufacturing (OCN) facilities at One Antibody Way and other adjacent land.

The companies expect the transaction to close in the third quarter of this year, subject to satisfaction of certain conditions. As part of the acquisition, approximately 55 current Genentech clinical manufacturing and process development employees will be offered employment at Gilead. All

August 2011

The companies expect the transaction to close in the third quarter of this year, subject to satisfaction of certain conditions. As part of the acquisition, approximately 55 current Genentech clinical manufacturing and process development employees will be offered employment at Gilead. All employees joining Gilead from Genentech will be working in the OCP facility.

The OCP facility is currently designed and equipped to produce biologic compounds for toxicological, Phase 1 and Phase 2 clinical studies. Initially, Gilead will use the facility for the process development and manufacture of GS 6624 (formerly AB0024), an investigational monoclonal antibody candidate in development for treatment of certain cancers and for fibrotic diseases, and another antibody which is currently in preclinical testing.

GILEAD AND GENETECH TOGETHER

February 2015: just like Sars-Cov-2 Coincidenc

The venom phospholipase (PLA_2) is probably the key factor responsible for tissue injury by disturbing cell membrane permeability through disorganizing of lipid bilayer on the plasma membrane resulting pore formation with subsequent influx of Na^+ and water [21]. Interaction between plasma membrane and phospholipase encourages the reduction of Na^+/K^+ ATPase activities with subsequent changes in the ionic gradients and followed by disordering the membrane lipid bilayer ultimately leading to cell death of envenomated person [22]. It is predicted that all the noticed renal injury

February 2015

3.2 Histopathological Changes in Lung Tissue

Pulmonary tissues of control mice (Fig. 2A) showed the normal and compact organization of bronchii, bronchioles and terminal bronchioles followed by specialized sac-like structures called alveoli consisting surface epithelium, blood vessels and supporting tissue surrounded by a double layer membrane structure called plura. Crude cobra venom persuaded some severe changes in their histological structure by showing significant inflammatory cellular infiltration and edema (Fig. 2B). The organism of envenomated group also showed alveolar haemorrhage and mionecrosis after 6 hours of envenomation with LD_{50} dose of cobra venom.

February 2015: Like Those on Remdesivir

edema (Fig. 2B). The organism of envenomated group also showed alveolar haemorrhage and mionecrosis after 6 hours of envenomation with LD_{50} dose of cobra venom.

The essentiality to maintain the integrity of lung is inevitable for any higher animal due to its gaseous exchange activity and cleaning of blood cells with oxygen.

February 2015

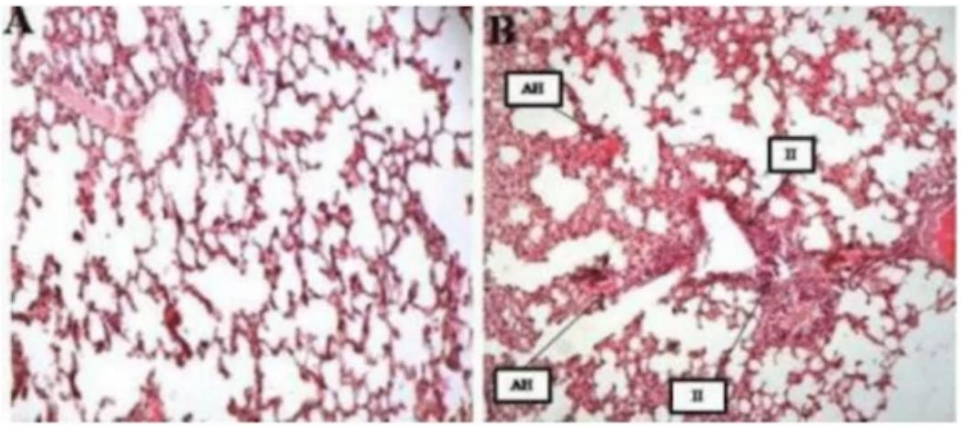


Fig. 2. Photomicrograph of histological section of lung tissue of albino mice. (A) The image from control pulmonary tissue showing compact configuration with intact alveoli and associated vessels and capillaries. (B) Lung tissue of envenomated group indicated extensive tissue damages and showing inflammatory cellular infiltration (II) and alveolar haemorrhage (AH). Sections were stained with hematoxylin and eosin (400 X H and E)

Individuals death occurred by cobra envenomation were mainly claimed due to the neurotoxic action of both presynaptic and structure of finger-like extensions villus, the mucosa and submucosa (Fig. 3A). But the tissue of envenomated grouped showed minor

REMDESIVIR TREATED VICTIMS SUFFERED THE SAME EFFECTS AS A SNAKE VENOM VICTIM

February 2015: Just like Hospitalized & on Remdesivir

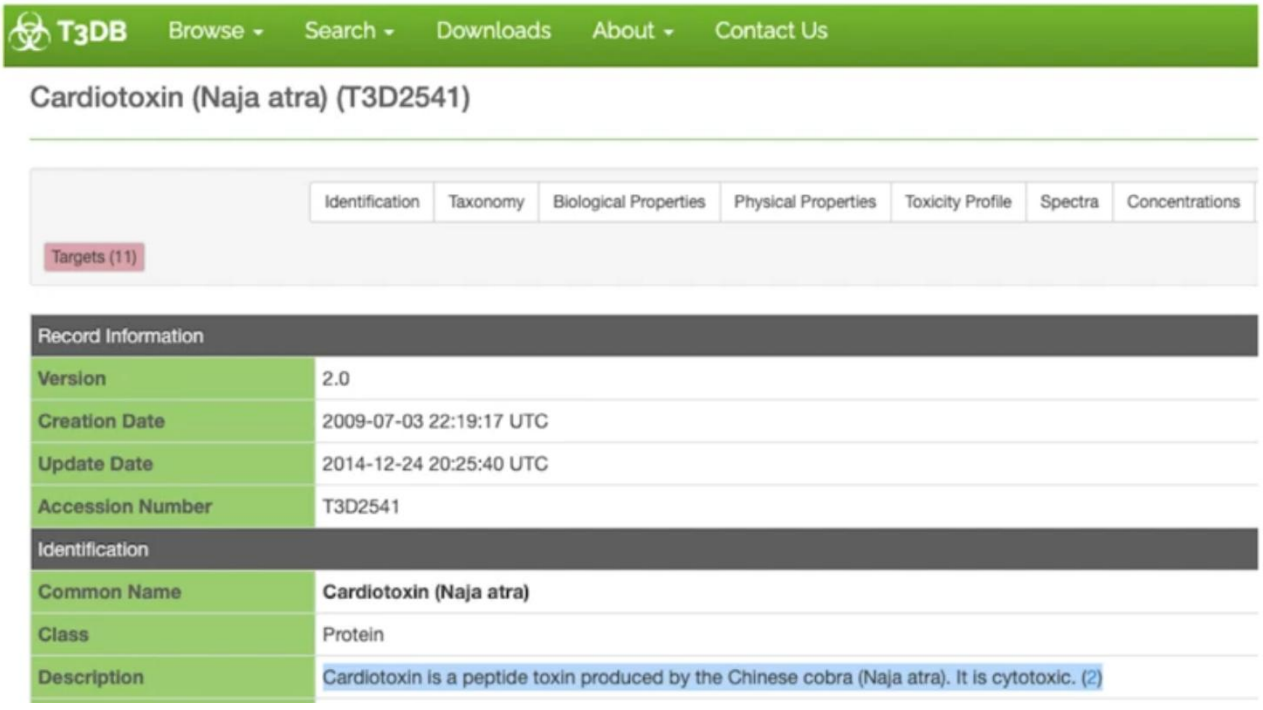
airway compartments. Edematous swelling of lung tissue with subsequent accumulation of pulmonary infiltrate blocks the alveolar airspaces disrupting gas exchange and lung mechanics, leading eventually to respiratory failure.

February 2015: Ironic or Damning?

4. CONCLUSION

It can be concluded that the exposure of *Naja naja* venom encourages serious histopathological alterations on renal and pulmonary tissue and moderately on intestinal tissue of envenomed mice. Therefore, further studies need to be carried out for the isolation and purification of cobra venom and applying this valuable natural raw material in the discovery of anti-venom related drug along with other pharmaceutical valuable product.

February 2022: Cobratoxin is Cardiotoxic



February 2022: Guess what else is Cardiotoxic

Toxicity Profile	
Route of Exposure	Injection (sting/bite) (4)
Mechanism of Toxicity	Cardiotoxin binds to the cell membrane and depolarizes cardiomyocytes. It also shows lytic activities on many other cells, including red blood cells. It also targets the mitochondrial membrane and induces mitochondrial swelling and fragmentation, binds to the integrin alpha-V/beta-3 with a moderate affinity, and inhibits protein kinases C. (2)
Metabolism	Free toxin may be removed by opsonization via the reticuloendothelial system (primarily the liver and kidneys) or it may be degraded through cellular internalization via the lysosomes. Lysosomes are membrane-enclosed organelles that contain an array of digestive enzymes, including several proteases.
Toxicity Values	LD50: 0.29 mg/kg (Subcutaneous, Mouse) (5) LD50: 0.345 mg/kg (Intravenous, Mouse) (5)
Lethal Dose	Not Available
Carcinogenicity (IARC Classification)	No indication of carcinogenicity to humans (not listed by IARC).
Uses/Sources	Cardiotoxin is a peptide toxin produced by the Chinese cobra (Naja atra). (2)
Minimum Risk Level	Not Available
Health Effects	Cardiotoxin is cardiotoxic. (2)
Symptoms	Bites from snakes in the Elapidae family produce pain at the site of the bite, followed by drowsiness, weakness, excessive salivation, decreased blood pressure, difficulty breathing, and paralysis of the facial muscles, lips, tongue, and larynx. In addition, ptosis, blurring of vision, convulsions, and headache may occur. (1)
Treatment	An antivenom exists for Chinese cobra venom. (3)

Review > Cardiovasc Toxicol. 2021 Oct 13;1-5. doi: 10.1007/s12012-021-09703-9.
Online ahead of print.

Potential Cardiotoxic Effects of Remdesivir on Cardiovascular System: A Literature Review

Maryam Nabati [1], Homa Parsaee [2]

Affiliations + expand

PMID: 34643857 PMCID: PMC8511861 DOI: 10.1007/s12012-021-09703-9
Free PMC article

Abstract

Corona disease 2019 (COVID-19) pandemic continues to spread around the world with no efficacious treatment. Intravenous remdesivir is the only authorized drug for treatment of COVID-19 disease under an Emergency Use Authorization. Remdesivir is a 1'-cyano-substituted adenosine nucleotide prodrug which inhibits viral RNA synthesis. This metabolite is an adenosine analog but with a significantly longer half-life than adenosine. Adenosine is a powerful vasodilator that can cause profound hypotension which is followed by the compensatory release of catecholamines. It can also shorten atrial action potential and refractoriness and lead to atrial fibrillation (AF). These effects may also occur in ventricular cells and predispose patients to ventricular fibrillation. Remdesivir can also induce significant cytotoxic effects in cardiomyocytes that is considerably worse than chloroquine cardiotoxic effects. Remdesivir-induced cardiotoxicity is due to its binding to human mitochondrial RNA polymerase. On the other hand, remdesivir can increase field potential

January 2020

nature.com/articles/s41588-019-0559-8

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The Indian cobra reference genome and transcriptome enables comprehensive identification of venom tox

Currently, snake antivenom is the only treatment effective in the prevention or reversal of the effects of envenomation. Since 1896, antivenom has been developed by immunization of large mammals, such as the horse, with snake venom to generate a cocktail of antibodies that are used for therapy[12]. Given the heterologous nature of these antibodies, they often elicit adverse immunological responses when treating snakebite victims[13]. Moreover, the antivenom composition is not well defined and its ability to neutralize the venom components is poorly understood. This is further exacerbated by the lack of access to antivenom and its high cost in many developing countries[14]. Although several alternative approaches have been proposed, large animal-based antivenom production using extracted snake venom as the antigen continues to be the standard practice[15,16,17,18].

September 2020

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COSTA RICA-HEALTH-VIRUS-PLASMA-HORSES

A scientist manipulates a velvet snake to extract venom at the Clodomiro Picado Institute, in San Jose, Costa Rica, September 24, 2020. - The Clodomiro Picado Institute obtained coronavirus proteins from laboratories in China and the United Kingdom to immunize six donated horses for treatment, and which plasma was used to produce a viral treatment to be tested in 26 patients infected with the new Covid-19. To develop the drug, the institute based on its half-century experience in the production of antivenom, which it currently exports to other Central American countries, Ecuador, Colombia, Peru and several African nations. (Photo by Ezequiel BECERRA / AFP) (Photo by EZEQUIEL BECERRA/AFP via Getty Images)

COVID 19 TREATED WITH ANTI-VENOM

January 2021

1 **Snake venom phospholipases A2 possess a strong virucidal activity against SARS-CoV-2 in vitro**
2 **and block the cell fusion mediated by spike glycoprotein interaction with the ACE2 receptor**

3 **Andrei E. Siniavin [1,2], Maria A. Nikiforova [2], Svetlana D. Grinkina [2], Vladimir A. Gushchin [2],**
4 **Vladislav G. Starkov [1], Alexey V. Osipov [1], Victor I. Tsetlin [1] and Yuri N. Utkin [1]**

5 [1] *Department of Molecular Neuroimmune Signalling, Shemyakin-Ovchinnikov Institute of Bioorganic*
6 *Chemistry, Russian Academy of Sciences, Moscow, 117997, Russia.*

7 [2] *N.F. Gamaleya National Research Center for Epidemiology and Microbiology, Ivanovsky Institute of*
8 *Virology, Ministry of Health of the Russian Federation, Moscow, 123098, Russia.*

January 2021

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Venom from one of Brazil's largest snakes could reduce COVID's ability to multiply

01/09/2021

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Snake venom could be used as a tool in the fight against coronavirus, a study suggests.

Commentary

BMJ Global Health

Snakebites and COVID-19: two crises, one research and development opportunity

Diogo Martins ,[1,2] Julien Potet ,[3] Isabela Ribeiro[4]

To cite: Martins D, Potet J, Ribeiro I. Snakebites and COVID-19: two crises, one research and development opportunity. *BMJ Global Health* 2021;**6**:e006913. doi:10.1136/bmjgh-2021-006913

Handling editor Soumyadeep Bhaumik

As the world battles COVID-19, other long-standing global health challenges continue to cause illness, suffering and death. Among them is the neglected crisis of snakebite envenoming (SBE): in the year after the COVID-19 pandemic was declared, an estimated 2.7 million SBE led to over 100 000 deaths and 400 000 long-term disabilities

Summary box

- Despite inherent differences, Snakebite Envenoming and COVID-19 have much in common in terms of research and development (R&D) challenges and opportunities.
- Both crises require a diversified portfolio of R&D solutions, ranging from diagnostics to treatments, that can effectively work and be accessible in differ-

COVID 19 AND SNAKE BITES ARE THE SAME

March 2021

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$1.58 Billion Anti-venom Market - Global Growth, Trends, COVID-19 Impact, and Forecasts 2021-2026 - ResearchAndMarkets.com

March 03, 2021 12:03 PM Eastern Standard Time

DUBLIN--(BUSINESS WIRE)--The "Anti-venom Market - Growth, Trends, COVID-19 Impact, and Forecasts (2021 - 2026)" report has been added to **ResearchAndMarkets.com's** offering.

"Texas snake bites increasing during COVID-19 pandemic"

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The Antivenom Market was valued at USD 969.38 million in 2020 and it is anticipated to reach USD 1585.01 million in 2026, by registering the CAGR of nearly 8.54% during the forecast period.

There is a significant increase in the number of deaths reported due to snake bites during the COVID-19 pandemic in few areas. This is creating a substantial demand for anti-venoms. More than 350 snake bites were reported in Texas in 2020, which is an increase of 40% over the value registered in 2019, as per the June 2020 article titled "Texas snake bites increasing during COVID-19 pandemic".

February 2021

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Review > Drug Dev Res. 2021 Feb;82(1):38-48. doi: 10.1002/ddr.21732. Epub 2020 Aug 5.

Snake venom-derived bradykinin-potentiating peptides: A promising therapy for COVID-19?

Ahmed S Gouda [1], Bruno Mégarbane [2]

Affiliations + expand

PMID: 32761647 PMCID: PMC7436322 DOI: 10.1002/ddr.21732

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Abstract

TheGuardian
Conscience, Nurtured by Truth

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Maurice Iwu

Scientists have advanced more cures for COVID-19. Top on the list are: combination of ivermeticin, zinc and vitamin C; Andrographis paniculata, the key ingredient of IHP Detox Tea; extract of Artemisia annua, which interferes with replication of SARS-CoV-2; snake venom enzyme; metformin; colchicine, melatonin; and essential oils.

Reacting to the advances in traditional medicine as cures for COVID-19, the pioneer of natural cures for COVID-19 in Nigeria, Chief Executive Officer (CEO) of Bioresources Development and Conservation Programme (BDCP) and a professor of pharmacognosy, Maurice Iwu, told The Guardian: "The containment of the pandemic has not failed. It is rather a work in progress. We understand the virus better now. I believe that soon Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS CoV-2) will be like any other persistent virus and not so deadly."

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September 2021

Snake venom can stop Covid-19 from multiplying

2 September 2021 Healthcare Communications

Researchers in Brazilian have discovered that a particle in a in the venom of a jararacussu pit viper's venom has the ability to stop the reproduction of coronavirus. The jararacussu is one of the biggest snakes in Brazil and can grow up to 6 feet in length. It habituates in the coastal Atlantic Forest, Bolivia, Paraguay, and Argentina.

According to the study released in August 2021 in the scientific journal 'Molecules', the particle that is produced by the snake reduced corona virus's capability to reproduce in monkey cells by 75%.

September 2021

News > Snake venom can stop Covid-19 from multiplying

Snake venom can stop Covid-19 from multiplying

2 September 2021 Healthcare Communications

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"We were able to show this component of snake venom was able to inhibit a very important protein from the virus"

December 2021

WSC Wall Street Call

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Anti-Venom Market Future Growth Outlook: Merck, MicroPharm, Pfizer

December 16, 2021 5 Min Read

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November 2021

Umi

Pfizer files EUA application for Covid-19 drug Paxlovid

alpha

Health

11/16/2021, 9:24:53 PM

266 0 0

Pfizer announced EUA application for Covid-19 drug " Paxlovid, a combo drug of a novel SARS-CoV-2-3CL C30 Endopeptidase inhibitor also known by the experimental name PF-07321332, a Cysteine protease inhibitor, and older protease inhibitor ritonavir to treat HIV/AIDS , that was found to reduce the risk of hospitalization or death by 89% compared to placebo in non-hospitalized high-risk adults with COVID-19 in phase 2 trials AFTER JUST 4 WEEKS.

Pfizer reported 389 patients In the overall study population through Day 28, no deaths in patients who received PAXLOVID™ as compared to 10 deaths in patients who received placebo

.8% or 3 out of 389 of patients who received PAXLOVID™ were hospitalized through Day 28 following randomization (3/389 hospitalized with no deaths), compared to 7.0% of patients who received placebo and were hospitalized or died (27/385 hospitalized with 7 subsequent deaths).

November 2021

Pfizer reported very limited info on side effects but mentioned rates of problems were similar between the groups around 20%. One of the concerns is related to longer term effects but as usual, the trial was recommended to be stopped early when "INTERIM results show such a clear benefit" while the data have not yet been published for outside review.

Older component in this combo is Ritonavir developed in 1980s for Treatment of HIV-1 infection per Pfizer serves to slow down metabolism of PF-07321332 to maintain higher circulating concentrations of the main drug.

Among previously reported ritonavir side effects are fatal pancreatitis and liver damage, arrhythmias with Prolongation of PR interval and 2nd- or third-degree AV block. use with caution in patients with structural heart disease, cardiac conduction abnormalities, ischemic heart disease or cardiomyopathies is recommended as these individuals may be at increased risk for cardiac conduction abnormalities. Contraindications for hypersensitivity (toxic epidermal necrolysis) were also previously noted with ritonavir use. Perhaps different dosages in this combo drug were used but not yet disclosed. Some expect to use Merck's molnupiravir together with Paxlovid but since Merck's molnupiravir actually speeds up mutations it may contribute to resistance to Pfizer's Paxlovid.

The novel component PF-07321332 is a 3CLprotease inhibitor, a covalent cysteine protease inhibitor, binding directly to the cysteine (Cys145). As noted, Side effects were not investigated or reported in a one month long study, but concerns may include ones to related to its effects on coagulation().

PF-07321332 inhibits cysteine protease from the PA clan proteases that play coagulant role as they are involved in blood clotting cascade. As a cysteine protease inhibitor, it may disrupt coagulation and have blood thinning qualities leading to predisposition to internal bleedings. Several snake venoms also belong to PA clan proteases and interfere with blood clotting cascade. This is interesting in light of presence of neurotoxin like motifs noted earlier in the sarscov2 sequence related to snake venom neurotoxin superantigens.

Another major concern is cysteine protease inhibition SPECIFICITY as Cysteine proteases play roles in every aspect of physiology and development.

June 2021

molecules MDPI

Molecules. 2021 Jun; 26(11): 3373.
Published online 2021 Jun 3. doi: 10.3390/molecules26113373

PMCID: PMC8199771
PMID: 34204855

Venom-Derived Neurotoxins Targeting Nicotinic Acetylcholine Receptors

Ayaulym Bekbossynova, Albina Zharylgap, and Olena Filchakova*

Clelia Dallanoce, Academic Editor

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Abstract Go to: ▸

Acetylcholine was the first neurotransmitter described. The receptors targeted by acetylcholine are found within organisms spanning different phyla and position themselves as very attractive targets for predation,

NICOTIN PATCHES/GUM BLOCKS NEUROTOXINS OF VENOM

June 2021

Keywords: nAChR, α-conotoxins, three-finger α-neurotoxins

1. Introduction

Go to:

1.1. Structural Features of Nicotinic AChRs for Ligand Interaction

Nicotinic acetylcholine receptors (nAChRs) are ch el-coupled membrane receptors activated endogenously by acetylcholine (ACh) [1]. Together with ionotropic GABA (gamma-aminobutiric acid), glycine, 5-HT3 (5-hydroxytryptamine), and zinc activated ion channels, they belong to a cys-loop superfamily of ligand-gated ion channels [2]. The receptors are characterized by radial symmetry and have pentameric organization, with five subunits arranged radially around a central ion-conducting pore. The ACh binds at the interface between adjacent subunits. There are 17 subunits described in vertebrates: α1 to α10, β1 to β4, γ, δ, and ε. The α8 subunit is found in the avian genome [3] and is not present in the human genome. The difference between α and β subunits lies within the structure of the ligand-binding site—an α-like subunit is considered to contribute to the ligand-binding site with a principal (+) subunit interface,

November 2009

Journal List > HHS Author Manuscripts > PMC2775451

Mol Ther. Author manuscript; available in PMC 2009 Nov 10.
Published in final edited form as:
Mol Ther. 2008 Nov; 16(11): 1833–1840.
Published online 2008 Sep 16. doi: 10.1038/mt.2008.200

PMCID: PMC2775451
NIHMSID: NIHMS156788
PMID: 18797453

Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability

Katalin Karikó,[1] Hiromi Muramatsu,[1] Frank A Welsh,[1] János Ludwig,[2] Hiroki Kato,[3] Shizuo Akira,[3] and Drew Weissman[4]

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REMEMBER THESE TWO NAMES KATALIN KARIKO [KK] AND DREW WEISSMAN [DW]

November 2009

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This work was supported by the National Institutes of Health (NIH) grants NIAID AI-050484, NHLBI HL87688, and NINDS NS-29331. H.M. was supported by Ruth L. Kirschstein National Research Service Awards postdoctoral fellowship. We thank Houping Ni for technical assistance. K.K. and D.W. have formed a small biotech company that receives funding from the NIH to explore the use of nucleoside-modified mRNA for gene therapy.

November 2009

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November 2009

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A likely contributing factor to the enhanced translation observed with Ψ modification is an increase in biological stability of the mRNAs (Figure 4d). Indeed, higher resistance to hydrolysis by phosphodiesterases from snake venom and spleen has been reported when uridine was replaced with Ψ in dinucleotide substrates.19 Previous studies have also demonstrated that Ψ stabilizes RNA secondary structures by promoting base stacking,20 which could slow degradation. However, stability of mRNAs containing either uridines or pseudouridines was the same when tested by *in vitro* assays using human skin–associated RNases21 (data not shown). Enhanced translation might be another factor that improves stability by protecting the RNA with high ribosome occupancy.

August 2011

Published online 3 August 2011 *Nucleic Acids Research, 2011, Vol. 39, No. 21* ***9329–9338***
doi:10.1093/nar/gkr586

Nucleoside modifications in RNA limit activation of 2′-5′-oligoadenylate synthetase and increase resistance to cleavage by RNase L

Bart R. Anderson[1], Hiromi Muramatsu[2], Babal K. Jha[3], Robert H. Silverman[3], Drew Weissman[1] and Katalin Karikó[2,*]

[1]Department of Medicine, 3610 Hamilton Walk, 522B Johnson Pavilion, University of Pennsylvania, Philadelphia, PA 19104, [2]Department of Neurosurgery, 371 Stemmler Hall, University of Pennsylvania, Philadelphia, PA 19104 and [3]Department of Cancer Biology NB40, Lerner Research Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Received April 17, 2011; Revised June 27, 2011; Accepted June 30, 2011

August 2011

RNA stability in rabbit reticulocyte lysate

Equal mass (25 ng/μl) or equal molar (40 μM) mRNAs-encoding firefly and *Renilla* luciferases were incubated in 15 μl rabbit reticulocyte lysate (RRL) (Promega) at 30°C. At the indicated times, a 2 μl aliquot was removed and the RNA was recovered using Trizol for subsequent detection by northern blotting.

RNA stability in cell culture

HEK293T, WT MEF or RNase $L^{-/-}$ MEF cells were nucleofected with 5 μg mRNA using nucleofector program T-020 and nucleofector V kit (Lonza). After 15 min recovery in RPMI, cells were plated in complete media and incubated at 37°C. At the indicated time, RNA was recovered from cells using Trizol for subsequent detection by northern blotting.

Northern blotting

RNA was isolated from RRL or cells using Trizol.

Immunoprecipitation

HEK293T cells were seeded into 96-well plates at a density of 5.0×10^4 cells/well 1 day prior to transfection. Cells were exposed to 50 μl DMEM containing lipofectin-complexed RNA (0.25 μg) for 1 h, which was then replaced with complete medium and further cultured. Cells were incubated in methionine/cysteine-free medium (Invitrogen) for 1 h, then pulsed with complete medium supplemented with ^{35}S-methionine/cysteine (140 mCi/ml) (PerkinElmer) for 3 h prior to lysis in 50 μl RIPA buffer supplemented with protease inhibitor cocktail (Sigma). *Renilla* luciferase was immunoprecipitated from lysates using an anti-*Renilla* luciferase antibody (PM047, Medical & Biological Laboratories) and protein G-coated Dynabeads (Invitrogen) and separated by 15% polyacrylamide gel electrophoresis. Gels containing the labeled samples were treated with 1 M sodium salicylate, dried and a fluorogram was generated by exposure to BioMax MS film (Kodak).

> PLoS One. 2012;7(8):e41888. doi: 10.1371/journal.pone.0041888. Epub 2012 Aug 7.

Unusual stability of messenger RNA in snake venom reveals gene expression dynamics of venom replenishment

Rachel B Currier [1], Juan J Calvete, Libia Sanz, Robert A Harrison, Paul D Rowley, Simon C Wagstaff

Affiliations + expand

PMID: 22879897 PMCID: PMC3413681 DOI: 10.1371/journal.pone.0041888
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Abstract

Venom is a critical evolutionary innovation enabling venomous snakes to become successful limbless predators; it is therefore vital that venomous snakes possess a highly efficient venom production and delivery system to maintain their predatory arsenal. Here, we exploit the unusual stability of messenger RNA in venom to conduct, for the first time, quantitative PCR to characterise the dynamics of gene expression of newly synthesised venom proteins following venom depletion. Quantitative PCR directly from venom enables real-time dynamic studies of gene expression in the same animals because it circumvents the conventional requirement to sacrifice snakes to extract mRNA from dissected venom glands. Using qPCR and proteomic analysis, we show that gene

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Unusual Stability of Messenger RNA in Snake Venom Reveals Gene Expression Dynamics of Venom Replenishment

Rachel B. Currier, Juan J. Calvete, Libia Sanz, Robert A. Harrison, Paul D. Rowley, Simon C. Wagstaff

Published: August 7, 2012 • https://doi.org/10.1371/journal.pone.0041888

Abstract

Venom is a critical evolutionary innovation enabling venomous snakes to become successful limbless predators; it is therefore vital that venomous snakes possess a highly efficient venom production and delivery system to maintain their predatory arsenal. Here, we exploit the unusual stability of messenger RNA in venom to conduct, for the first time, quantitative PCR to characterise the dynamics of gene expression of newly synthesised venom proteins following venom depletion. Quantitative PCR directly from venom enables real-time dynamic studies of gene expression in the same animals because it circumvents the conventional requirement to sacrifice snakes to extract mRNA from dissected venom glands. Using qPCR and proteomic analysis, we show that gene expression and protein re-synthesis triggered by venom expulsion peaks between days 3–7 of the cycle of venom replenishment, with different protein families expressed in parallel. We demonstrate that venom re-synthesis occurs very rapidly following depletion of venom stores, presumably to ensure venomous snakes retain their ability to efficiently predate and remain defended from predators. The stability of mRNA in venom is biologically fascinating, and could significantly empower venom research by expanding opportunities to produce transcriptomes from historical venom stocks and rare or endangered venomous species, for new therapeutic, diagnostic and evolutionary studies.

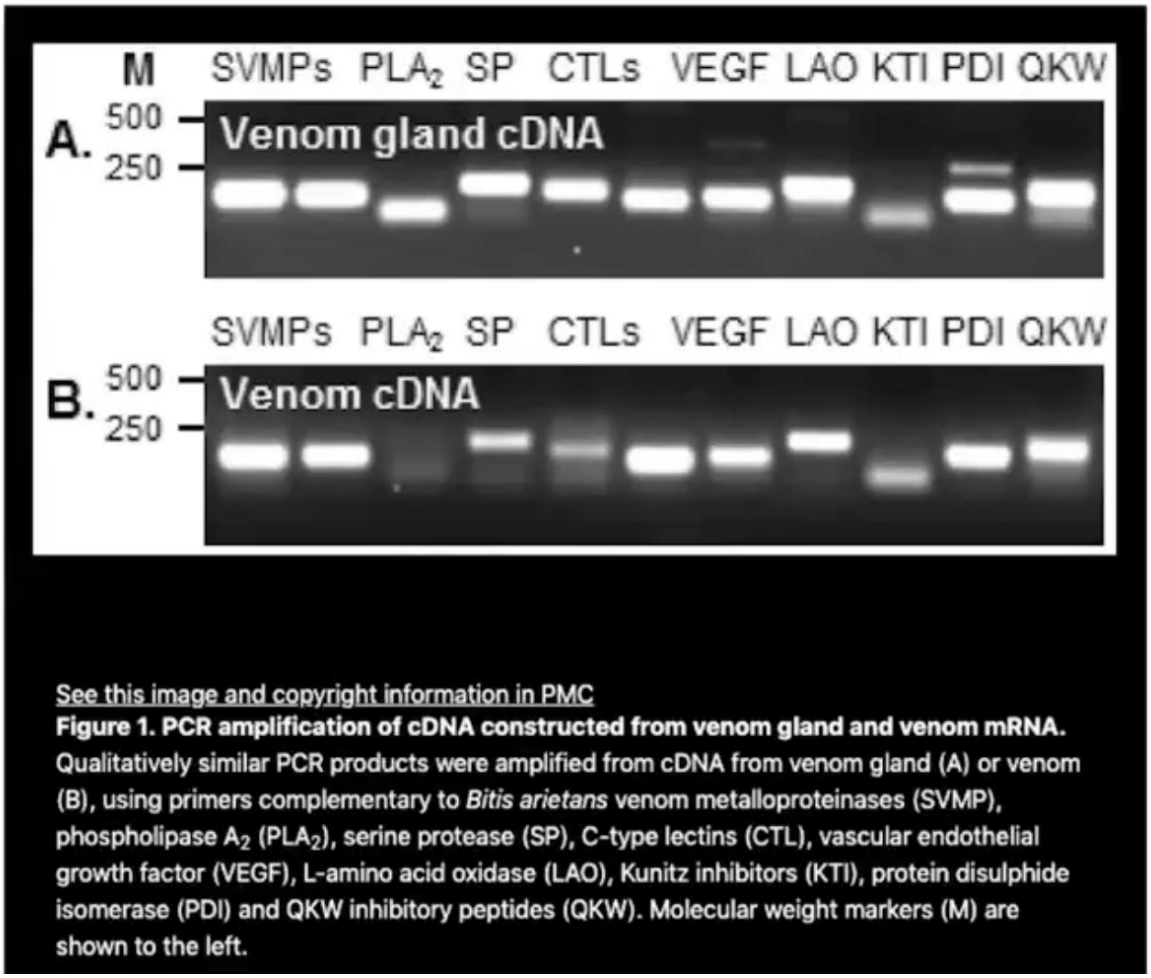

Figure 1. PCR amplification of cDNA constructed from venom gland and venom mRNA. Qualitatively similar PCR products were amplified from cDNA from venom gland (A) or venom (B), using primers complementary to *Bitis arietans* venom metalloproteinases (SVMP), phospholipase A_2 (PLA_2), serine protease (SP), C-type lectins (CTL), vascular endothelial growth factor (VEGF), L-amino acid oxidase (LAO), Kunitz inhibitors (KTI), protein disulphide isomerase (PDI) and QKW inhibitory peptides (QKW). Molecular weight markers (M) are shown to the left.

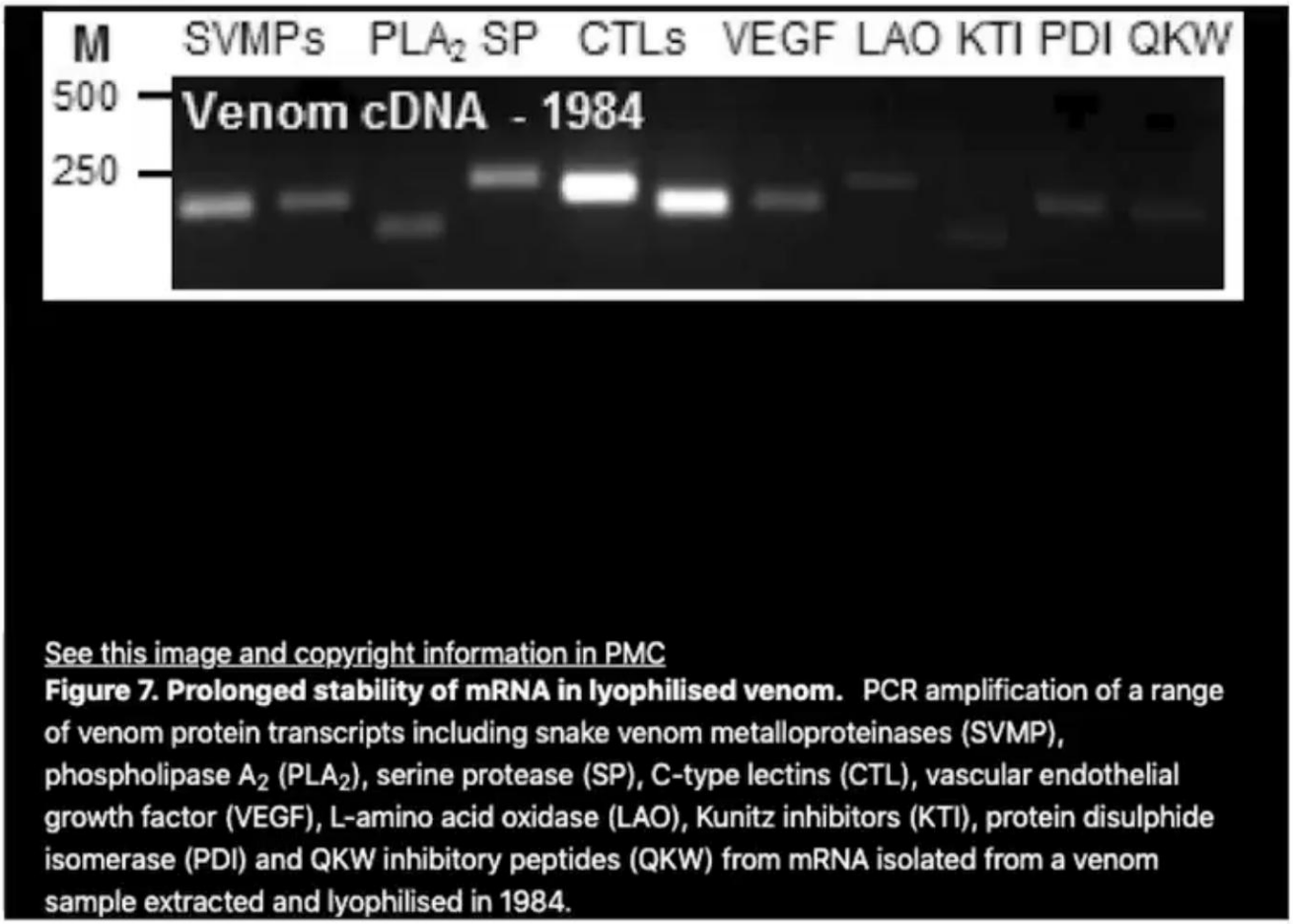

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Figure 7. Prolonged stability of mRNA in lyophilised venom. PCR amplification of a range of venom protein transcripts including snake venom metalloproteinases (SVMP), phospholipase A_2 (PLA_2), serine protease (SP), C-type lectins (CTL), vascular endothelial growth factor (VEGF), L-amino acid oxidase (LAO), Kunitz inhibitors (KTI), protein disulphide isomerase (PDI) and QKW inhibitory peptides (QKW) from mRNA isolated from a venom sample extracted and lyophilised in 1984.

THEY ARE CREATING VENOM AND USING TO STABILIZED MRNA, MRNA LASTED 30 YEARS WITHOUT BREAKINGDOWN, STILL INTACT

August 2012

mRNA Extractions from Venom

Poly adenylated messenger RNA (mRNA) was purified from lyophilised venom using Dynabeads® mRNA DIRECT™ Kit (Dynal, Invitrogen) using the manufacturer's protocol. Briefly, 2 mg of each lyophilised venom sample was reconstituted in 300 µl lysis/binding buffer (100 mM Tris-HCl pH 7.5, 500 mM LiCl, 10 mM EDTA pH 8, 1% LiDS and 5 mM dithiothreitol) and mixed with 50 µl magnetic oligo $(dT)_{25}$ coated Dynabeads® at room temperature for 10 minutes. The mRNA-coated beads were magnetically separated from the unbound material, washed twice using 600 µl washing buffer A (10 mM Tris-HCl pH 7.5, 0.15 M LiCl, 1 mM EDTA and 1% LiDS) and once with 300 µl washing buffer B (10 mM Tris-HCl pH 7.5, 0.15 M LiCl, 1 mM EDTA). mRNA was eluted from beads in 10 µl of 10 mM Tris-HCl, pH 7.5 at 70°C for 2 minutes. The remaining unbound material was transferred back to fresh pre-washed magnetic beads and the mRNA isolation protocol was repeated to ensure complete capture of mRNA from venom. mRNA obtained from the first and second elution was pooled to obtain a total volume of 20 µl.

August 2012

Optimisation of venom qPCR.

Quantitative PCR experiments were conducted with reference to the Minimum Information for Publication of Quantitative Real-time PCR experiments (MIQE) guidelines [17] (table S1). Standard curves for each gene of interest and reference gene were performed to (i) obtain PCR reaction efficiencies and identify the optimal cDNA concentration required to obtain linear amplification. Melt curve analysis was used to assess the specificity of primers - a single post-amplification peak on the melt curve denoting a specific PCR product. To generate standard curves, 1 μg of cDNA synthesised from mRNA isolated from pooled mature venom was diluted across ten doubling dilutions. Reactions were prepared using the KAPA SYBR® FAST qPCR Kit (KAPA Biosystems, AnaChem) containing 1 μl venom cDNA template, 5.5 μl KAPA SYBR® FAST 2×qPCR master mix (including DNA polymerase, SYBR green fluorescent dye, $MgCl_2$, dNTPs and stabilisers), 0.22 μl 10 mM 3′ primer, 0.22 μl 10 mM 5′ primer and 4.06 μl PCR-grade water. Amplifications were performed in duplicate alongside no template controls using a BioRad CFX 384 real-time PCR detection system with an initial denaturation step of 95°C for 3 minutes followed by 40 cycles of 95°C for 10 seconds, 55°C for 30 seconds. Melt curve analysis was performed by heating the amplicon at 95°C for 10 seconds followed by repeated

August 2012

Quantity and Quality of mRNA Recovered from Venom

An average yield of 46.2 ng (±13 ng std. dev) mRNA was purified from the 2 mg venom samples (approximately 7% of the typical venom yield) and, separately, we recovered 420 ng from 10 mg lyophilised venom. These venom mRNA recovery figures varied little from days 0–1 to mature venom. The average 260/280 absorbance ratios of the venom mRNA samples was 2.43±0.57. These results demonstrate that potentially large quantities of mRNA, of high quality, can be reproducibly recovered from *B. arietans* venom. More than adequate amounts of mRNA were recovered from each venom sample for downstream qPCR analysis: a representative cDNA synthesis reaction yielded 22.74 μg (±3.03 μg std. dev) of cDNA (20 μl) per reaction from 18.5 ng of mRNA (8 μl) - amounts easily sufficient for 20 qPCR reactions.

Amplification of Similar Products from PCR of cDNA Originating from Venom or Venom Gland mRNA

We designed PCR primers complementary to representatives of the spectrum of proteins expressed in viper venom such as the highly toxic snake venom metalloproteinases and serine

August 2012

The prolonged presence/stability of mRNA in snake venom is very unusual as in most organisms, mRNAs are typically highly labile with rapid turnover rates [26], [27]. This natural instability of mRNA is biologically important as it permits the cell to adapt and respond to changing environmental or developmental cues requiring rapid up or down-regulation of gene expression [28]. Our demonstration that mRNA can be detected in venom at each time point during the complete time course of venom synthesis is remarkable because we would expect snake venom glands to present a highly unfavourable environment for mRNA preservation due to the diverse array of destructive nucleases and phosphodiesterases [29], and naturally acidic conditions [5]. In an extreme extension of this investigation, we also report that mRNA encoding snake venom metalloproteinase, serine protease, C-type lectin, Kunitz inhibitor, protein disulphide isomerase and QKW inhibitory peptide was PCR amplified from *B. arietans* venom which was extracted and lyophilised in 1984 (Figure. 7).

METALLOPROTEINASE DEPLETES THE ESSENTIAL MINERALS IN YOUR BODY(ZINC,IRON,ETC)

August 2011: mRNA study continues

The presence of Ψ has been shown to enhance the stability of RNA secondary structures, but has not previously been demonstrated to cause resistance to nucleases. RNA containing Ψ was cleaved efficiently by RNase A, RNase H (36), RNase T1, RNase T2, nuclease P1 and snake venom phosphodiesterase, although there is some indication that pancreatic diesterase and snake venom phosphodiesterase may cleave Ψ-RNA with reduced efficiency (37). A previous report based on cleavage of a $C_{11}N_2C_7$ oligo RNA showed that RNA containing 2′-deoxy-2′-α-fluorouridine was bound by RNase L but cleaved slowly, whereas RNA containing 2′-*O*-methyluridine was not bound by RNase L (38). Here, we used a similar approach and demonstrated that purified RNase L readily cleaved

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Snake Venom Phosphodiesterase I Purified Lyophilized

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Quantity
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ADD TO CART

Snake Venom Phosphodiesterase I Purified lyophilized from Innovative Research is prepared by process of Williams, Sung and Laskowski, JBC, 236, 1130 (1961) and treated to inactivate contaminating 5'-nucleotidase activity according to Sulkowski

Quantity
1

ADD TO CART

Snake Venom Phosphodiesterase I Purified lyophilized from Innovative Research is prepared by process of Williams, Sung and Laskowski, JBC, 236, 1130 (1961) and treated to inactivate contaminating 5'-nucleotidase activity according to Sulkowski and Laskowski, Biochim. Biophys. Acta, 240, 443 (1961). This is a lyophilized in vials with a concentration of 20 Units/mg dry weight.

This product is useful successively hydrolyzing 5'-mononucleotides from 3'-OH-terminated riboand deoxyribo-oligonucleotides. The enzyme has an optimal pH range of 9.8-10.4 and a molecular weight of 115 kDa. Phosphodiesterase is inhibited by reducing agents such as glutathione, The enzyme has an optimal pH range of 9.8-10.4 and a molecular weight of 115 kDa. It is inhibited by reducing agents such as glutathione, cysteine and ascorbic acids and completely inhibited by 5 mM EDTA. ATP, ADP and AMP are partial inhibitors. The enzyme has an absolute requirement for Mg2+.

THIS WHY VITAMIN C AND THESE OTHER TREATMENTS WERE PULLED OR BANNED BECAUSE THEY NEGATE THE EFFECTS OF THE SNAKE VENOM

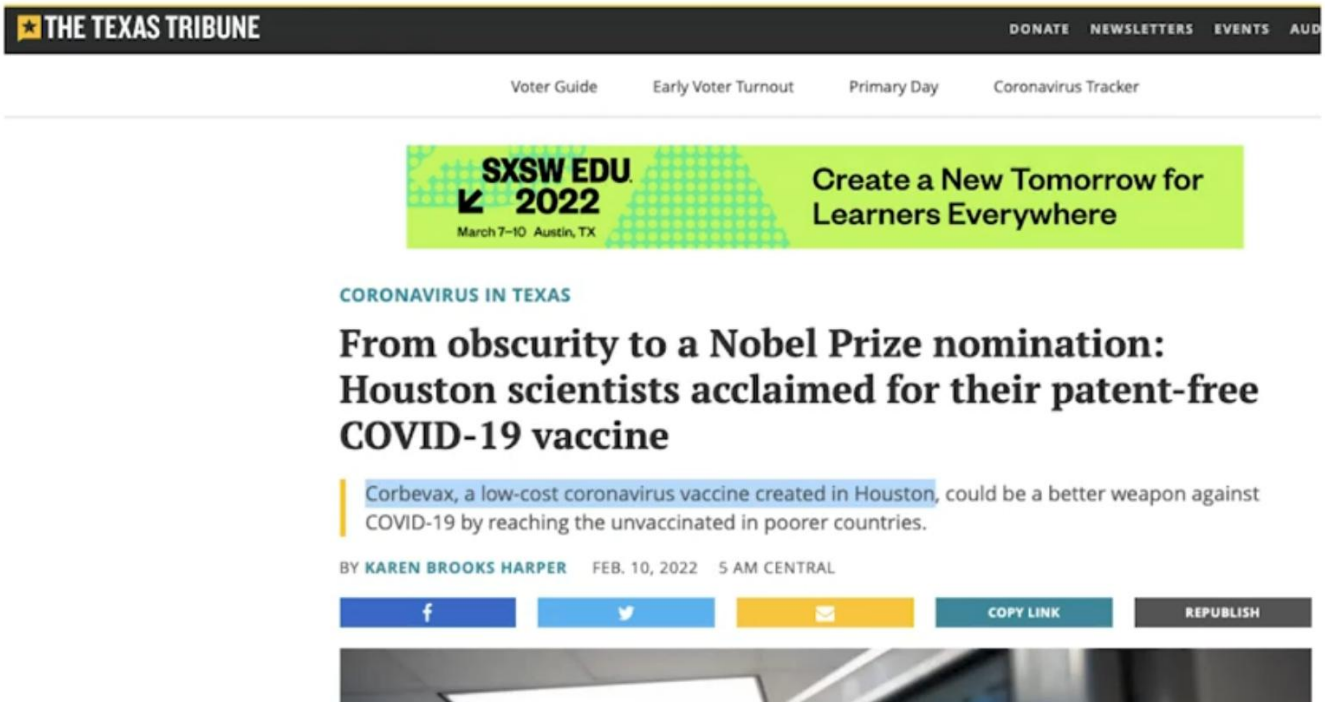
August 2011

FUNDING

National Institutes of Health (R01AI50484 and R21DE019059 to D.W.; T32GM07229, T32DK07748 and T32RR007063 to B.R.A.; R01NS029331 and R42HL87688 to K.K.; R01CA044059 to R.H.S). Funding for open access charge: National Institutes of Health (grant R42HL87688 to K.K.).

Conflict of interest statement. K.K. and D.W. have formed a small biotech company RNARx that receives funding from the National Institutes of Health to explore the use of nucleoside-modified mRNA for gene therapy.

February 2022



January 2022

Microbiologist Maria Bottazzi, her colleague Peter Hotez and their team at the Texas Children's Hospital's Center for Vaccine Development last month unveiled Corbevax, "the world's COVID-19 vaccine", and doctors say it could be a game changer.

January 2022

Why did you decide to announce a free of cost transfer of technology for the traditionally made "Corbevax" vaccine?

Well, just to clarify..the producer of the vaccine and the owner of the vaccine is Biological E in India. Corbevax is their vaccine, and they're the ones who work

INDIA NEWS | BUDGET 2022 | MARKETS | STOCK | HEALTHCARE | ECONOMY | MONEY | AUTO | DIGITAL CURRENCY | SME | BRANDWAGON

HOME / LIFESTYLE / HEALTH / Corbevax Gets Nod For 12 18 Yr Group

Covid-19 vaccine: Biological E's Corbevax gets EUA for use in 12-18 year age group

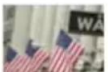
The Union government had made an advance payment of Rs 1,500 crore in June 2021 for reserving 30 crore doses.

Written by Geeta Nair
February 22, 2022 6:10:00 am

US Stock Market

Dow futures plunges over 800 points after Russia invades Ukraine

5 Wall Street strategists on year-end S&P 500 target and why stock



Feb 2022 (look at date of EUA)

COBRA VACCINE USED BEFORE COVID PLANDEMIC, SPREADING THE "VIRUS" VENOM

What Does India's Biological E. Manufacture?

I am sure this is just coincidental… don't you?

February 2022

PRODUCT LIST

SERA

Biological E. Limited
Celebrating Life Every Day

ANTI-SNAKE

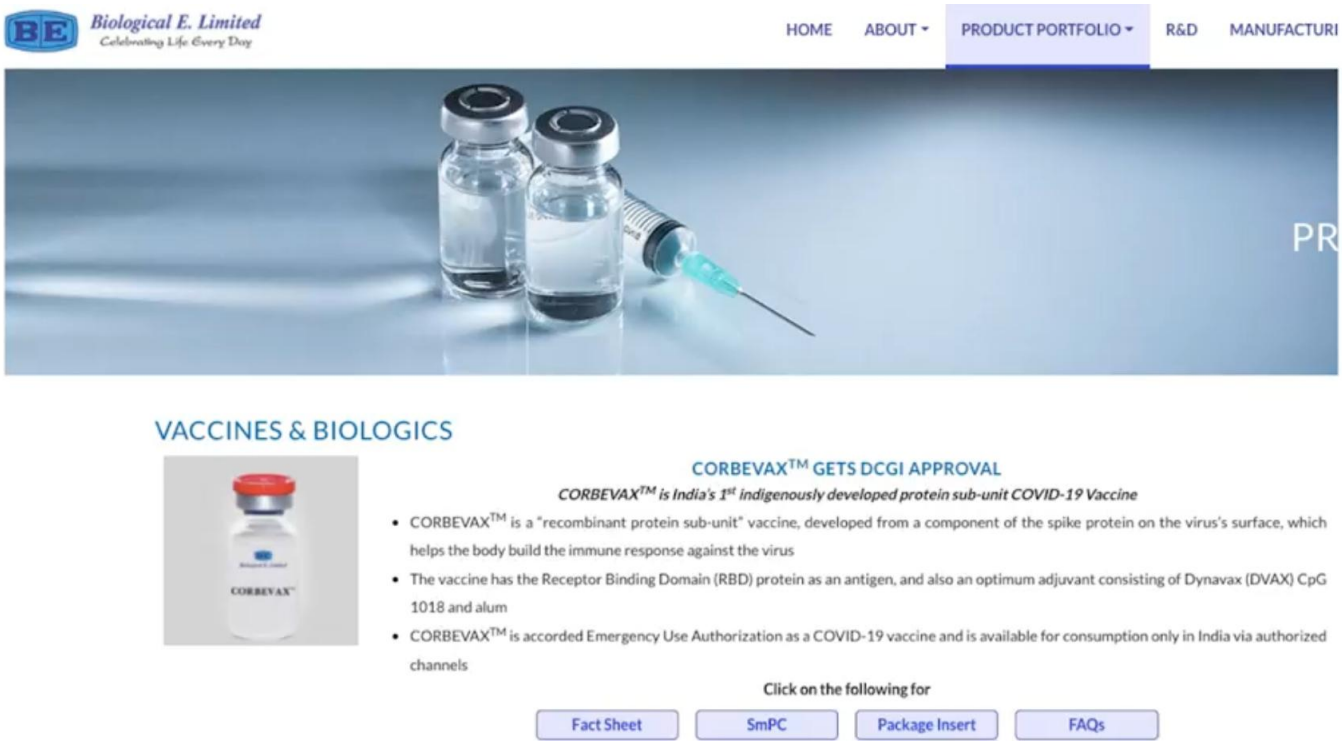
1. Product : **SNAKE ANTIVENIN (Polyvalent) IP**
   (Enzyme Refined Equine Globulins)

   Label Composition : Each mL of Antiserum Neutralizes :
   - Cobra Venom *(Naja naja)* ..... 0.60 mg
   - Common Krait Venom *(Bungarus caeruleus)* ..... 0.45 mg
   - Russell's Viper Venom *(Vipera russelli)* ..... 0.60 mg
   - Saw Scaled Viper Venom *(Echis carinatus)* ..... 0.45 mg
   - Preservative : Phenol IP ..... ≤ 0.25% w/v

   Pack : Liquid & Lyophilized 10 mL Vial

   Indication : Passive Immunization against Snake bite

THE TWO MAIN SNAKES FOUND IN COVID-19



July 2021

Moderna co-founder using mRNA technology to treat venomous snakebites

By Salmaan Farooqui · The Canadian Press
Posted July 6, 2021 5:49 am · Updated July 6, 2021 5:52 am

COVID VAX IS SNAKE VENOM, SAME MANUFACTURES MAKING MONEY OFF THE VIRUS

Medscape Wednesday, April 13, 2022

NEWS & PERSPECTIVE | DRUGS & DISEASES | CME & EDUCATION | ACADEMY | VIDEO | DECISION POINT

Drugs & Diseases > Laboratory Medicine > D-Dimer Q&A

How are elevated D-dimer levels interpreted?

Updated: Nov 18, 2019 | Author: Reka G Szigeti, MD, PhD; Chief Editor: Eric B Staros, MD more...

References

Answer

D-dimer is the degradation product of crosslinked fibrin; therefore, it reflects ongoing activation of the hemostatic system. Since there is constant minimal physiologic fibrin formation and degradation in vivo, healthy individuals have a minimal D-dimer level.

Answer

D-dimer is the degradation product of crosslinked fibrin; therefore, it reflects ongoing activation of the hemostatic system. Since there is constant minimal physiologic fibrin formation and degradation in vivo, healthy individuals have a minimal D-dimer level.

Elevated D-dimer levels reflect ongoing activation of the hemostatic and thrombolytic system, providing clinical utility in the following:

- Evaluation of thrombus formation
- Ruling out DVT (discussed further below)
- Monitoring anticoagulative treatment (a decreasing value indicates effective treatment)
- Disseminated intravascular coagulation (DIC)
- Snake venom poisoning

Additionally, D-dimer levels may be elevated in the setting of pregnancy, inflammation, malignancy, trauma, postsurgical treatment, liver disease (decreased clearance), and heart disease.[2, 3] It is also frequently high in hospitalized patients.[4]

THE ANSWER IS RIGHT IN FRONT OF YOUR FACE, DON'T LET THE MAINTREAM MEDIA "FACT CHECKERS" PAID BY BIG PHARMA LIE TO YOU. YOU HAVE SEEN THE FACTS, USE YOUR GOD GIVEN COMMON SENSE…

COVID-19 CORONAVIRUS ETYMOLOGY

CORONA

corona (n.)

1650s, "a crown," from Latin *corona* "a crown, a garland," in ancient Rome especially "a crown or garland bestowed for distinguished military service" (from a suffixed form of PIE root ***sker-*** (2) "to turn, bend").

With many extended senses in botany, anatomy, etc. As a brand of Cuban cigar, 1876. The brand of Mexican pale lager beer dates from 1925. The astronomical sense of "luminous circle observed around the sun during total eclipses" is from 1809. The two "crown" constellations, ***Corona Borealis*** and ***Corona Australis***, both are Ptolemaic.

Corona Borealis "certainly is much more like that for which it is named than usually is the case with our sky figures," according to Richard Hinckley Allen ("Star-Names and Their Meaning," 1899), and he adds that to the Greeks it was *stephanos*, a wreath, and from Roman times on typically it was ***Ariadne's Crown***. To Arab astronomers, however, it was *Al Fakkah* "the dish" (sometimes "the pauper's dish" or "the broken dish" — Latinized as *Discus parvus confractus* — as the celestial circle is incomplete), a word wrestled into European languages as ***Alphaca*** or ***Alphecca***, and used as the name of the constellation's none-too-bright brightest star.

VIRUS

virus (n.)

late 14c., "poisonous substance" (a sense now archaic), from Latin *virus* "poison, sap of plants, slimy liquid, a potent juice," from Proto-Italic **weis-o-(s-)* "poison," which is probably from a PIE root **ueis-*, perhaps originally meaning "to melt away, to flow," used of foul or malodorous fluids, but with specialization in some languages to "poisonous fluid" (source also of Sanskrit *visam* "venom, poison," *visah* "poisonous;" Avestan *vish-* "poison;" Latin *viscum* "sticky substance, birdlime;" Greek *ios* "poison," *ixos* "mistletoe, birdlime;" Old Church Slavonic *višnja* "cherry;" Old Irish *fi* "poison;" Welsh *gwy* "poison").

19 = 19 TOXINS IN KING COBRA

The Indian cobra reference genome and transcriptome enables comprehensive identification of venom toxins

Kushal Suryamohan, Sajesh P. Krishnankutty, ... Somasekar Seshagiri + Show authors

Nature Genetics **52**, 106–117 (2020) | Cite this article

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Abstract

Snakebite envenoming is a serious and neglected tropical disease that kills ~100,000 people annually. High-quality, genome-enabled comprehensive characterization of toxin genes will facilitate development of effective humanized recombinant antivenom. We report a de novo near-chromosomal genome assembly of *Naja naja*, the Indian cobra, a highly venomous, medically important snake. Our assembly has a scaffold N50 of 223.35 Mb, with 19 scaffolds containing 95% of the genome. Of the 23,248 predicted protein-coding genes, 12,346 venom-gland-expressed genes constitute the 'venom-ome' and this included 139 genes from 33 toxin families. Among the 139 toxin genes were 19 'venom-ome-specific toxins' (VSTs) that showed venom-gland-specific expression, and these probably encode the minimal core venom

SATAN IS THE KING OF SERPENTS

REV 12:9 And the great dragon was cast out, that old serpent, called the Devil, and Satan, which deceiveth the whole world: he was cast

out into the earth, and his angels were cast out with him.

ONLY THE BLOOD OF YAHSHUAH JESUS CAN SAVE YOU. THE APOSTLE PAUL WAS BIT BY A VENOMOUS SNAKE AND IT HAD NO EFFECT ON HIM BECAUSE HE WAS COVERED IN THE BLOOD OF YAHSHUAH JESUS.

Paul on Malta

Act 28:1 And when they were escaped, then they knew that the island was called Melita.

Act 28:2 And the barbarous people shewed us no little kindness: for they kindled a fire, and received us every one because of the present rain, and because of the cold.

Act 28:3 And when Paul had gathered a bundle of sticks, and laid *them* on the fire, there came a viper out of the heat, and fastened on his hand.

Act 28:4 And when the barbarians saw the *venomous* beast hang on his hand, they said among themselves, No doubt this man is a murderer, whom, though he hath escaped the sea, yet vengeance suffereth not to live.

Act 28:5 And he shook off the beast into the fire, and felt no harm.

Act 28:6 Howbeit they looked when he should have swollen, or fallen down dead suddenly: but after they had looked a great while, and saw no harm come to him, they changed their minds, and said that he was a god.

Act 28:7 In the same quarters were possessions of the chief man of the island, whose name was Publius; who received us, and lodged us three days courteously.

Act 28:8 And it came to pass, that the father of Publius lay sick of a fever and of a bloody flux: to whom Paul entered in, and prayed, and laid his hands on him, and healed him.

Act 28:9 So when this was done, others also, which had diseases in the island, came, and were healed:

Act 28:10 Who also honoured us with many honours; and when we departed, they laded *us* with such things as were necessary.

Act 2:38 Then Peter said unto them, Repent, and be baptized every one of you in the name of Jesus Christ for the remission of sins, and ye shall receive the gift of the Holy Ghost.

Act 3:19 Repent ye therefore, and be converted, that your sins may be blotted out, when the times of refreshing shall come from the presence of the Lord;

Act 8:22 Repent therefore of this thy wickedness, and pray God, if perhaps the thought of thine heart may be forgiven thee.

Rom 10:8 But what saith it? The word is nigh thee, *even* in thy mouth, and in thy heart: that is, the word of faith, which we preach;

Rom 10:9 That if thou shalt confess with thy mouth the Lord Jesus, and shalt believe in thine heart that God hath raised him from the dead, thou shalt be saved.

Rom 10:10 For with the heart man believeth unto righteousness; and with the mouth confession is made unto salvation.

Rom 10:11 For the scripture saith, Whosoever believeth on him shall not be ashamed.

Rom 10:12 For there is no difference between the Jew and the Greek: for the same Lord over all is rich unto all that call upon him.

Rom 10:13 For whosoever shall call upon the name of the Lord shall be saved.