INTERNATIONAL SOCIETY ON TOXINOLOGY

INTERNATIONAL SOCIETY ON TOXINOLOGY NEWSLETTER

December 2018

UPCOMING MEETINGS

The next IST Congress will be in Buenos Aires, Argentina and will be a "World Congress", hosted by the Pan-American Section of IST. Our President, Prof. Jay Fox is working hard with members in the Americas, especially our Argentinian members, to put together the foundation for this congress, including dates, venues, accommodation etc. The current anticipated dates are September 8th to 13th, 2019.

As soon as we have more details we will let members know, but please reserve these dates in your callendars, in anticipation.

The UK venoms/toxinology group will host the next Oxford Venoms meeting, in Oxford of course, August 28th & 29th. The timing means that it will be possible for toxinologists to attend the Oxford meeting and then go on to the IST congress in Argentina. IST is working with the Oxford group to try and harmonise respective programs.

The next Clinical Toxinology Short Course will be held in Adelaide in late 2019. Tentative dates are December 12th to 19th, but this is yet to be confirmed.

The next European Association of Poisons Control and Clinical Toxicology Congress will be in Naples, Italy, May 21st to 24th, with a special clinical toxinology session included.

FROM THE IST EXECUTIVE

2018 has been another interesting year for the IST. We had an IST congress in Armenia, for the first time; the IST European Section Congress held in the capital, Yerevan, in September. Prof. Naira Ayvazyan and her local team worked hard to make a successful congress, with about 200 registrants and many interesting presentations, plus a good social program, in a delightful city. I certainly enjoyed visying Yerevan and Armenia and others I spoke with at the congress echoed my feelings. So a big thank you to Naira and her colleagues!

At our AGM we received a bid from Cairns, Australia, for the 2020 Asia-Pacific Section congress. At that time there were no other bids for this congress, but then Singapore presented a bid. IST Council are deciding which bid to accept. Both were well presented and promise exciting meetings.

IST Council met in person in Yerevan and a number of changes are being considered for your Society. Incorporation, in the USA, is progressing and may be finalised in 2019, though it will require a major revision of our constitution to meet legal requirements for incorporation. These changes will require a vote by members, for approval. We are also exploring possibilities for changing the IST website, with help from members in Denmark. Our Society journal Toxicon is splitting into two; the current hard-copy version and a new open-access version; more news soon.

Lastly, I wish all members who celebrate Christmas a Very Merry Christmas and a Happy New Year. I will send out notices about IST dues for 2019 early in the new year.

Julian White AM, Secretary/Treasurer, IST

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MEMBERSHIP ANNOUNCEMENTS

The IST Membership Database has been updated, a process that will be ongoing. Please let the IST Secretary know if you change any of your contact details (email, phone, address etc). The Membership Database is available to all IST members via the IST website, with password protection for access. User name and password details have been sent out to all IST members previously. Please keep these details safe. If you cannot find your details then please email Dr. David Bates (Chief Scientist in my Toxinology Dept.) on david.bates@adelaide.edu.au.

Because of file size, the Newsletter is too big to email and so it is more practical to post the Newsletter on the IST website and just email members advising it is ready to download, via a link.

As discussed in an email to members earlier in 2011, changes at my workplace meant that as of June 2011 I was no longer able to use my hospital to collect IST dues by credit card. We now have an online payment system for all IST dues, on the IST website. This commenced in early January, 2012. The old system, of sending in forms for credit card payments, or cheques, no longer apply. ALL payments must be through the online website system.

Julian White AM
Secretary/Treasurer IST

IST Council 2017-19

President: J Fox
Secretary/Treasurer: J White
President Elect: vacant
Immediate Past President: A Harvey
Toxicon Editor: G King

A number of other Council positions will shortly be up for election. The 2015-17 Councillors were:

President European Section: J Calvete
Secretary European Section: R Harrison
President Pan-American Section: D Tambourgi
Secretary Pan-American Section: Y Cury
President Asia-Pacific Section: Songping Liang
Secretary Asia-Pacific Section: Sulan Luo

General Councillors
Europe: D Warrell & J Tytgat
Pan-America: JM Gutierrez & F Mari
Asia-Pacific: G King & M Kini

IST STUDENT MEMBERS - THIS IS FOR YOU - The Special Interest Group for Student Toxinologists

Students have been an important and valued part of IST since the inception of the Society in 1962. To emphasize the importance of the role of students in the IST, the Society has created a Special Interest Group for Student Toxinologists.

The aims of the Special Interest Group for Student Toxinologists include: to increase opportunities for students to network with possible collaborators and employers; to work with the Executive and Council, IST to ensure students are included and supported in future decisions of the IST; and to train students to become contributing members to the IST and other professional societies.

As part of the porevious process of developing the student group, we established a special wiki site which allowed student members to interact directly with fellow students. We also investigated a way of interfacing student members with established members prepared to answer questions on methodology. Established members prepared to engage in such a process should let the IST President know of their interest. Our new President, Prof. Jay Fox, has indicated his strong desire to better engage with IST Student Members and he will be making contact with Members about this in the near future, either directly, or through a special group he has established to promote this, currently headed by Brian Fry.

julian.white@adelaide.edu.au

MESSAGE FROM THE PRESIDENT (I.S.T)

Greetings from the President:

Fellow IST members, I hope as this year winds down you reflect and find both personal success and happiness and a greater appreciation for the science, education and service you provide to your respective professions. This year has been a very active one for the IST; notably we enjoyed an outstanding European Section congress in Yerevan Armenia organized by Professor Naira Ayvazyan and her team. The program was excellent and the venue wonderful! The society and its members also actively participated in the first annual Snakebite Awareness Day on September 19th. Further, close inspection of the literature demonstrates that our members have been incredible active and productive and as such are fruitfully carrying out the mission of the IST.

Alan Harvey and I have been actively engaged in revising the constitution and by-laws and soon the Executive Committee will be working to refine the documents prior to presentation to the general membership for approval. Our aim is to generate a modern constitution and by-laws that better enable the effective operation of the society with enhanced benefits and opportunities for the membership.

I am very pleased to announce that the next World Congress of the IST will be held in Buenos Aires, September 8th – 12th, 2019. I, along with Dr. Adolfo de Roodt and Dr. Soledad Bustillo, are teaming up to organize the meeting. We have some new ideas to try out for the meeting in part focusing on enhanced student member involvement. Also, we plan on a novel organization of talks to highlight the multifaceted ways toxins from all sources impact organ systems. Finally, there will be a strong component of the public health aspects of toxinology in the program. I am very excited about this meeting and the outstanding venue Buenos Aires provides and hope you will join us there in September. We expect a congress website to be up for information and registration in January 2019. Be warned: Start practicing your Tango (and I don't mean the kind we usually do when answering questions at our talks!) as there will be an all IST Tango Competition at the meeting!

In closing, I again wish you and your families a happy holiday and wonderful New Year and all the best in the coming year for your personal and professional life.

Jay W. Fox, IST President

Department of Microbiology, Immunology and Cancer Biology
Director, Research Infrastructure
Assoc. Director, UVA Cancer Center
University of Virginia School of Medicine
PO Box 800734, Charlottesville, VA, 22908
434 4924 0050

International Society on Toxinology

Annual General Meeting
Wednesday 26th September, 2018
Elite Plaza, Yerevan, Armenia

MINUTES

1. **Meeting opened:** by Prof. Jay Fox, IST President & Prof. Julian White, IST Secretary/Treasurer
   Members present 36. A quorum was achieved.

2. **Apologies:** Nil

3. **President's Report:** delivered by Prof. Fox
   Prof. Fox noted IST had an interesting year since the last IST Congress in China, 2017. There is a need to redouble efforts to maintain and attract membership. An upgrade of the IST web-site, to help achieve this, is being investigated. Congresses remain a central part of the value proposition for IST membership and rule changes will be considered to strengthen the value of membership in regard to congress presentations and registration. IST may be able to provide funding for innovative proposals to strengthen IST membership and congresses. The Society is progressing towards formal legal Incorporation, probably in the State of Virginia, USA, to facilitate tax free support from institutions and companies.

   Motion: That the IST membership support IST Executive and Council proceeding to complete Incorporation of IST in Virginia, USA.
   Moved: J Fox
   Seconded: J White
   Motion carried

4. **Toxicon Editor's Report:** to be delivered by Prof. Glenn King, Editor in Chief
   Prof. King was unable to attend the Congress and AGM, so no report was available.

5. **Secretary/Treasurer's Report:** delivered by Prof. Julian White (see later in this newsletter)
   Motion: That Treasurer's report be accepted.
   Moved: J Fox
   Seconded: M Kini
   Motion carried

6. **Annual dues:**
   Motion: That the Annual Dues for the Society be maintained at US$55.00
   Moved: J White
   Seconded: D Mebs
   Motion carried

7. **Election of Office Bearers for the European Section of the Society:**
   Nominations for Chairperson (term 2018-2021):
   Prof. Naira Ayvazyan (Armenia) (nomination accepted by Prof. Ayvazyan)
   No other nominations were received, either during the AGM, or afterwards, when Members were contacted by email. Therefore Prof. Ayvazyan is declared elected.

   Nominations for Secretary (term 2018-2021):
   Dr. Nicholas Casewell (UK) (Dr. Casewell was not present to accept the nomination)

Members were subsequently emailed for nominations. A single nomination was received:
Dr. Ornella Rossetto (Italy) (nomination accepted by Dr. Rossetto)

The IST Secretary/Treasurer will hold an email election of IST European Section Members for the 2 candidates.

8. **The next IST World Congress:**
The President and Secretary discussed mechanisms for determining the next IST World Congress. This should be held in 2019, hosted by the Pan-American Section of IST. A tentative expression of interest has been indicated by IST members in Argentina. Council will work on firming up this proposal.

C Vogel: Suggested that a representative from each of the Brazilian Toxinology Society and the North American Society of Toxinology be invited to be part of the Organising Committee for the 2019 IST World Congress.

This proposal was supported by President J Fox and Secretary J White and other Members present.

9. **Other business:**

9.1 **Thank you to the organisers of the Yerevan IST Congress, 2018.**
Motion: That Members thank Prof. Ayvazyan and her colleagues for organising the IST Yerevan Congress, 2018.
Moved: J White
Seconded: J Fox
Motion carried

9.2 **IST Asia-Pacific Section Congress 2020 bid:**
Prof. R Norton (Australia) presented a bid from Australia to host the next IST Asia-Pacific Section Congress in 2020. The proposal was for Cairns in far north Queensland, using the Cairns Convention Centre. Prof. Norelle Daly and Prof. Jamie Seymour would be the joint Congress Organisers. While dates are not yet fixed, November 1-6, 2020 was suggested.

IST President J Fox and Secretary J White indicated their thanks for this offer and suggested Profs. Norton, Daly and Seymour proceed to develop a firm proposal following IST congress guidelines.

9.3 **IST European Section World Congress 2021 bid:**
Prof. A Laustsen (Denmark): Proposed that Denmark might be interested in hosting the next IST World Congress for the European Section in 2021, possibly in July.

IST President J Fox and Secretary J White indicated their thanks for this offer and suggested Prof. Laustsen proceed to develop a firm proposal following IST congress guidelines.

10. **Close meeting:**

INTERNATIONAL SOCIETY ON TOXINOLOGY
SECRETARY-TREASURER'S REPORT 2017-2018

In the past year, since the IST World Congress in Hainan, China, 2017, the Society has been comparatively quiet. Our Constitution has remained unchanged since last revised at the 2016 Pan-American Section Congress in Miami Beach, USA. Some progress has been made in regard to moving the Society to Incorporation, led by President Jay Fox, who has determined legal requirements for incorporation in West Virginia, USA. This may require some specific amendments to the IST constitution which Council will consider in coming months, with an expectation that IST members vote on changes at the 2019 Congress.

Annual dues have remained unchanged at US$55.00 per year. Notice for payment of 2018 annual fees to IST was sent out by email to members early in the year, with several follow ups.

As of 18-9-18 160 members (excluding Life Members) have paid their 2018 dues; this figure includes 6 student members who have paid the newly-introduced student fees last year (this time last year 13). This compares to 149 members who paid (excludes student members) in 2014, 223 in 2015, 220 in 2016 and 231 in 2017. A number of members have paid past dues owing, when paying their 2018 dues and I thank them for this support of our Society. Several members chose to become Life Members of IST in 2018, utilising this new membership class, which requires a large up-front payment. We now have 10 Life Members. There are a further 15 in the "special" category currently unable to pay dues due to technical issues. There are 78 student members currently listed as "active" (ie contactable and student status confirmed), but only 6 have paid dues for 2018. There are a further 326 members listed as "active", but who have not paid 2018 dues. Of these, 53 paid dues in 2016, of whom 31 paid in both 2015 and 2016 and of this latter subgroup, 24 paid in 2014, 2015 and 2016. There are 97 unfinancial members who paid dues in 2017. We therefore have a significant attrition rate. 39 new members joined IST since the IST China congress in 2017. Overall we are seeing a slow but steady decline in membership which, if it continues, will see the dissolution of IST. Our current total financial membership across all categories is 176.

Our Society finances, however, are in a less concerning state, for the present. At the IST World Congress, Oxford, UK, 2015, I reported that the total funds held by IST, adjusted to US$ at prevailing exchange rates (always subject to change) were US$58,723.06. At the AGM in Miami Beach in 2016 this figure was US$68,176.12. At the AGM in China in 2017 this figure was US$73,009.07. At this 2018 AGM I can report that the adjusted amount is now US$77,338.43 (see below for details). This amount includes a large loan to the organisers of this 2018 Congress (US$5,000), which we expect to be repaid. I recommend that IST maintain annual dues at the current rates for the next 12 months. The rate can again be reviewed at the next AGM in 2019.

As of 18-9-2018 the Society bank accounts held Aus$8,846.11 (US$6,342.69 on current exchange rates), while the Society PayPal account held Aus$96,196.21 (US $70,995.74). On 8-8-2018 Aus$9,217.16 was transferred from the Society PayPal account to the Society main bank account, together with a loan of Aus$400.00 from the Secretary/ Treasurer, to enable transfer of funds to the organisers of the 2018 IST European Congress. The loan transfer of funds to Armenia occurred in two stages, on August 9th and 15th, totalling Aus$7,117.18, following which the loan from the Secretary/Treasurer, of Aus$400.00, was repaid. Therefore the total funds held by IST as of 18-9-2018 across all accounts was Aus$105,042.32 (subject to exchange rate variations; US$ equivalent at current exchange rates US$77,338.43).

An IST newsletter was made available to members via the Society website (toxinology.org) in December, 2017. There remains a problem in producing newsletters, because members are not supplying material for inclusion. The newsletter is a potentially valuable communication mechanism, but to function it does require active involvement by members.

Item/ Account	Explanation	Amount			
		2015	2016	2017[a] (as of 19/10/17)	2018[b] (as of 18-9-18)
Income (shown as US$ (Aus$))					
PayPal	Online annual dues payments[1]	$16,370.00	$14,465.00	$14,510.00	US$12,080.00
	Number of members financial[2]	238 (223)	241 (220)	231	154
Life Members		N/A	N/A	2	10
Special member category[3]		17	13	13	15
Student member category[3]; those unfinancial in brackets		86	80	83	6 (72)
New members joining (all categories)		33	30	22	39
Congresses[4]		$0.00	$0.00	Aus$3,875.66 (US$3,049.27)[a]	$0.00
Total income (US$)		***$16,370.00***	***$14,465.00***	***$17,559.27***	***US$12,080.00***
Expenditure (where paid from IST bank accounts, amount shown is in Aus$)					
Congress related	Grant/loan to 2015 congress	Aus $3,027.74			
	Other 2015 congress related costs paid directly by IST		Aus$752.37		
	Costs associated with 2015 IST Business Meeting paid directly by IST to StHildas College, Oxford		Aus$533.51		
	IST loan to Miami congress		Aus$4,371.6		

Item/ Account	Explanation	Amount			
		2015	2016	2017[a] (as of 19/10/17)	2018[b] (as of 18-9-18)
	IST loan to China congress			Aus$13,753.74 (US$10,000.00 + fees)	
	IST payment of airfare for Redi awardee			Aus$2,450.53	
	IST loan to Yerevan congress				US$7,000.00
PayPal	Fees deducted (occurs when funds enter account)[5]	*US$621.41*	*US$576.99*	*US$578.13*	*US$459.77*
Other expenditure	Refund of legal fees regarding incorporation			Aus$716.81	
Total expenditure in that calendar year (for 2017 & 2018 converted to US$[a])		Aus $3,027.74	Aus $5,657.48	Aus$16,931.14 (US$13,893.71)	US$7,000.00
Total expenditure related to that calendar year[6]		Aus $10,963.27	Aus $4,371.60	Aus$16,931.14 (US$13,893.71)	US$7,000.00
Excess Income over Expenditure				**US$3,665.56**	**US$5,080.00**
Net Position				**US$73,009.07**	**US$77,338.43**
Total amounts held in IST accounts at last assessment date for year					
PayPal account[7]		US $47.911.04	US $61,799.05	US$65,675.92 (Aus$81,502.50)[9]	US$70,995.74 (Aus$96,196.21)
NationalAustraliaBank[8] 120941438		Aus $13,586.26	Aus $7,927.78	Aus$6,739.11	Aus$8,801.10
NationalAustraliaBank[8] 153618880		Aus $1,901.95	Aus $1,901.95	Aus$2,610.27	Aus$45.01

a: Based on exchange rate applicable on 19/10/2017. Exchange rate at the time of transaction may have been substantially different.
b: Based on exchange rate applicable on 18/9/2018. Exchange rate at time of transaction may have been substantially different.
1: Some members in any given year choose to pay annual dues in arrears for 1+ previous years. Therefore the income in any given year may represent dues for that year plus some dues for previous years. The figure is money received by IST, after PayPal fees deducted.
2: The number of members listed as financial in a given year is based on whether fees were paid for that year, but not necessarily in that year, as some members choose to pay dues in arrears for

1+ years, when asked to do so. The number in brackets represents the number of members listed as financial at the end of that year (ie. those who paid during the year that dues were owed). This includes Life Members, except for 2018, where they are counted separately.
3: The “Special” category covers members who have been unable to pay because of technical issues, despite attempts to pay. This applies to members from certain countries.
4: Congresses have not been returning any profits made to IST, nor repaying any amount loaned to the congress, until the 2016 Miami congress, where funds were returned in early 2017 and show in that year. Regrettably, and despite assurances when bidding for the congress, the organisers of the 2017 China congress did not repay any funds to IST, a loss of $10,000.00 to the Society.
5: PayPal deducts their processing fee automatically from any amounts collected, so only the remaining amount enters the PayPal account. This deducted amount in US$ is shown in this row.
6: The adjusted total expenditure for each year shows money paid for IST activities occurring that year, in nearly all cases relating directly to support for the IST congress. In some cases money may be paid 2 or more years in advance, as occurred with the 2015 Oxford congress.
7: Annual dues collected via PayPal online are in US$ and held in that currency. The Aus$ amount shown is based on current exchange rates as calculated by PayPal.
8: The funds held in NationalAustraliaBank accounts are in Aus$, so US$ amounts are shown.
NOTE: To establish the online annual dues payment system using PayPal it was a legal requirement that there be a Society bank account in an Australian bank and a local responsible person (myself) for any accounts. This may change if IST becomes incorporated.
9: The apparent fall in Aus$ value despite a rise in US$ value is purely an artefact of changing currency exchange rates and funds in this account are held in US$, not Aus$.

International Society on Toxinology

Council Meeting

Held during the IST Congress, Yerevan
September 2018

Those present: J Fox (IST President), J White (IST Secretary/Treasurer), A Harvey (Immediate Past President), J Calvete (European Section Chair), M Kini, D Warrell, J Tytgat, S Luo, plus by invitation, N Ayvazyan, R Norton, J Wigge.

Matters discussed:
Issues around developing and promoting IST. Issues with PayPal were flagged and a request made to add WeChat for Chinese members; these matters will be investigated.

An apparent drop in membership numbers was noted; it was also noted that this may reflect insufficient chasing members to pay.

It was suggested that for future congresses, anyone registering who is not an IST member will automatically be joined up and charged accordingly.

The need to use social media was strongly advocated by some Councillors. IST does have a Facebook page but it is not being used much at present. Strategies to improve this were discussed.

It was agreed that the IST website needs to be re-examined and, if possible, updated, modernised, made more user friendly. Council will seek help for this from members (some Denmark members have since volunteered to assist with updating the website).

It was suggested that IST should explore acquiring a smartphone app to support membership.

J Fox brought Council up to date with progress on the next IST congress, now likely to be held in Buenos Aires, Argentina in September 2019. He is working closely with Argentinian members to finalise plans for this congress and has visited Buenos Aires to assist with this and is optimistic about success.

The next Asia-Pacific Section IST congress, in 2020, was discussed, including a bid from Cairns, Australia. Council decided that a call should be made to allow others to bid, though considered the Cairns bid very strong. R Norton spoke to the Cairns bid.

J Fox informed Council about progress with incorporating IST in Virginia, USA and Council agreed to support this process through to completion. This will require a major revision of the IST constitution to make it consistent with Virginia incorporation legal requirements. J Fox will lead this revision process, assisted by A Harvey and J White.

REPORT ON INTERNATIONAL SOCIETY ON TOXINOLOGY CONGRESS

Yerevan, Armenia
September 22-26, 2018

Prof. Julian White

Introduction

The European Section of the International Society on Toxinology (IST) was held at Elite Plaza, central Yerevan, Armenia, Organised by the local Organising Committee, led by Prof Naira Ayvazyan. About 200 people were registered for the congress, both from within Europe and globally. The congress had a full 4.3 day schedule, without parallel sessions. Morning, afternoon tea and lunches were provided, plus three social functions; an opening night welcome reception, a “cheese and wine” evening with traditional dance troupe and a wonderful conference dinner on the last night, with entertainment. The congress was opened by Prof. Rouben Aroutiounian from the Orbeli Institute, Yerevan.

Group photo for Congress

Prof. Naira Ayvazyan

Prof. Rouben Aroutiounian

Prof Jay Fox

Opening ceremony for Congress

Within the scientific program there were 6 plenary lectures, plus opening and closing lectures, plus many invited lectures as well as oral paper presentations. An afternoon was devoted to brief 5 minute presentations by student members of IST and these were evaluated and the best awarded prizes, the main winner being Ana Cristina Nogueira Freitas from Brazil, who was also awarded complimentary registration for the next IST congress in 2019, likely to be in Buenos Aires, for her presentation on “ Antinociceptive effect induced by a PnPP-19 derivative: new insights into venom

peptides targeting opioid receptors". Runner up awards were made to Harry Williams (UK; " Mechanisms underpinning the permanent muscle damage induced by snake venom metalloprotease."), Cecile Knudsen (Denmark; " Harnessing human monoclonal antibodies for neutralisation of dendrotoxins in a murine model") and Rahini Ragavan (Australia; " Cardiovascular collapse induced by Echis ocellatus venom: an in vivo and in vitro examination"). The prize for best poster went to Oksana Sintcova from Vladivostok, Russia.

Opening Lecture

Snakebite clinical aspects; challenges and opportunities

Prof. David Warrell (Oxford, UK)

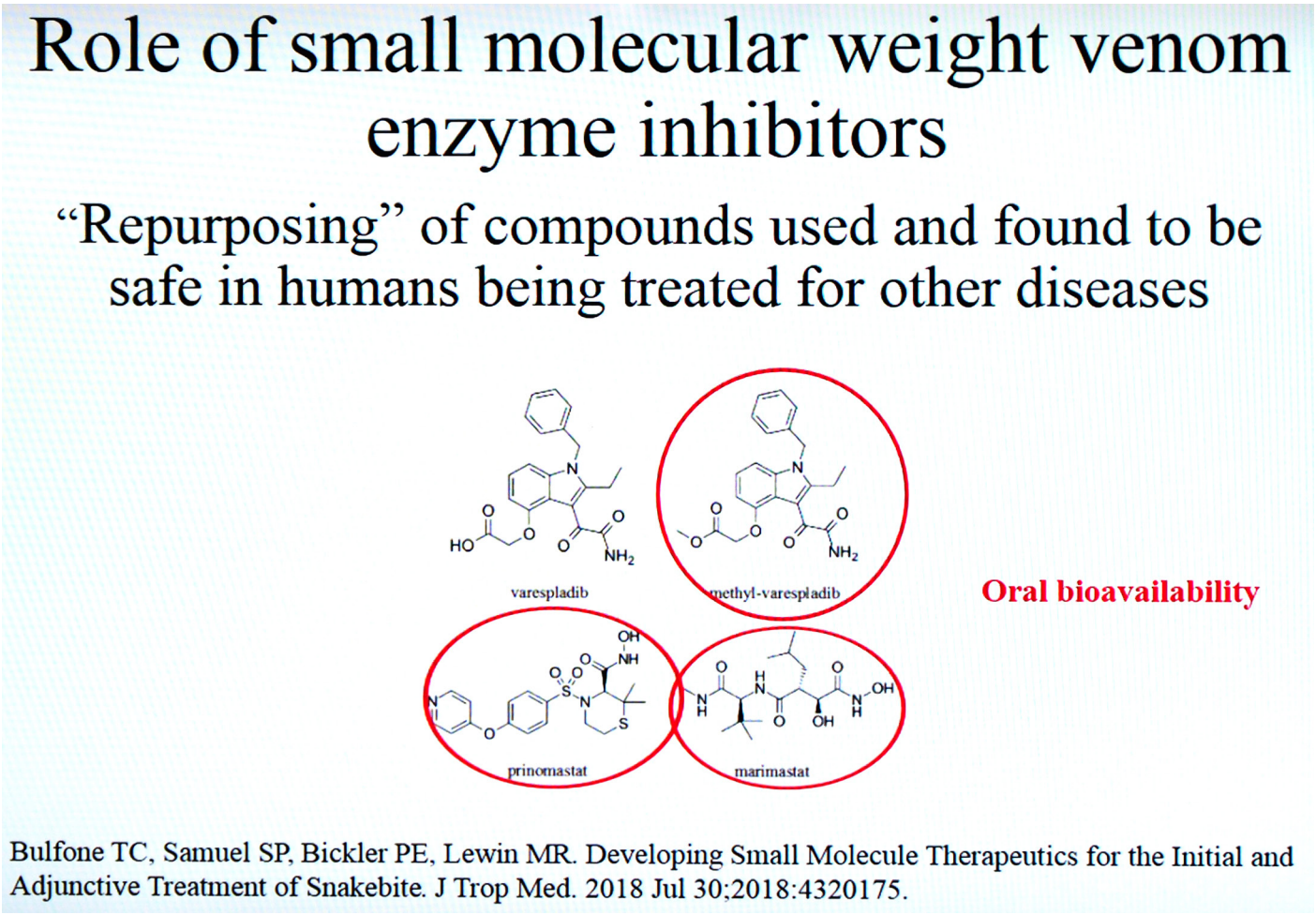
Prof. Warrell provided an overview of the problems presented by snakebite globally, segueing into the new opportunities presented by the recent prioritisation of snakebite by the World Health Organisation (WHO) as a class A Neglected Tropical Disease (NTD), which should allow significant resource allocation and requires governments to prioritise snakebite within their health planning, a highly relevant and positive change in much of the developing world where snakebite has the highest impact, medical, social and economic.

He reiterated the still inadequate and likely underestimated epidemiological data on snakebite, which even so is considered to affect about 5 million people annually (as bitten victims), with around 400,000 of these requiring amputations, and with at least 100,000, but possibly as many as 200,000 deaths annually. Indeed the impact, in terms of number of humans bitten, quite apart from the vast social and economic cost, exceeds the total number of cases for all the other NTDs put together. MAP

A WHO working group has been established for snakebite, led by Dr. David Williams (IST member), and a roadmap for change developed. PHOTO This involves tackling the antivenom crisis, building supportive infrastructure, including training of health personnel, and creating a global coalition of interested parties to promote positive change and action. Clinical research priorities include testing of preventative methods such as use of personal protective equipment (PPE) by those at most risk (particularly poor rural workers), developing new antivenom (AV) options and testing both of these and existing AVs, and exploring and evaluating through clinical trials, novel non-AV ancillary treatments. The latter may include small molecular weight enzyme inhibitors already ap-

proved and used as treatment in other diseases. These may potentially be effective both for local necrotic envenoming and some forms of systemic envenoming. An example is varespladib.

Prof. Warrell ended his lecture by noting this may be the “best time ever” to be interested in snakebite, both clinically and in lab research, with expanding global knowledge and funding opportunities, finally exporting everyone to “go for it”!



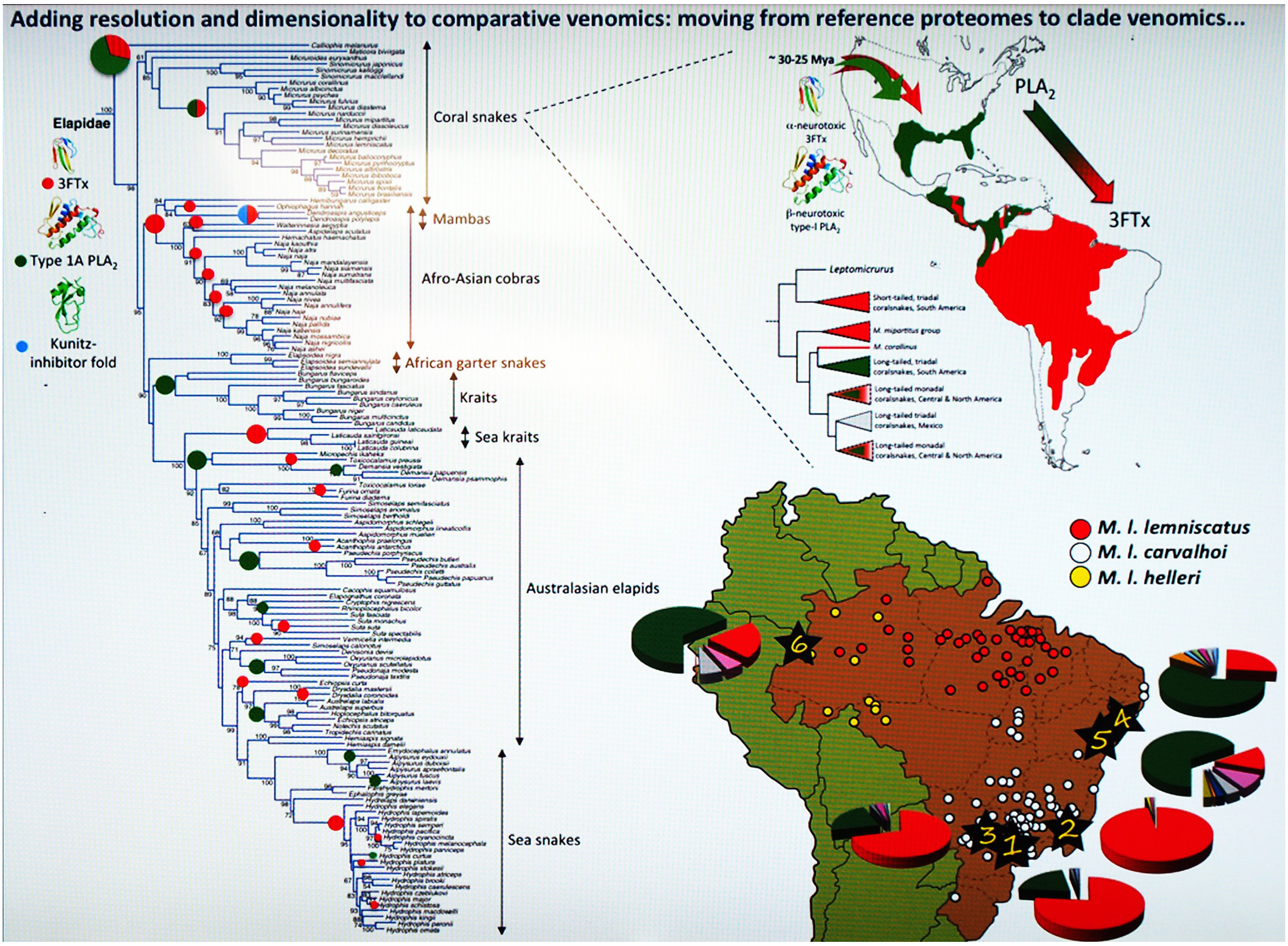
Plenary Lectures

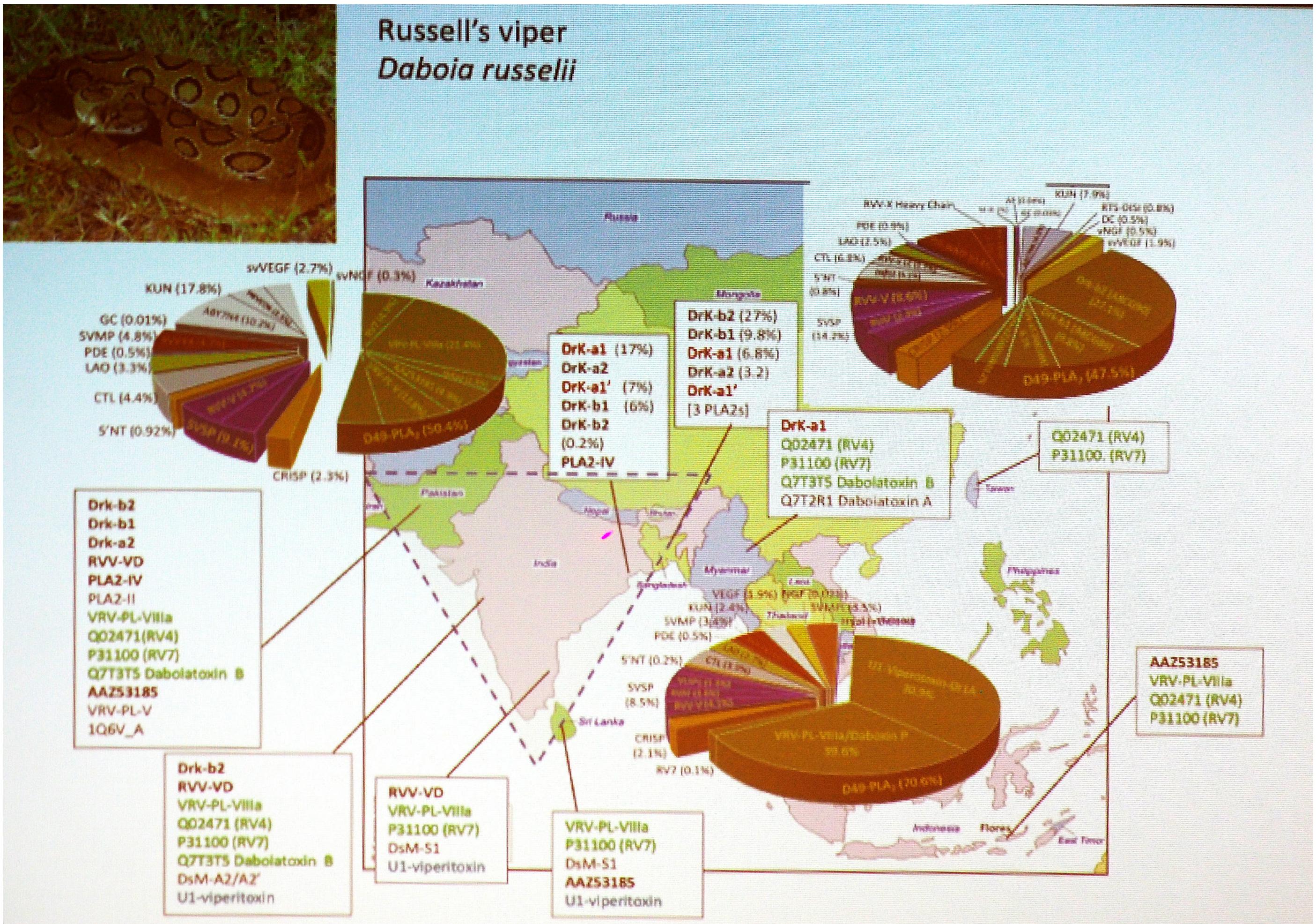
1. Toxin-resolved venom proteomes; a challenge in evolutionary and translational venomics

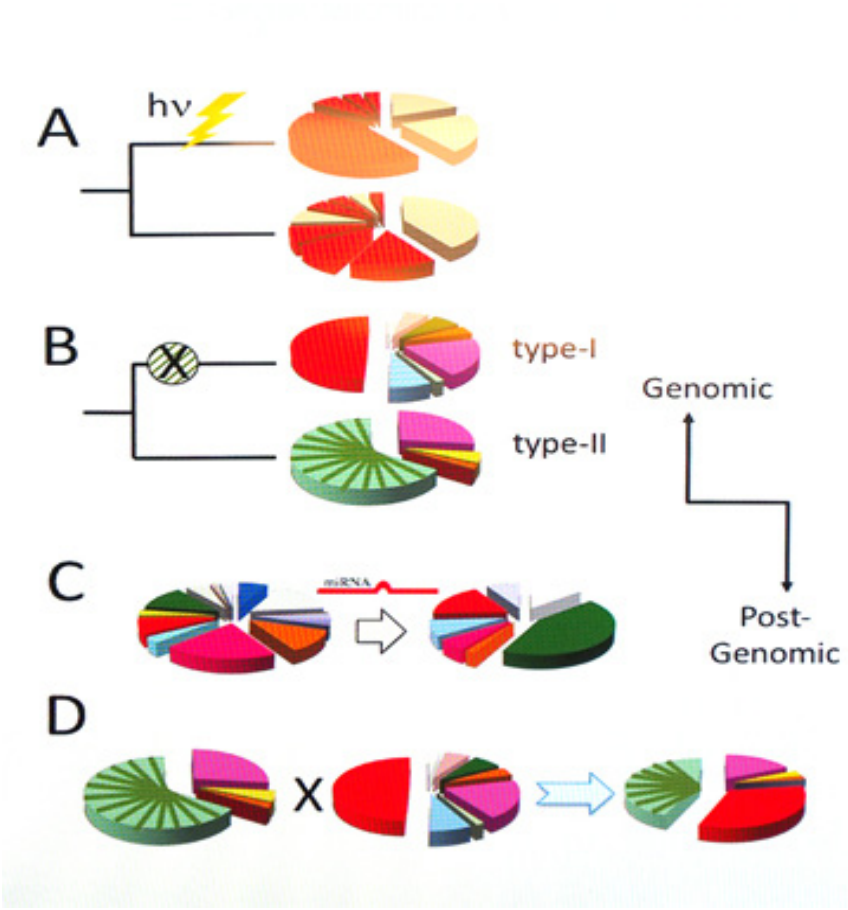
Prof. Juan Calvete (Valencia, Spain)

Prof. Calvete discussed his long term proteomics/venomics research, spanning snakes globally, and how this can be a tool for elucidating the evolution of venom diversity. He considers that active genome recruitment has allowed for accelerated evolution of venoms. He suggested a holistic approach involving elements of biology and natural history of venomous animals, analysis of antivenoms, use of toxins as molecular tools, and studies on the pathophysiology of envenoming, all focussed on the central role of venoms. PHOTO Mapping entire snake genomes is allowing for major advances in our understanding of how venoms may have evolved; examples of such elucidated genomes include the king cobra (*Ophiophagus hannah*), the hundred pace snake (*Deinagkistrodon acutus*) and the tabu (*Protobothrops flavoviridis*). This allows matching to specific toxin classes. Putting diverse information together now allows hypothesising about evolutionary mechanisms involved in venom development.

Prof. Calvete used the analogy of chess, where knowing certain pieces and available moves permits accurate prediction of missing pieces and possible outcomes. This includes concepts such ass the “founder effect” and the role of population bottlenecks which result in either recovery or extinction of populations or traits. Vipera latastei was used as an example, as was the invasion of Elapid snakes into the Americas, via Alaska, finally culminating in the diversification of coral snakes


Adding resolution and dimensionality to comparative venomics: moving from reference proteomes to clade venomics...
Elapidae
3FTx
Type 1A PLA2
Kunitz-inhibitor fold
Coral snakes
Mambas
Afro-Asian cobras
African garter snakes
Kraits
Sea kraits
Australasian elapids
Sea snakes
~30-25 Mya
α-neurotoxic 3FTx
β-neurotoxic type-I PLA2
PLA2
3FTx
Leptomicrurus
M. l. lemniscatus
M. l. carvalhoi
M. l. helleri


Russell's viper
Daboia russelii
KUN (17.8%)
svVEGF (2.7%)
svNGF (0.3%)
GC (0.01%)
SVMP (4.8%)
PDE (0.5%)
LAO (3.3%)
CTL (4.4%)
5'NT (0.92%)
CRISP (2.3%)
D49-PLA2 (50.4%)
DrK-a1 (17%)
DrK-a2
DrK-a1' (7%)
DrK-b1 (6%)
DrK-b2
(0.2%)
PLA2-IV
DrK-b2 (27%)
DrK-b1 (9.8%)
DrK-a1 (6.8%)
DrK-a2 (3.2)
DrK-a1'
[3 PLA2s]
DrK-a1
Q02471 (RV4)
P31100 (RV7)
Q7T3T5 Daboiatoxin B
Q7T2R1 Daboiatoxin A
Q02471 (RV4)
P31100. (RV7)
D49-PLA2 (47.5%)
Drk-b2
Drk-b1
Drk-a2
RVV-VD
PLA2-IV
PLA2-II
VRV-PL-VIIIa
Q02471(RV4)
P31100 (RV7)
Q7T3T5 Daboiatoxin B
AAZ53185
VRV-PL-V
1Q6V_A
Drk-b2
RVV-VD
VRV-PL-VIIIa
Q02471 (RV4)
P31100 (RV7)
Q7T3T5 Daboiatoxin B
DsM-A2/A2'
U1-viperitoxin
RVV-VD
VRV-PL-VIIIa
P31100 (RV7)
DsM-S1
U1-viperitoxin
VRV-PL-VIIIa
P31100 (RV7)
DsM-S1
AAZ53185
U1-viperitoxin
AAZ53185
VRV-PL-VIIIa
Q02471 (RV4)
P31100 (RV7)
D49-PLA2 (70.6%)




Medically important differences in snake venom composition are dictated by distinct postgenomic mechanisms

The Deep Origin and Recent Loss of Venom Toxin Genes in Rattlesnakes
Noah L. Dowell, Matt W. Giorgianni, Victoria A. Kassner, Jane E. Selegue, Elda E. Sanchez, Sean B. Carroll
Current Biology 26, 1–12, September 26, 2016

proteome research
Integrated Venomics and Venom Gland Transcriptome Analysis of Juvenile and Adult Mexican Rattlesnakes *Crotalus simus*, *C. tzabcan*, and *C. culminatus* Revealed miRNA-modulated Ontogenetic Shifts

The effects of hybridization on divergent venom phenotypes: Characterization of venom from *Crotalus scutulatus scutulatus* × *Crotalus oreganus helleri* hybrids
Cara Francesca Smith, Stephen P. Mackessy

toxins
Is Hybridization a Source of Adaptive Venom Variation in Rattlesnakes? A Test, Using a *Crotalus scutulatus* × *viridis* Hybrid Zone in Southwestern New Mexico

ORIGINAL RESEARCH Ecology and Evolution 2017;7:3951–3966
Insight into the roles of selection in speciation from genomic patterns of divergence and introgression in secondary contact in venomous rattlesnakes

in Central and Both America, with distinct venom subgrouping, either in PLA2 dominant, or 3FTx (3 finger cobra toxin) dominant species groupings. He argued for use of toxin-resolved venomics using top-down MS, as significantly more productive than bottom up methods. He then provided prodigious amounts of data to illustrate his contention.

2. Myanmar snakebite project; initial analysis of 3880 cases.
Prof. Julian White (Adelaide, Australia)

Prof. White first provided an overview of the global snakebite problem, using experience from Myanmar to illustrate some of the major problems and potential solutions. Points discussed included both the systemic and local effects of snakebite envenoming and their direct and indirect social and economic consequences. In Myanmar, snakebite is responsible for > 70% of all cases of acute kidney injury (AKI), which imposes a significant load on a stretched healthcare system. As developed nation diseases become more prevalent as Myanmar develops, this will impose a new load of AKI from diseases such as type 2 diabetes and unless snakebite AKI can be reduced, it is likely that the health system may be unable to cope with AKI adequately. Even with free access to healthcare and antivenom, including dialysis, there remain non-health costs such as loss of income and the family having to move to support the patient in hospital, that equate to about a years total family income, thereby entrenching poverty, both for that family, and for whole villages and regions, holding back development and economic emancipation.

The Myanmar Snakebite Project, an Australian government funded foreign aid initiative, has used a holistic approach, encompassing improvement in AV production (making Myanmar now self sufficient for AV), improvement in distribution (AV will be available at selected rural health centres), and strengthening of the healthcare system to better respond to snakebite (improved protocols, training, focus). This was only achievable because of an equal partnership of collaboration/cooperation between Project staff and local Myanmar colleagues, including support from the highest levels of the Myanmar government. Now in its final stages, the Project has achieved even more than expected and the achievements are clearly sustainable. This experience indicates that a holistic and

collaborative approach may provide a viable solution in tackling the snakebite problem in areas of high need.

In the second part of the lecture, Prof. White provided an initial analysis of patient data collected prospectively as part of the Project, with 3,880 cases already available for analysis and an expectation that case data collection may continue after the formal end of the Project, to better inform Myanmar health authorities, allowing rational resource allocation. Most cases in this series are from the Mandalay region, involving poor farmers, bitten while working (snakebite as an occupational disease) by Russell's viper, with a high incidence of coagulopathy and AKI, carrying a >10% mortality rate. Also emerging form the data analysis is a recognition that green pit viper bite is also a medical problem and for the first time it is possible to characterise envenoming by the endemic Mandalay spitting cobra, *Naja mandalayensis*. This is possible through collection, retention and expert identification of dead snakes brought in by snakebite patients. This cobra causes predominantly local effects rather than neurotoxicity, based on the current, though limited, case series.

3. Improving the transition from toxins to medicines

Prof. Alan Harvey (Glasgow, UK)

Prof. Harvey first outlined those venom-to-drug transitions that have been successful, demonstrating that successes, so far, have been few, though some of the successes have been very important (e.g. captopril & ACE inhibitors for hypertension; tirofiban and eptifibatide, GPIIb/IIa receptor antagonists; ziconotide, for analgesia; eventide, for control of type 2 diabetes; plus a number of novel powerful insecticides). However, if considered objectively, between 1981 and 2017, out of 1595 new classes of drugs approved by the US FDA, only 22 were derived from venoms/toxins. Of these, nearly half were actually new ACE inhibitors, so really just building on a past success with captopril, and a further 4 were botulinum toxin preparations, so new venom/toxin-based drugs have been a rarity. There are 10-20 agents in clinical trials. Prof. Harvey posed the question, "what's the problem?". He indicated that drug discovery is

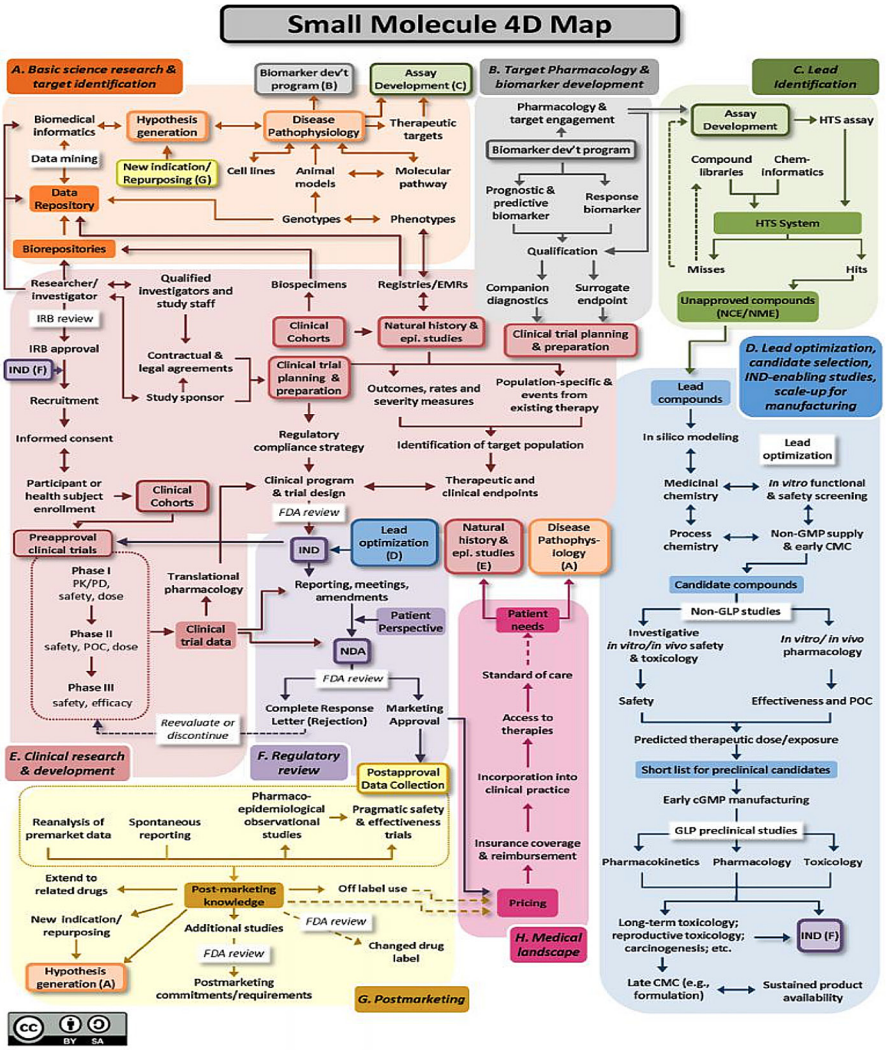
Further products

Drug	Lead	Approved
captopril	snake venom: bradykinin potentiating peptide	1981
tirofiban	snake venom: GPIIb/IIIa receptor antagonist	1998
eptifibatide	snake venom: GPIIb/IIIa receptor antagonist	1998
ziconotide	ω-conotoxin	2004
exenatide	Gila monster venom: GLP-1 agonist	2005
Sero-X	*Butterfly pea cyclotides*	*2017*
Spear-T	*Funnel web spider: Ca^{2+} blocker*	*2018*

quite different from toxinology research and that toxicologists may be ill equipped to be drug discovery successes. He therefore proposed 10 commandments, ideas to help guide toxicologists to, potentially, more success in drug discovery, based on his significant experience in this field.

(1) Remember that drug discovery is hard. Even for new drugs that reach Phase 1 studies, only 11% make it to market.
(2) Don't get confused. It is essential to be focussed.
(3) Don't patent or publish too early. Publication destroys novelty, essential for patents.
(4) Don't form a company. Companies may have 3-5 years of funding, but it takes around 11+ years to reach market.
(5) Don't be greedy. 1% of something is better than 100% of nothing, so expect to dilute your share by bringing in essential external financial backing.
(6) Don't forget a mouse is not a human. Animal models may not successfully translate into human efficacy or safety.
(7) Remember Paracelsus. Essentially everything may be poisonous; it just depends on dose. The therapeutically effective dose may be too close to the toxic dose.
(8) Don't be proud; accept lucky finds.
(9) Don't do it all yourself.
(10) Don't expect favours or novelty prizes.

So to succeed, first find a genuine unmet therapeutic need, then seek unique bioactivity, define selectivity, specificity, side effects and find the right partner.



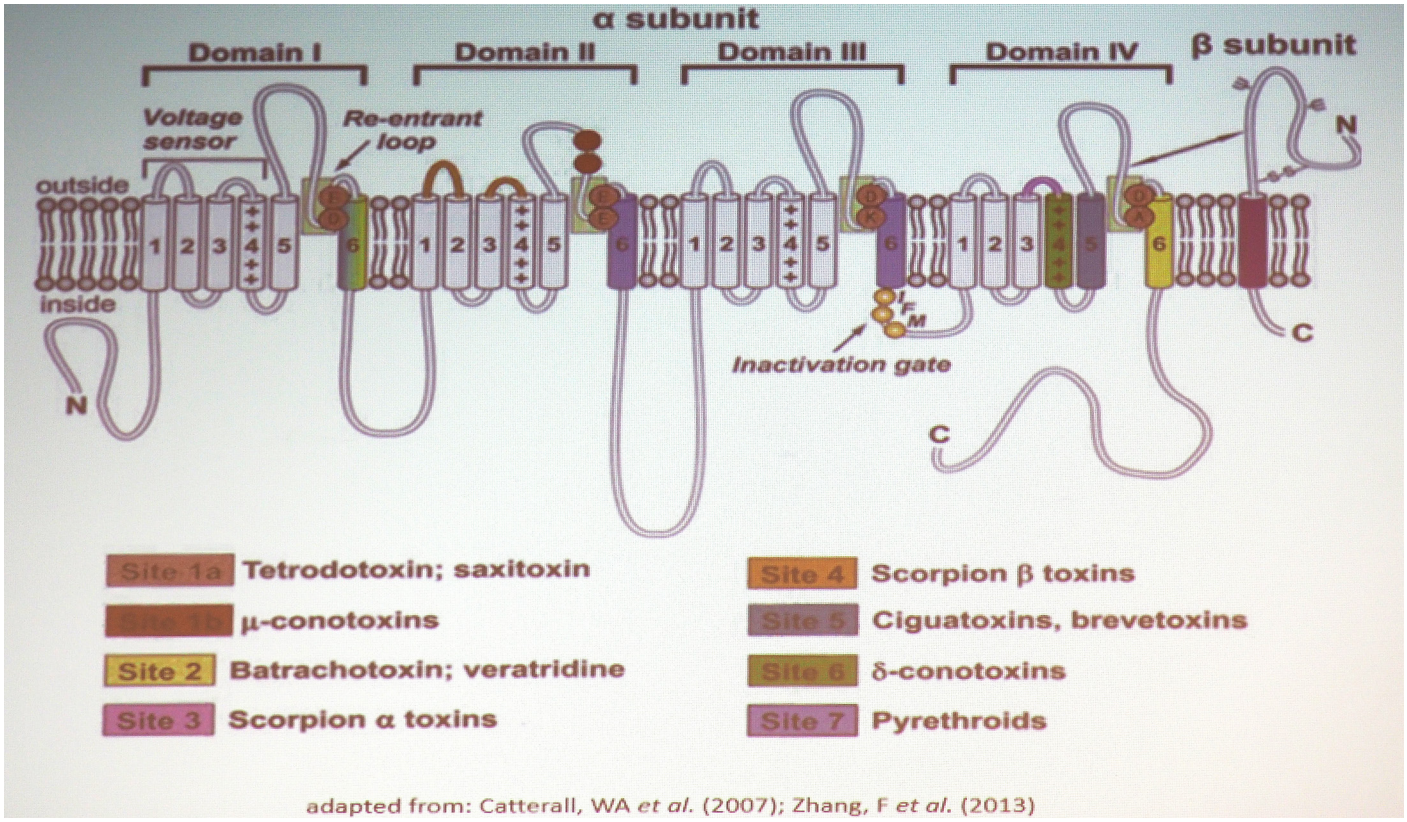
Wagner JA, Dahlem AM, Hudson LD, Terry SF, Altman RB, Gilliland CT, DeFeo C, and Austin CP. Drug Discovery, Development and Deployment Map (4DM): Small Molecules

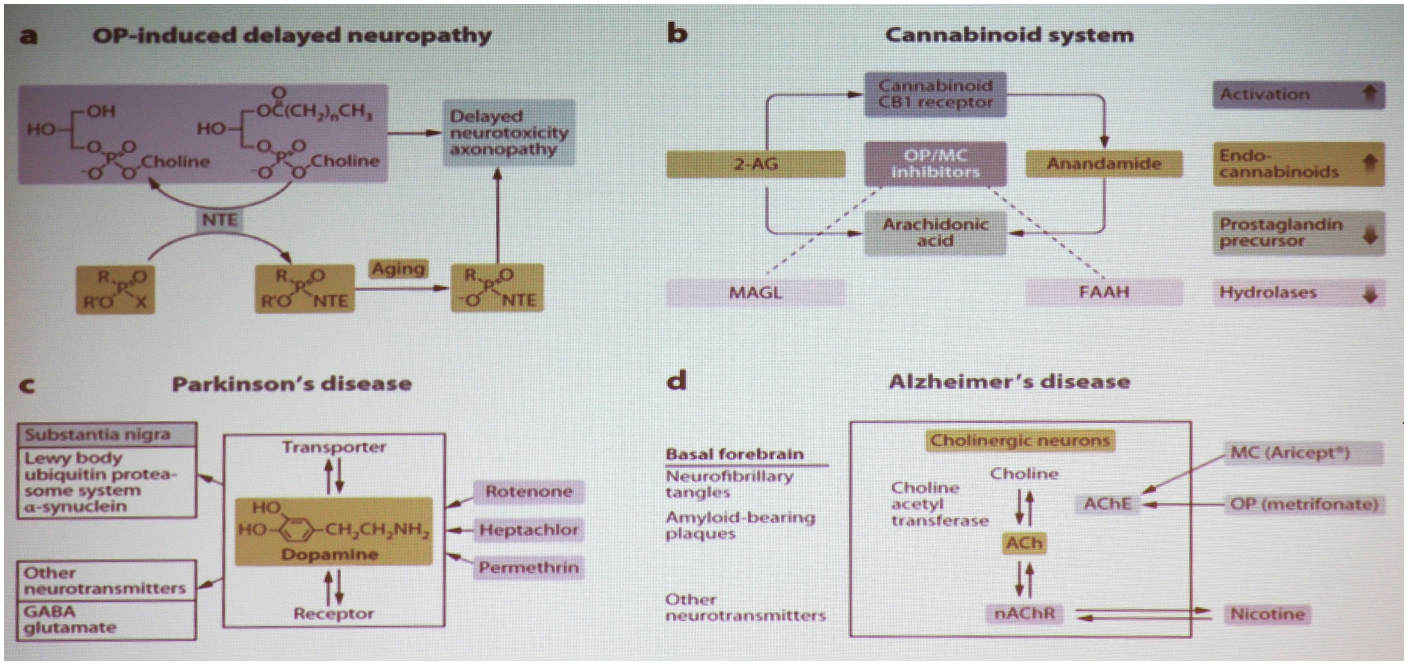
4. The potential of recombinant antibody technology in venom therapeutics.
Dr. John McCafferty (Cambridge, UK)

Dr. McCafferty, from IONTAS, discussed pathways to development of therapeutic antibodies, from murine, through chimeric, to humanised, following the invention of hybridoma technology in 1975. He discussed, in detail, the use of phage display libraries in the process of amplification of desired gene products. IONTAS has a current library of about 40 billion phage displays. He outlined the processes involved PHOTO, using examples such as blocking antibodies to human TACE and antibodies to black mamba venom neurotoxins. The Phage Display process is high throughput, capturing high affinity antibodies and using a 2-round methodology, may deliver results in a week. He also noted development of chimeric antibodies PHOTO, then touched on Knottins (ion channel inhibitor scaffold).

5. Venom components with insecticidal activity found in major animal phyla.
Prof. Jan Tytgat (Leuven, Belgium)

Prof. Tytgat first provided an overview of the range of animals, venoms and toxins that can contribute towards novel insecticides, then focussed on toxins targeting the voltage dependent Na+ channels (Nav), starting with the structure of the target channels with their mix of α and β subunits making up the 5-subunit channel with a central pore. There are a variety of ways toxins may bind to Nav channels and either block closed or open. New high throughput electrophysiology techniques such as HiClamp can greatly speed assessment processes for testing large numbers of toxin variants. The site of binding largely determines the effect, with blockade at binding site 1 and modulation at site 3. Insects can rapidly modify their Navs, mating at key positions to defeat toxicity. The risk of cross toxicity between insects and humans was discussed, as well as selectivity between insects (to spare honey bees, for instance). There is evidence of organophosphate-related insecticides causing longer term effects in humans, such as induced neuropathy and possible aetiology within Parkinson's and Alzheimer's diseases. Examining the example of Pompilidotoxin-like peptides from the wasp Cyphononys per-





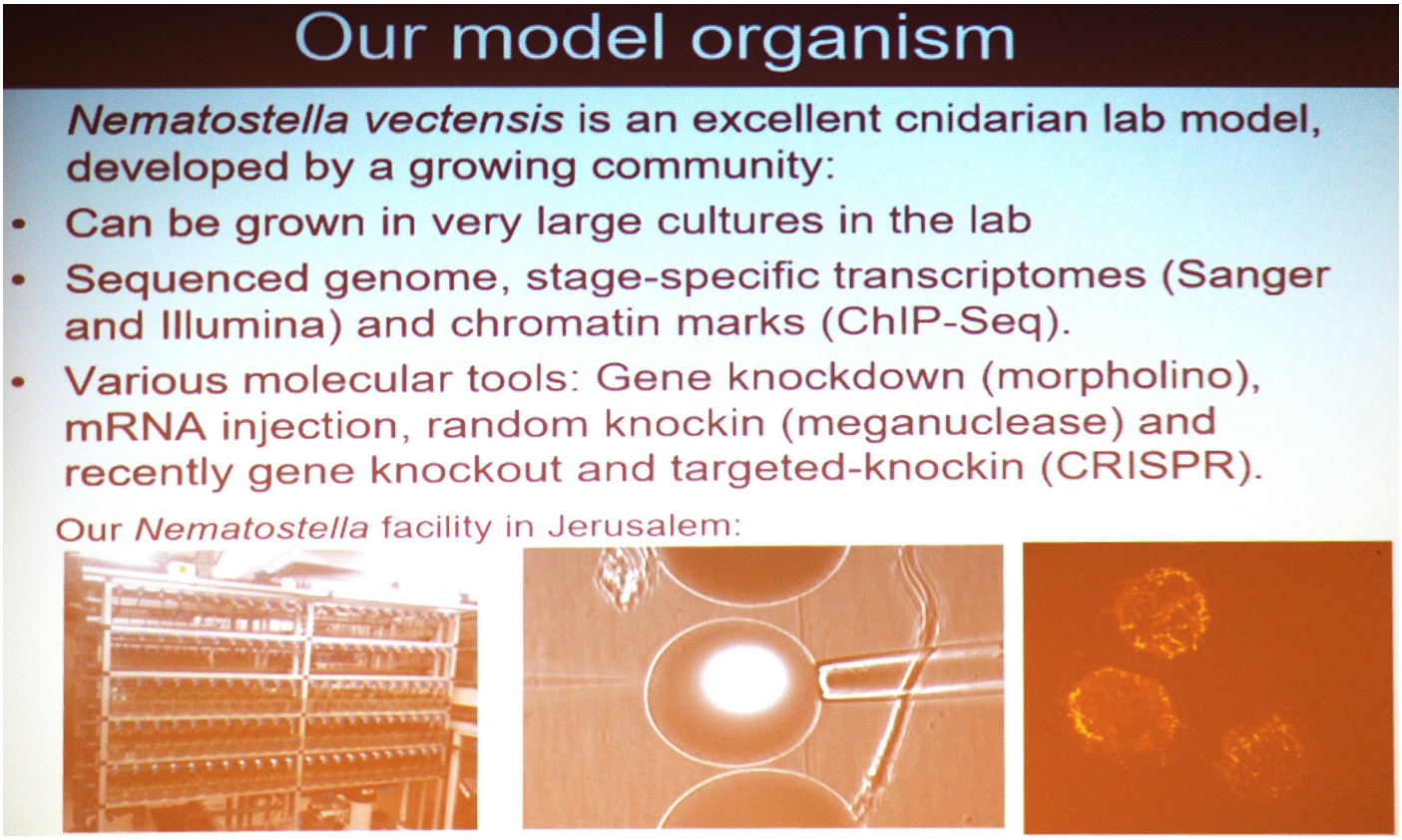
egrines, site 3 Navs can discriminate between insect types. It appears that it may be secondary Ca++ overload that is lethal rather than the primary Nav effect. By cloning and making minor AA changes, markedly different effects cab be produced and this may be used to increased insect species selectivity to spare useful species such as bees.

Prof. Tytgat then introduced the longest animal known, the ribbon worm, Lineus longissimus, which may reach 55m long and is an active predator on crustaceans. Humans touching the integument can develop local marked swelling. The mucus secreted by these nemertines has similarities to conotoxins. Inhibitory cysteine knot toxins (ICKs) are highly toxic in crabs, causing a slow neurotoxic paralysis.

6. Applying systems biology and genomic manipulation approaches for characterising the dynamics and complexity of venom production in a cnidarian.

Dr. Yehu Moran (Jerusalem, Israel)

Dr. Moran detailed his work with the sea anemone, *Nematostella vectensis*, as a valuable model and tool for understanding venom production and evolution. These anemones have a 5-6 moth lifecycle in the lab, are safe to touch, readily grown and have been shown to be ideal alb animals, easily genetically engineered. They are currently in use in at least 20 labs. They are venomous predators, and at 9 days old can catch, envenom and consume shrimps larger than the anemone. They utilise a Na channel moderator toxin, selective for invertebrates, and produced in gland cells more than in nematocysts, from primary polyp to adulthood. Nematocyst toxins expressed early in the life cycle, before the anemones have become predators, but remain prey for fish, are defensive, causing fish to regurgitate/spit out any ingested anemone larvae, unharmed. The toxin mix therefore changes ontogenetically. Adult females produce a fish-specific toxin designed to dissuade predation, which is then found in the egg stage as both RNA and protein, as a protective effect, but which disappears for the remainder of the lifecycle. A number of toxins are involved, expressed either in gland cells, or nematocysts, with varying and specific targets against either predators (fish), or prey (shrimps etc). Dr. Moran suggested this complex toxin strategy provides evolutionary flexibility, allowing ready adaptation to changing threes and prey availability. Studies on ShK-like toxins from anemones indicates that original ShK-like peptide was likely a neuropeptide, but through gene duplication, morphed into a specific class of toxins. Dr. Moran considered this was influenced by environmental changes and was not evidence of “intelligent design”.



Closing lecture

Development of an "app" to assist management of mushroom poisoning.

Prof. Julian White (Adelaide, Australia) (coauthor Prof. Scott Weinstein)

Prof. White outlined the problems posed by mushroom poisoning, particularly around diagnosis, a vital first step in targeted treatment. The emergence of newly described syndromes of mushroom poisoning globally in recent years has rendered previous classifications of mushroom poisoning outdated, hindering diagnosis. A new classification has been developed and was outlined by Prof. White, together with the associated diagnostic algorithm. To manage the problem of diagnosis and treatment of mushroom poisoning locally in South Australia (SA), the Toxinology Service, headed by Prof. White, has developed a prototype iOS-based "app" for use on iPads, using a database (FileMakerPro) back end, to deliver a rapid diagnostic and reference tool to assist clinical toxicologists in SA when consulted about patients with mushroom poisoning. Prof. White demonstrated the layout and functioning of the app, the intention being to further develop and test it, first in SA, then after refinement based on that clinical experience, further test it in Europe, with an aim to ultimately have a globally useful tool for clinicians.

Invited Lectures

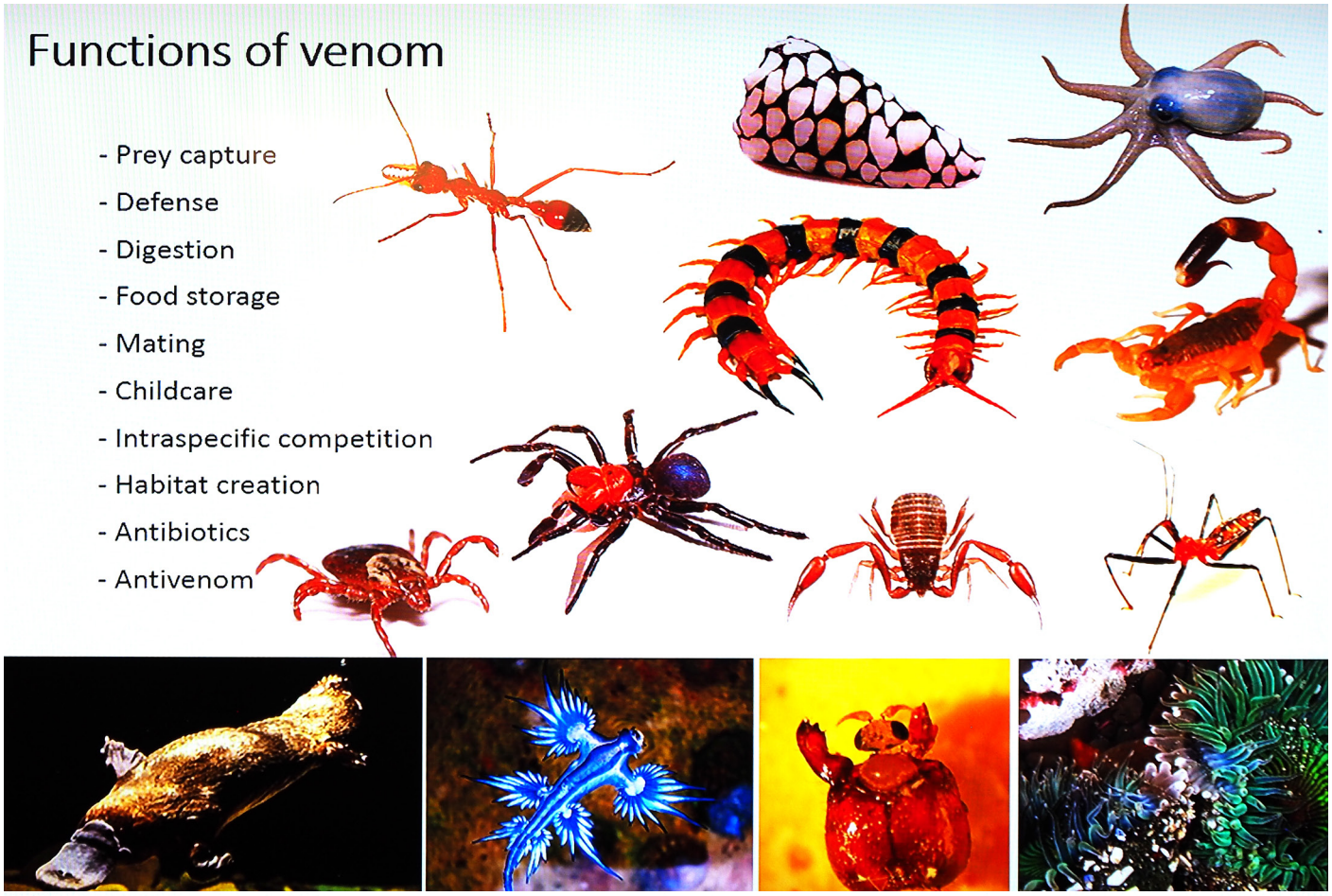
Venomics and Proteomics Session

Mass spectrometry imaging as a tool for providing a better understanding of venom biology.

Eivind A. Undheim. University of Queensland, Brisbane, Australia.

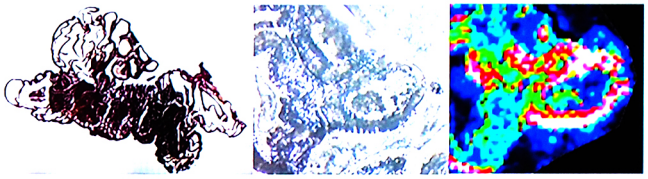
Dr. Undheim presented an overview of the diversity of venom evolution, across may taxa, noting that venom has many potential uses, including prey capture, defense, digestion, food storage, mating, childcare, infraspecific competition, habitat creation, antibiosis and for antivenom. He suggested there remains a poor understanding of the functions of toxins, including aspects of production, storage, secretion and targets, noting that toxin activity does not equal toxin function. He compared the differences between predation-evoked and defence-evoked venom production in cone snails, with similar findings

in reduviid bugs. Using mass spectrometry imaging it is possible to study which toxins, in response to specific stimuli, are produced in which parts of venom and related glands. Examples included spiders and anemones. His conclusion was that mass spectrometry imaging can be complementary to traditional venomous, providing new insights into venom biology, of assistance in both understanding venom evolution and in drug and bio pesticide discovery, and antivenomics.

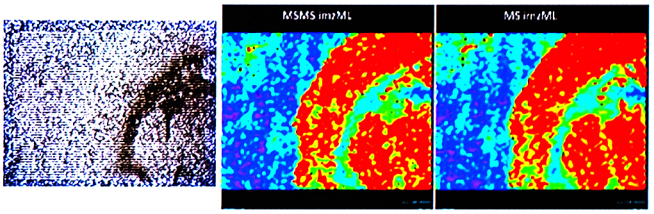


Mass Spectrometry Imaging in venomics

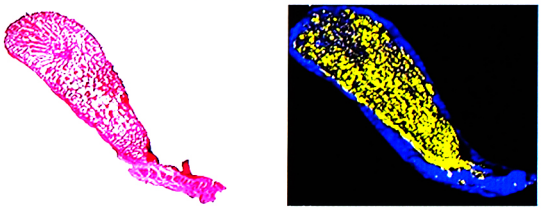
Complementary to 'traditional' venomics
- Non-targeted imaging
- Toxin imaging in non-model organisms



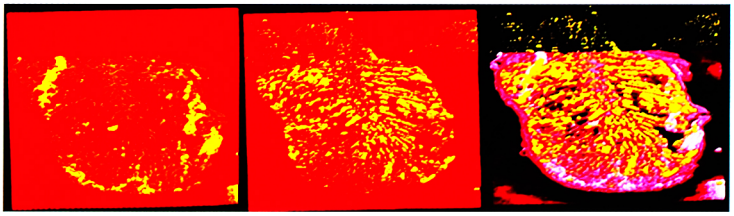
Provides new insight into fundamental aspects of venom biology
- Toxin production and storage
- Toxin secretion
- Toxin function



Applications and importance to
- Venom evolution
- Venoms-based drug discovery
- Venoms-based biopesticide discovery
- Antivenomics



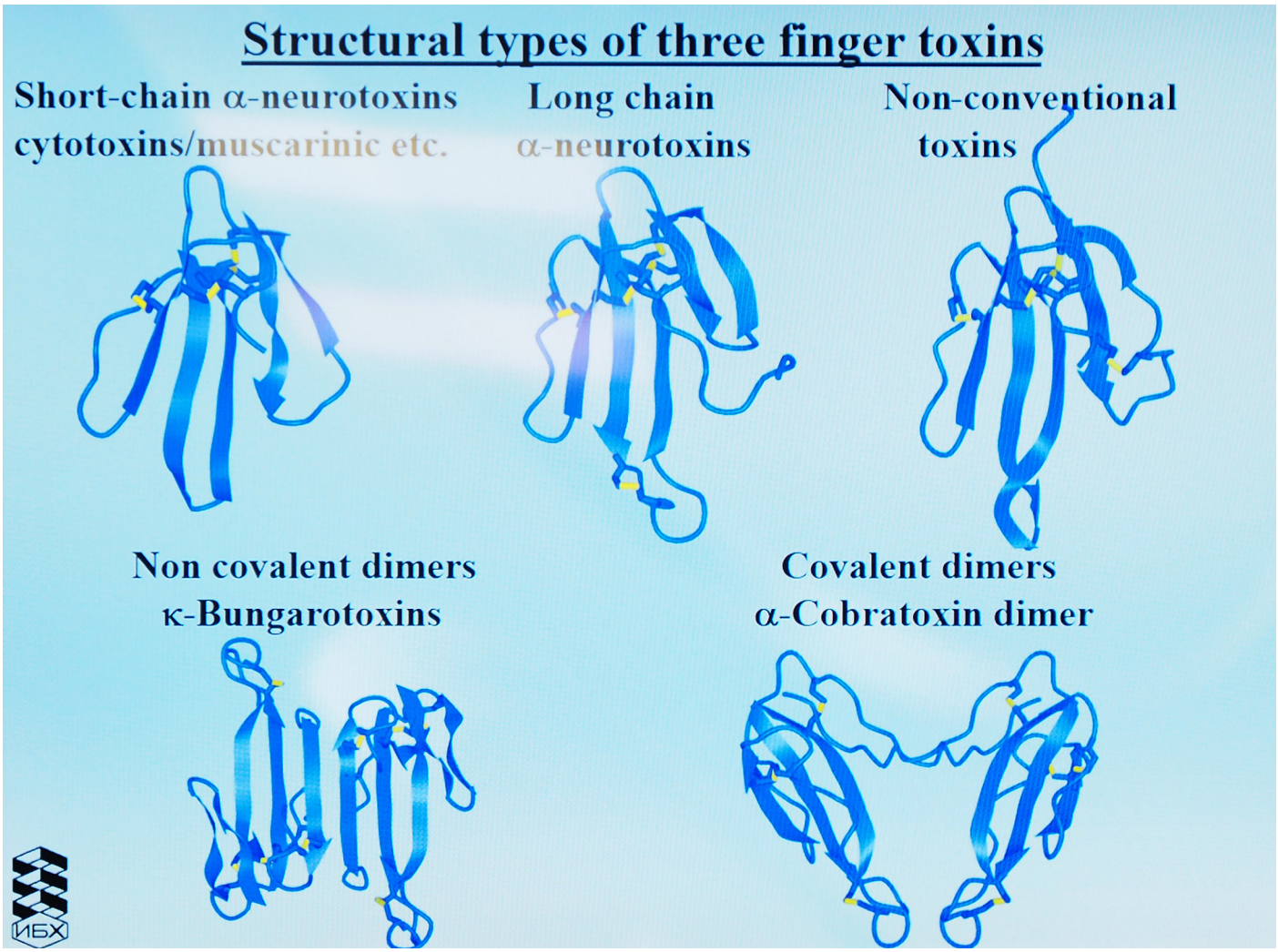
Biomedical imaging methods development

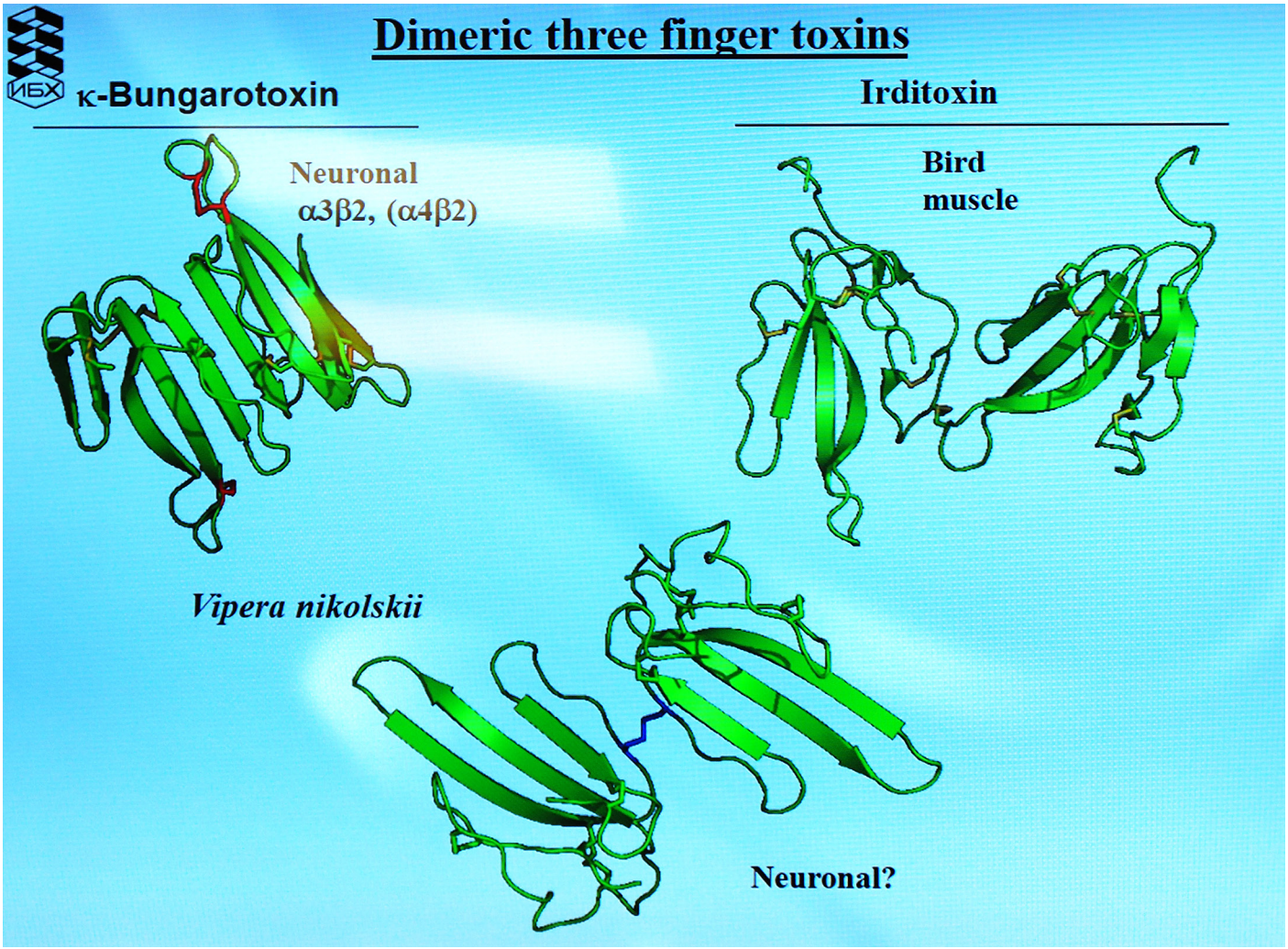


Three Finger Toxins: Recent Findings

Yuri Utkin. Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Moscow, Russian Federation.

Prof. Utkin first provided an overview of the range of three fingered toxins (3FTx), including their structural types, followed by an update of recent knowledge. Prof. Utkin also discussed, in more detail, the ligand-gated ion channels (receptors of the Cys-loop family), transmembrane proteins with 5 homologous subunits. Upon activation these GABAA receptors selectively conduct Cl- ions. An α-neurotoxin from *Bungarus multicinctus*, BMLCL, is the largest known such toxin, with 82 AA and 5 disulphide bridges. He then discussed dimeric 3Ftx such as κ-Bungarotoxin-like toxin from *Vipera nikolskii* and bird muscle toxin, Irditoxin. The former toxin potentiates α-Bungarotoxin activity and has structural identity with tens complex inhibitor, but has no currently known action on blood coagulation.

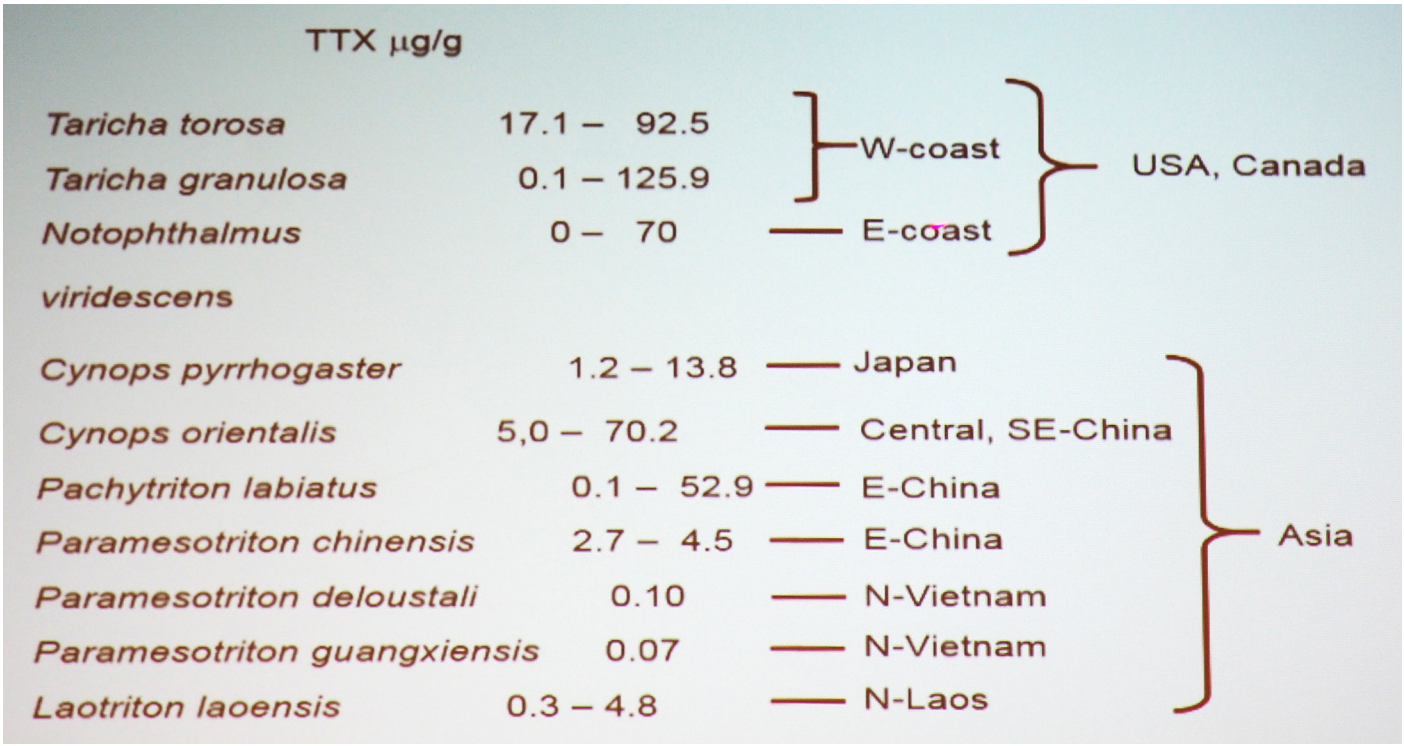




Natural History and Evolution of Venoms/Toxins

Tetrodotoxin in newts - Endogenous or exogenous origin?
Dietrich Mebs. Institute of Legal Medicine, University of Frankfurt, Germany.

Prof. Mebs provided a history of research into the origin of tetrodotoxin (ttx) in certain newt species, studies co-conducted with Prof. Mari Yotsu-Yamashita (Sendai, Japan). Newts involved included *Cyanops* spp., *Laotriton laoensis*, *Notophthalmos viridescens*, *Pachytriton labiatus*, *Paramesotriton* spp., *Taricha granulosa*, *T. torosa*. Amongst these newts, changes in amino acid composition in the voltage gated sodium channel Nav 1.4 have been studied, as these AA substitutions provide immunity against the actions of tetrodotoxin, which targets this channel. The concentrations of ttx in these newt species varies widely, both within and between species, the highest concentrations being found in North American species (*Taricha* app., *Notophthalmus viridescens*). Breeding experiments show that, in captivity, these newts do not contain ttx, but it remains unclear if the newts take up ttx from their environment in the wild, or whether some natural environmental factor, absent in captivity, is a trigger for native ttx synthesis by the newts. A current study of tetrodotoxic newts in an abandoned military area in Germany may possibly yield answers to these questions.



The impact of site-specific positive selection on the structurally and functionally important parts of the snake venom Kunitz/BPTI protein family

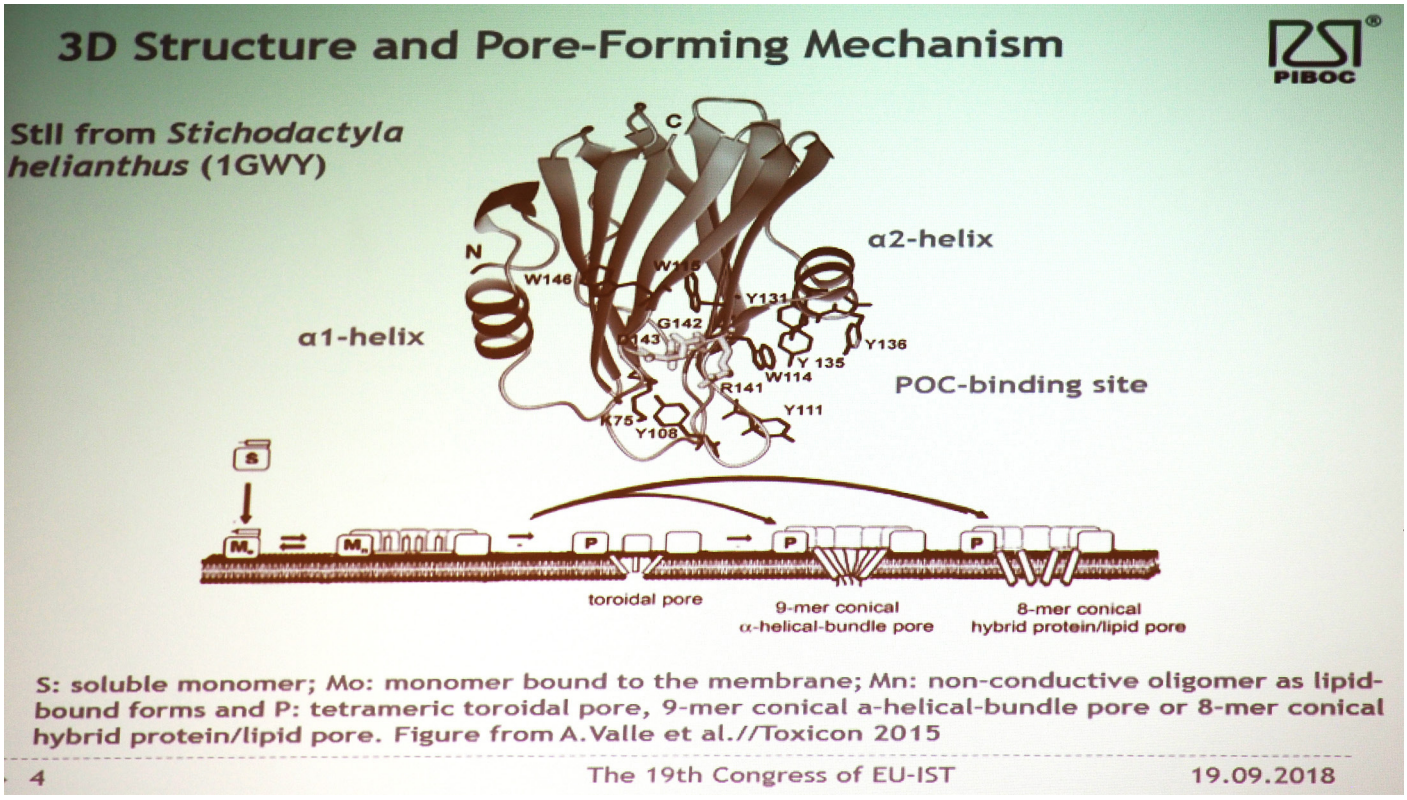
Dušan Kordiš. University of Ljubljana, Ljubljana, Slovenia.

Dr. Kordis discussed the Kunitz/BPTI proteins, inhibitors of the S1 family of serine proteases, which are largely found in metazoans, with Kunitz domains containing about 60 AA. They have a compact 3D structure with a hydrophobic core supporting the convex and exposed canonical binding loop at positions P3-P3'. The loop is highly complementary to the concave peptidase active site and is responsible for the extreme stability of the interaction with target serine proteases. The structure of these Kunitz/BPTI inhibitors is conserved throughout metazoans, from cnidarians through to mammals. Small changes in AA composition in key inhibitory sites on loops 1 & 2 affect electrostatic potential and may be important in determining selectivity of these toxins for specific serine protease target molecules. There is a constant "arms race" between snakes producing Kunitz toxins and their prey, modifying serine protease structure. Dr. Kordis discussed his research into the molecular evolution of snake Kunitz/BPTI toxins, using site-specific variability. Methodology included database mining, phylogenetic analyst, selection analyses, PyMOL visualisation of structures and TreeSAAP. The large number of S1 serine peptidases found in potential prey (up to several hundred per species) requires an equally diverse toxin response, hence venomous snakes have large Kunitz/BPTI multilane families, including both KU and WAP domains (both inhibitory regions against S1 Serine peptidases). In comparison with Kunitz?BPTI inhibitors found in ticks and vampire bats, only in venomous snakes has there been widespread site-specific positive selection for diverse S1 target molecules.

Pore-Forming Toxins from Sea Anemone Heteractis crispa: Diversity and Pharmacological Potential

Elena Leychenko. Elyakov Pacific Institute of Bioorganic Chemistry, Vladivostok, Russian Federation.

Dr. Leychenko presented research on peptide toxins from sea anemones, specifically *Heteractis crispa*, looking for cytolysis-based immunotoxins with selective activity killing cancer cells. PHOTO She then diverted to the 3D structure of a pore-forming toxin from another anemone, Stichodactyla helianthus, in relation to H. crispa toxin rHct-

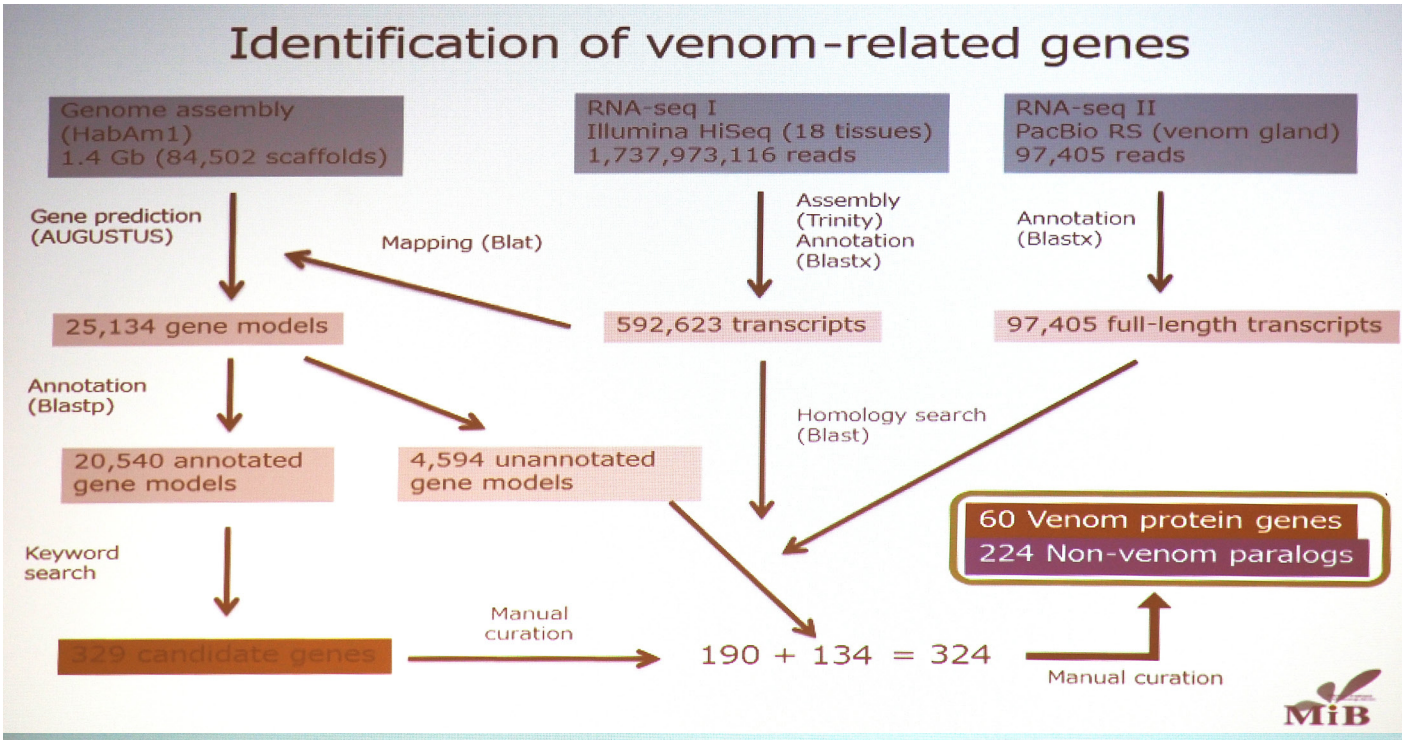


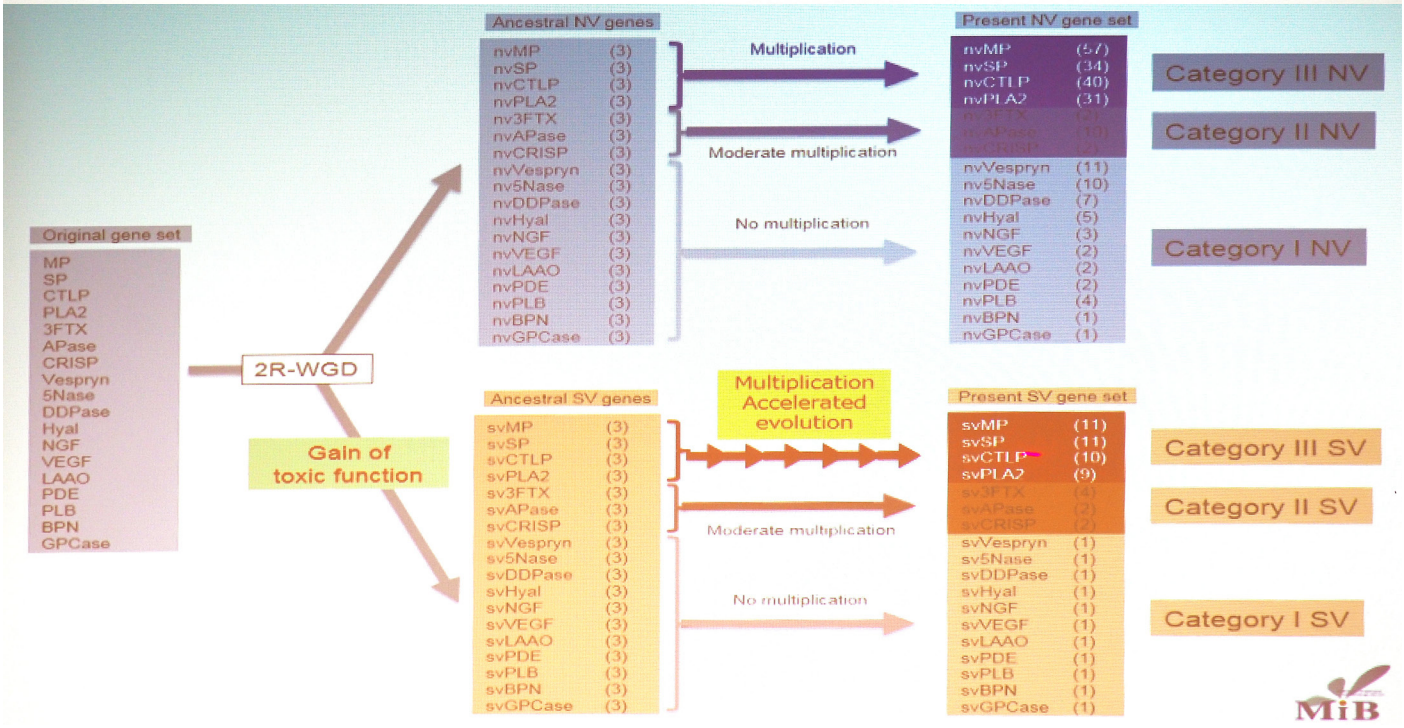
A2, an actinoporin. This latter toxin shows cytotoxicity against cancer cells for colon cancer, breast cancer and melanoma. Actinoporins are products of a multi-gene family, consistent with current taxonomy of sea anemones. Gene duplication and sequence divergence has allowed *H. crispa* and *H. magnifcia* to evolve a large repertoire of these toxins, which exhibit haemolytic activity. Even at non-toxic concentrations, rHct-A2 inhibits spontaneous colony formation of a variety of cancer cell types.

Whole genome sequencing of a Japanese endemic pit viper, habu, Protobothrops flavoviridis reveals accelerated evolution of venom protein genes enriched in microchromosomal regions

Hiroki Shibata. Kyushu University, Fukuoka, Japan.

Dr. Shibata first explained why the habu was chosen for genome sequencing; because it is a significant cause of snakebites with envenoming in Japan, has a range of toxins of potential interest in drug discovery, has a key position in the food chain, all four species are endemic in Japan and currently genetic diversity is almost unknown. Thus it is of interest due to public health, pharmacology, molecular evolution, genomics, ecology, conservative genetics and population genetics. The Habus of importance include *Protrobothrops flavoviridis* and *P. tokarensis*. The draft habu genome is about 1.4 Gb, with 84k scaffolds, 25k protein coding genes and 20k annotated genes. PHOTO The venom related genes, 284 (60 genes coding venom proteins, plus 224 non-non-genomic paralogs), cover a wide variety of toxin types, dominated by metalloproteinases, serine proteases, C-type lectins and PLA2s, which are all highly multiplicated. Dr. Shibata then discussed two-round whole genome duplication, noting that only one copy gained venom function. Accelerated evolution was observed exclusively in the multiplicated venom protein genes, rather than single-copy genes. He suggested that the genomic architecture of microchromosomes (MICs) might have facilitated the accelerated evolution of venom-related genes.





Clinical Aspects of Snakebites

Incidence of snakebites and medically relevant snakes in different regions in Laos and Vietnam

Jeorg Blessmann. Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany.

Jeorg first noted the addition of snakebite to the WHO NTD list, then discussed relative published incidences of snakebite in the SE Asian region, noting that it was particularl;y high in Nepal and Laos (all incidences per 100,000 population/yr; Eastern Terai Nepal, 1162; Savannakhet Phin, Laos 2014, 1105; Savannakhet Campone, Laos, 2018, 355; Myanmar, 2018, 116; Can Tho, Vietnam, 48). He then detailed work in Laos, comparing the Champone (lowland, higher population density, lower poverty rate) with Phin (mountainous, low population

Comunity based surveys in Savannakhet in 2013 and 2014

	Champone	Phin
geography	Lowland	Mountainous
Forest area	33%	90%
Population density	105/km^2	16/km^2
Poverty rate (%)	0	44

Mountainous, Phin district
1105 per 100,000 per year

Lowland, Champone district
355 per 100,000 per year

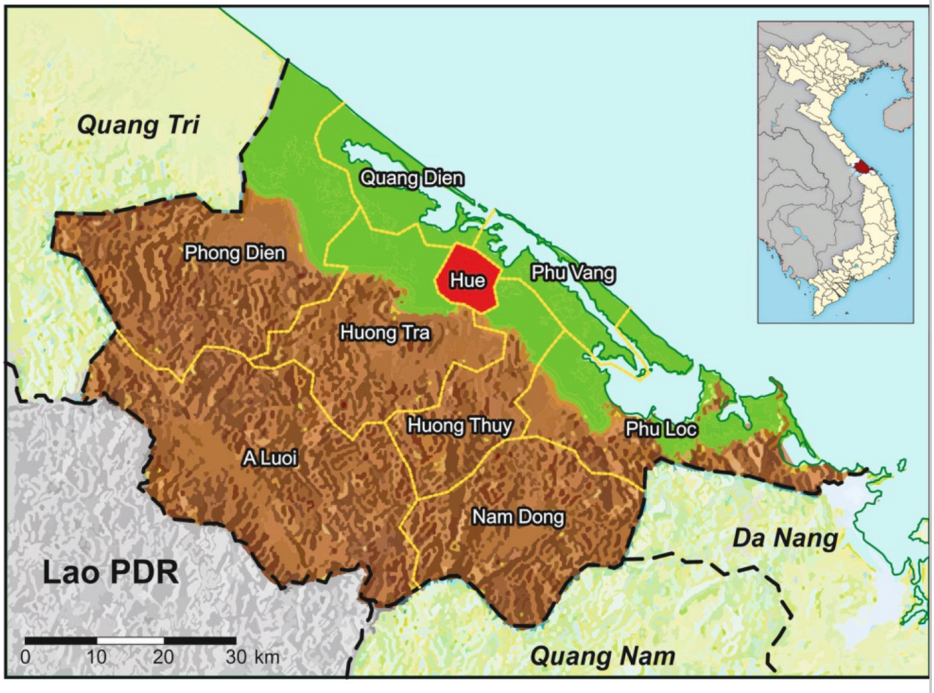
Incidence of snakebites in 3 different geographical regions in Thua Thien Hue province.

Mountainous
172 per 100,000 per year

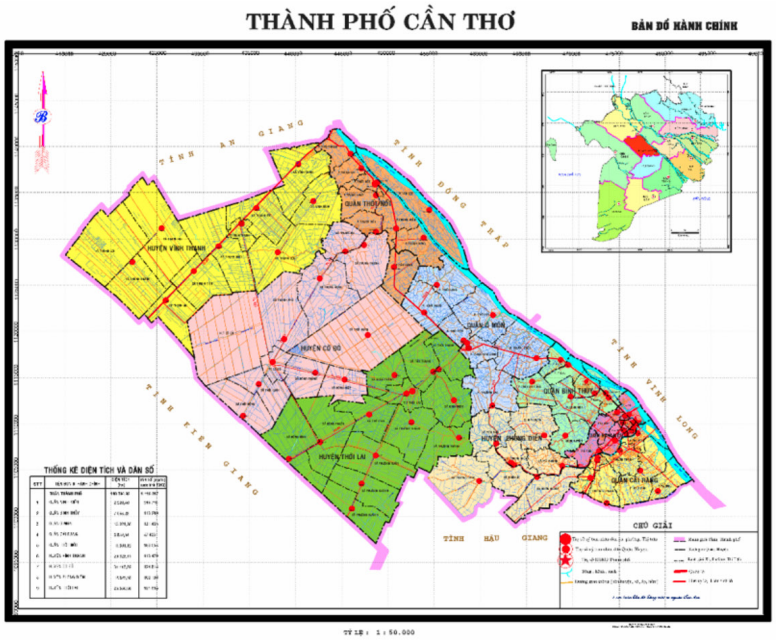
Lowland
69 per 100,000 per year

Urban
10 per 100,000 per year

Entire province
58 per 100,000 per year



Community based study on incidence of snakebites in **Can Tho municipality**, South Vietnam



Incidence of snakebites Can Tho municipality including 7 districts
48 snakebites per 100,000 per year

density, high poverty rate) districts of Savannakhet region, with, respectively, snakebite incidence of 355 and 1105/100,000/yr. Traditional healers were the major source of treatment, with no hospital system involvement. Studies in Thua Thien Hue Province, Vietnam revealed a similar pattern with a rate of 58/100,000/yr for the entire province, but only 10 in urban areas versus 172 in mountainous areas and 69 in lowland rural areas. Traditional healers were only involved in 19/31 cases, with hospital treatment involved in 12/31 cases. Hospital data on snakebites clearly under-represents actual community snakebite incidence (<2% of actual cases in Laos, only 20% of actual cases in Hue, Vietnam). Differences in snakebite between Laos and Vietnam may be explained, in part, by different snake fauna (no Malayan pit viper in central Vietnam and Mekong Delta; more mechanisation of agriculture in Vietnam; increased urbanisation in Vietnam; more community use of snakes in Vietnam). In studied regions of Laos, medically important snakes include the Malayan pit viper (*Calloselasma rhodostoma*), green pit vipers (*Trimeresurus* spp.) and a spitting cobra (*Naja siamensis*), compared to studied regions in Vietnam where green pit viper bites predominate (85-90+%), with few cobra bites (*Naja kaouthia* 10-15%) and no Malayan pit vipers. Krait (*Bungarus* spp.) bites appear to be minor (<1-5%) in both countries in areas studied.

Snakebite and antivenom management in Nepal

Chabilal Thapa Magar. Kaligandaki Hospital, Kawasoti, Nepal.

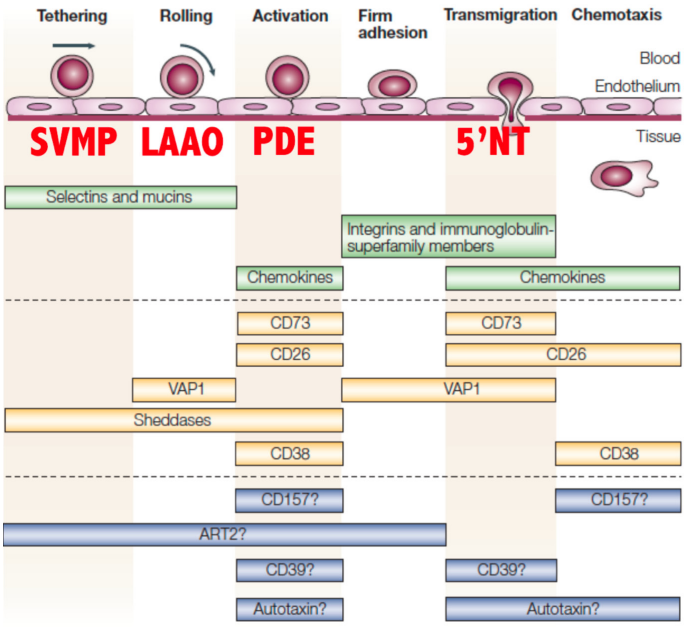
Dr. Thapa gave a broad overview talk on his work on snakebite in Nepal, without presenting any new or original data. He noted that WHO 1987 data indicated 20,000 cases and 1,000 fatalities from snakebite annually in Nepal, mostly in the Terai region bordering with India. He provided more recent data, presumably from government hospital statistics, indicating a fatality rate in the range 6.8 to 12.2%, with no clear decline in more recent years (most recent data 2012/13). He then discussed training on snakebite provided to health staff and

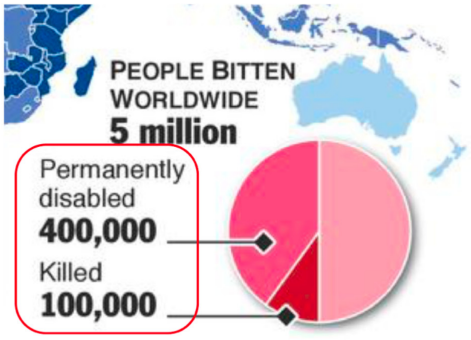
noted that antivenom is provided free. This was followed by information on antivenom dosing, with data from another published study which, he stated, indicated that there was no outcome difference between two regimes; initial low dose with escalating dose as required versus initial high dose. (A note to readers: on checking the paper, the conclusions include that the initial high dose regime is more practical, without an increased adverse effect profile, but that the tested antivenom (Indian VINS Polyvalent) is poorly effective for neurotoxic snake envenoming and the authors called for development of a more effective antivenom for use in Nepal). Dr. Thapa's presentation mainly focussed on his work teaching management of snakebite to various groups in Nepal, although it was unclear to me if there was any clear evaluation of effectiveness of this program.

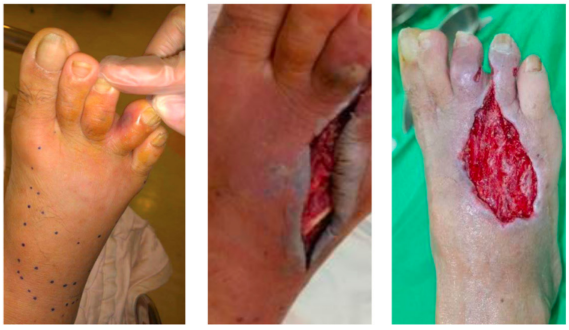
Understanding the local tissue necrosis of the bitten victim from cobra snakebite
Wen-guey WU. National Tsing Hua University, Hsinchu, Taiwan.

Dr. Wu discussed the snakebite problem in Taiwan, first listing the important species (*Trimeresurus stejnegeri*, *Protobothrops mucrosquamatus*, *Deinagkistrodon acutus*, *Daboia siamensis*, *Naja atra*, *Bungarus multicinctus*), noting the difference in problems presenting between the two sides of Taiwan. In the eastern part rhabdomyolysis is common, with no neurotoxicity, while in the western part neurotoxicity is more common than rhabdomyolysis. In both districts local tissue injury is the dominant clinical effect, especially in the eastern part. Rates of surgical intervention exceed 60% in the east, around 50% in the west. Dr. Wu then progressed to discuss the venomics of N. atra venom, including geographic variation, as an explanation for clinical differences noted between east and west Taiwan, in particular the lack of clinical neurotoxicity in the east, though cobra venom from that part does contain neurotoxins. He then compared *N. atra* venomics to *N. nivea* venomics (a non-spitter African cobra species). The latter has about 11% of venom as neurotoxins, compared to <4% for *N. atra*. Next he discussed the necrotic effects involving pore formation, of cobratoxins (CTX), noting that although *N. nivea* is a predominantly neurotoxic species, it still has high amounts of CTX in the venom, but not pore-forming CTX, nor PLA2, suggesting these may be critical in causation of tissue necrosis. Both these latter toxins are found in *N. atra* venom, with higher amounts in eastern populations, possibly explaining the higher rate of skin damage in eastern Taiwan, compared to the west. He then switched to a separate discussion of high molecular

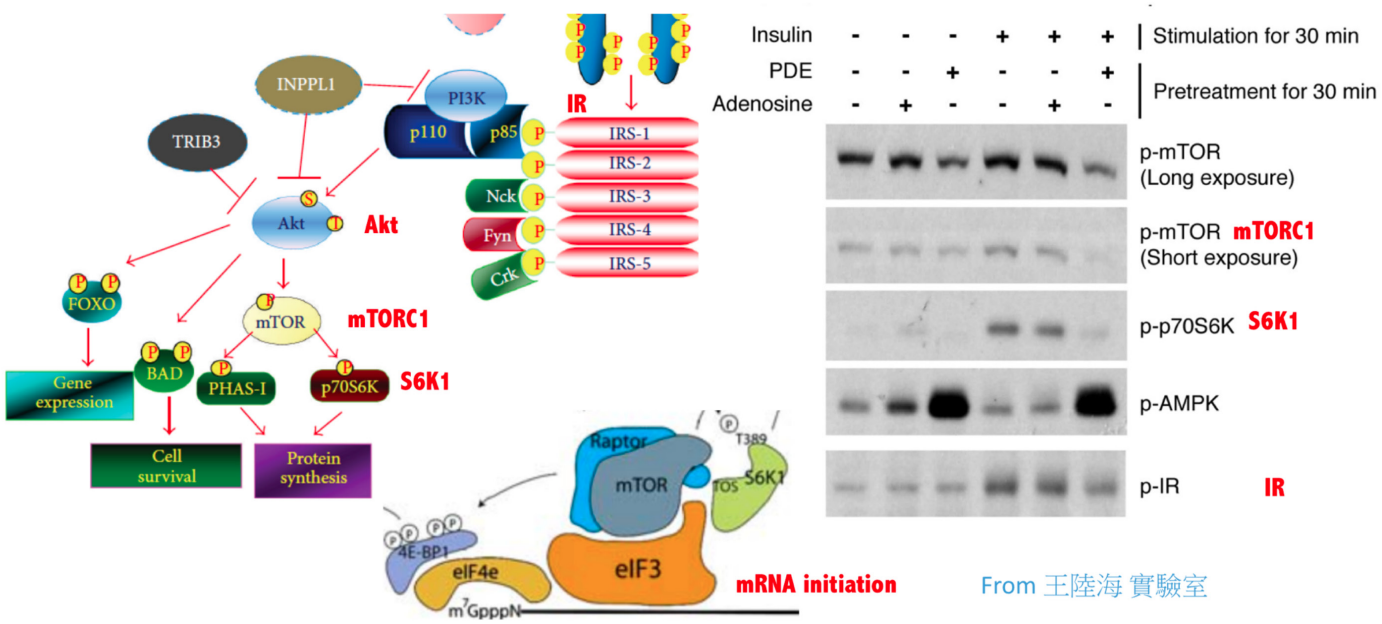
The human homologues of most HMW snake venom toxins have been implicated in immune cell trafficking



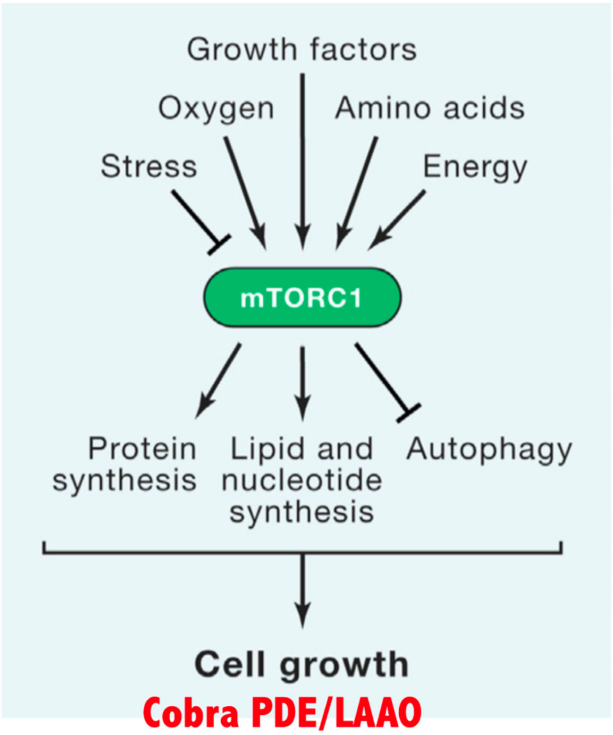


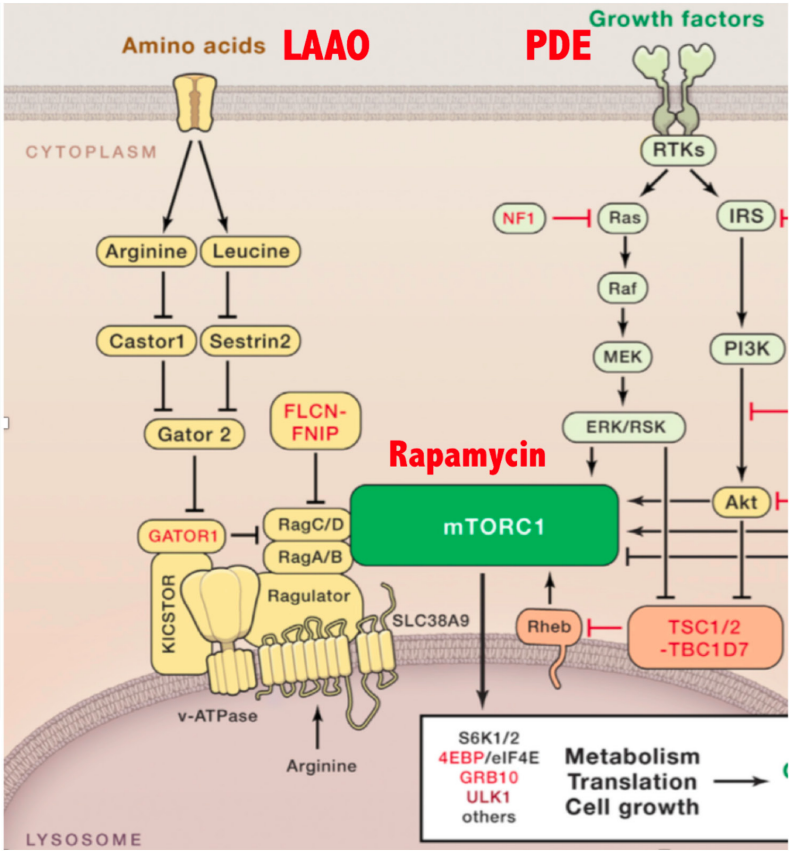


The inhibitory actions of cobra PDE on insulin receptor go through Akt-mTOR signaling axis to affect protein synthesis



From 王陸海 實驗室





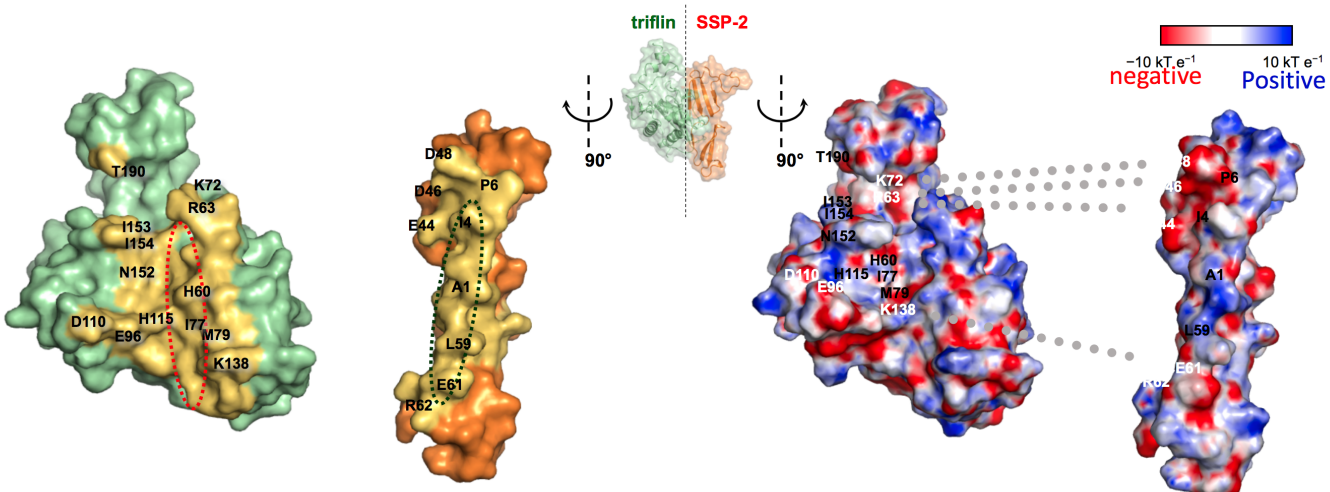
weight (HMW) toxins such as snake venom metalloproteinase disintegrins (SVMPs), cysteine rich secretory proteins (CRISPs), nucleotidases (5'NTs), phosphodiesterases (PDEs), l-amino acid oxidases (LAOs) and cobra venom factor (CVF), noting that human analogues of these toxins are implicated in immune cell function. These HMW toxins enhance CTX-dependent skin necrosis. Cobra venom PDEs inhibit the insulin receptor (mTORC1), thereby affecting protein synthesis and may act as potent immunosupressors, as does venom LAO (targets Arg and Leu AAs).

Rational design and development of anti-venom drugs for snakebites based on the endogenous inhibitors from Japanese Viper

Narumi Aoki Shioi. Fukuoka University, Fukuoka, Japan.

Dr. Aoki Shioi detailed her group's work on endogenous inhibitors from *Protobothrops flavoviridis* venom, particularly the small serum proteins (SSPs) purified using reverse-phase HPLC and SDS-PAGE. 5 SSPs were isolated, each binding to a different toxin. SSP-2 binds to the ion channel blocker triflin and the crystal structure of this complex was elucidated. The binding was investigated in detail; it is high affinity with a centrally located concave region in the N-terminal domain

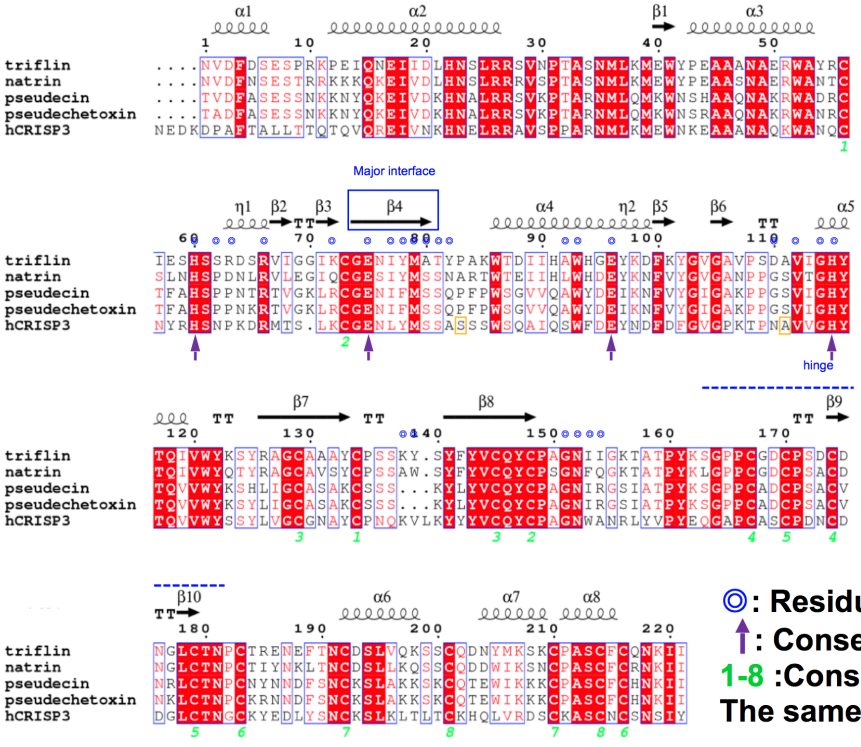
Characteristic feature of the binding interface



Buried surface areas **electrostatic potentials**

Interface of each protein was colored in yellow.
SSP-2 (1200.1 Å²) is contacting with triflin (1089.7 Å²).

9



Conserved amino acid sequence in the binding site of snake venom CRISP

◎: Residues involved in the interaction.
↑: Conserved Zn2+ binding motif.
1-8 :Conserved cysteine residues.
The same number forms disulfide bonds.

Involvement of Necroptosis and Ferroptosis pathway signaling in Hemiscorpius lepturus venom -induced acute kidney injury

Hossein Vatanpour. Shahid Beheshti University of Med. Sciences, Tehran, Iran.

Prof. Vatanpour first detailed the scorpion envenoming problem in Iran, focussing on *Hemiscorpius lepturus* (Family Hemiscorpiidae), a species almost exclusively found in Iran and with a quite distinct and severe type of scorpion envenoming characterised by skin necrosis and systemic effects including intravascular haemolysis, DIC, and secondary acute kidney injury (AKI). The venom has neurotoxic, haemolytic and cardiotoxic activities. He detailed some studies isolating some of these toxins, then discussed AKI as the main cause of fatal cases in humans. AKI is more likely in children who are therefore at higher risk. His research aimed to identify the nephrotoxic mechanism in the hope it might guide treatment. He used a mouse model with escalating venom doses and looking at biomarkers, gene expression, oxidative stress parameters and histological evaluation of damage. Neutrophil gelatinase associated lipocalin (NGAL) was selected as a suitable biomarker for injury, originating from damaged kidney cells in amounts reflecting damage level and detectable in both the mouse model and in human patients. A number of gene expression factors were examined (TNF-alpha, XIAP, Caspase 8, Caspase 3, Bax). Oxidative stress was determined via glutathione levels, lipid peroxidation and ATP levels. His conclusion was that AKI is induced via 2 pathways; regulated necrosis and inflammation induced by haemoglobinuria, secondary to intravascular haemolysis. This might require combination treatment, the subject of ongoing investigation.

Toxins and Drug Dosing

Gomesin inhibits melanoma growth by manipulating key signalling cascades that control cell death and proliferation

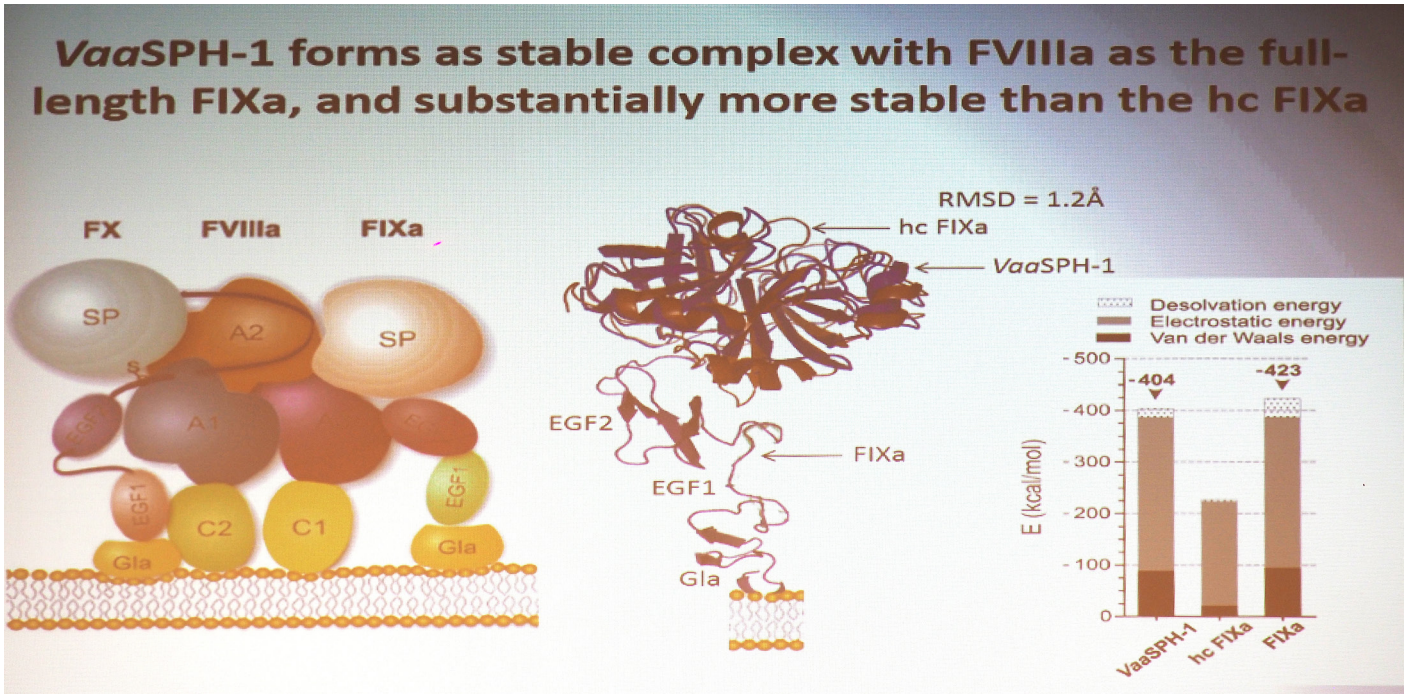
Maria P. Ikonomopoulou. Berghofer Medical Research Institute, Herston, Australia.

Dr. Ikonomopoulou discussed her work studying the effects of anemone toxins from *H. infensa* and *Acanthoscuria gomesiana*, specifically an 18AA peptide, Gomesin, which her group have shown to abolish melanoma cell viability, in a BRAF-mutated cell culture. The Gomesin peptides modulate the Hippo signalling cascade, thereby affecting the G0/G1 phase of cell growth and causing cell cycle arrest. They also activateAKT/mTOR pathways, which activate cell growth. Moving the model from cell culture to mice with induced melanoma, Gomesin decreased tumour growth, but did not kill the melanoma. Next they tried an Avatar zebra fish model with 70% homology to the human genome, testing multiple variants of Gomesin, which appear to hold promise in treating melanoma.

The first intrinsic tenase complex inhibitor with serine protease structure offers a new perspective in anticoagulant therapy

Igor Križaj. Jožef Stefan Institute, Ljubljana, Slovenia.

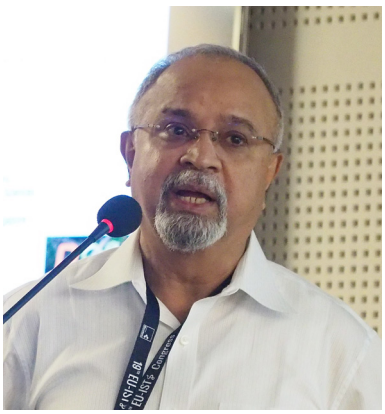
Dr. Krizaj' group investigated intrinsic tenase complex inhibitors as a potential treatment for thrombotic diseases including DVT and PE (pulmonary embolus). Current therapies are limited by increased bleeding requiring continuous dose monitoring. *Vipera ammodytes* venom was fractionated to isolate inhibitors. A 35KDa fraction was isolated, VaaSPH-1, strongly immunogenic, but not proteolytic (no action on fibrinogen, prothrombin, factors IX, X, protein C). It binds to negatively charged phospholipids and almost completely abolishes thrombin formation, with aPTT increase of 142%. It doesn't affect platelets



and is not lipid directed. It binds to Factor Va and Factor XIIIa, but not to Factors XIIa and XIa. It does not abolish hydrolysis of chromogen substrates.

Subtle substitutions in toxins: Design of natriuretic peptide analogues for personalized care of heart failure patients

Manjunatha Kini. National University of Singapore, Singapore



Prof. Kini discussed the problems associated with management of cardiac failure and efforts to develop “personalised” care using natriuretic peptides. Using an anaesthetised rat model a variety of candidate peptides were examined. Krait natriuretic peptide (KNP) is a potent vasodilator without diuretic activity. It has a K-ring structure; examination of roles of each AA revealed that Gly3 has potent vascular effects, Gly4 also is involved in vasculature action without diuretic activity, Gly14 maintains BP and heart rate. The NSFRY tail region imparts diuretic activity. It is therefore possible to create specific tailored peptides with either pure vasodilatory or diuretic activity. Experiments then shifted to sheep, demonstrating the highly specific actions of constructed peptides, pointing the way to potential new therapies for heart failure.

Molecular actions underlying the biomedical applications of recombinant variants of botulinum neurotoxins

Oliver Dolly. Dublin City University, Dublin, Ireland.

Prof. Dolly detailed some of his work on botulinum toxins, particularly BoNT/A which affects release of CGRP intracellularly (pain pathways). A receptor/acceptor on the axonal cell membrane allows exocytosis, affecting SNARE proteins and thereby stopping synaptic vesicle release. Recombinant toxins were developed using *E. coli* cultures, designed as single chain toxins (easier to express and fold). % serotypes showed good potency compared to native toxin and cheaper to make. He the considered why botulinum toxin has such a long therapeutic period (months). Again using expression of chimeras, AA changes on activity could be studied.

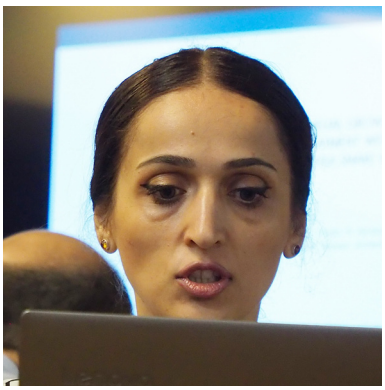
Purification and Partial Characterization of AIP1: a novel protein from Sea-Star (Astropecten indicus) Coelomic Fluid

Dibakar Chakrabarty. BITS Pilani, Goa, India.

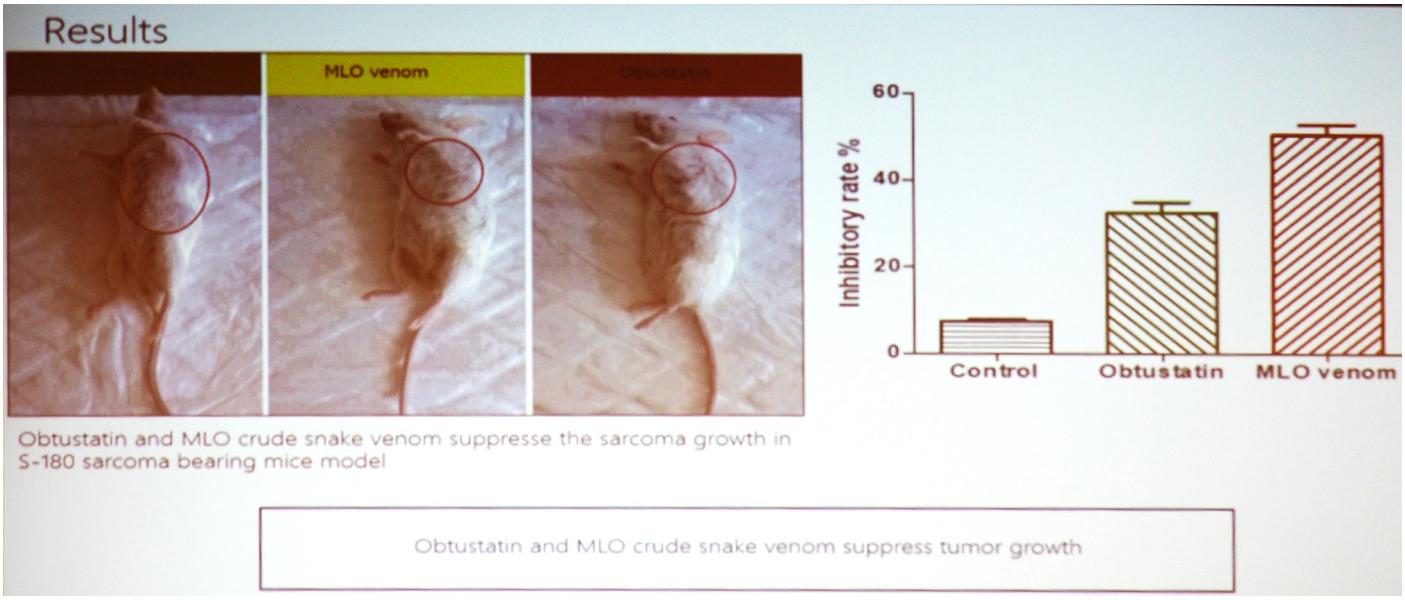
Prof. Chakrabarty detailed his work on toxins from a starfish, common in Goan waters, *Astropecten indicus*. Coelemic fluid was used, difficult to collect and requiring many starfish, which are then released. The toxins include fibrinogenolytic activity, platelet aggregation and wound healing actions. Activity was dependent on toxin concentration. Toxins were not cytotoxic at low concentration and stimulated cell proliferation, perhaps explaining wound healing properties. Toxins were isolated.

Expression of vascular endothelial growth factor in S-180 sarcoma-bearing mice after treatment with obtustatin and Macrovipera lebetina obtusa snake venom

Narine Ghazaryan. Orbeli Institute of Physiology of NAS, Yerevan, Armenia.



Dr. Ghazaryan first detailed the impact of sarcomas, which carry a 50% fatality rate due to a poor response to chemotherapy, though fortunately they represent <1% of all cancers. Tumour growth requires angiogenesis, reliant on VEGF production. The objective of this study was to examine the effect of obtustatin from *Vipera lebatina obtusa* venom on VEGF, using a mouse model. Obtustatin inhibits sarcoma cells in vivo and without evidence of toxicity for normal cells, resulting in focal necrosis in the tumour. Obtustatin does not appear to cause apoptosis in the tumour and in the chick embryo, while it causes increased vascularity, whole venom is more potent, so there may be other venom components involved in angiogenesis.



Antivenom; Innovations and Market

Cocktails of human monoclonal IgG antibodies capable of neutralizing dendrotoxin-mediated neurotoxicity of black mamba venom in vivo

Andreas H. Laustsen. Technical University of Denmark, Kongens Lyngby, Denmark

Dr. Laustsen provided an overview of the potential of recombinant multi-monoclonal Ab-based antivenom as a new alternative method of antivenom production, avoiding the need to either collect venom

(apart from initial venom), or use animals for polyclonal antibody production. He claims this methodology can deliver antivenom at a comparable cost to conventional methodologies. However, it has not yet been produced or subjected to clinical trial.

Challenges in antivenom downstream processing efficiency estimation

Beata Halassy. University of Zagreb, Zagreb, Croatia.

Dr. Halassy discussed her work trying to determine why there is loss of activity in downstream processing, during antivenom refinement. She highlighted problems with current in vivo AV neutralisation assays that require significant numbers of animals, subjected ton distressing effects, often with imprecise results which leads to imprecise yield quantification. For precise downstream AV processing it is necessary to precisely quantify the whole IgG content of the hyperimmune plasma. Neither FPLC, nor SDS-PAGE have been shown to be ideal in detecting pure IgG because of overlap with other plasma proteins. Different methodologies can give varying responses, possibly due to their effects on equine IgG subclass distribution. Protein-A affinity purification causes enrichment of IgGa and loss of IgG(T). If sample-specific standards are used, then the previously inaccurate ELISA IgG quantification methodology can deliver acuurate precise results, thereby enabling better plasma recovery estimation. Competitive ELISA may prove a valuable quantification tool, but remains to be validated. It is important to monitor IgG subclasses and changes in their distribution during processing of hyperimmune plasma.

Development of an Antivenom for Vipera and Macrovipera Bites of Western and Eastern Europe

Alejandro Alagon. Universidad Nacional Autónoma de México, Cuernavaca, México

Dr. Alagon detailed his efforts to produce a new snake antivenom for European viper envenoming (Inoserp Eurasia), using horses. He noted that horses must be “happy and healthy” for good output and that at least 6 months should elapse between starting immunisation and first bleeding. He predicts the new antivenom may be available in late 2019.

Equine F(ab’)2 based antivenom preparation by simultaneous caprylic acid fractionation and pepsin digestion

Tihana Kurtović

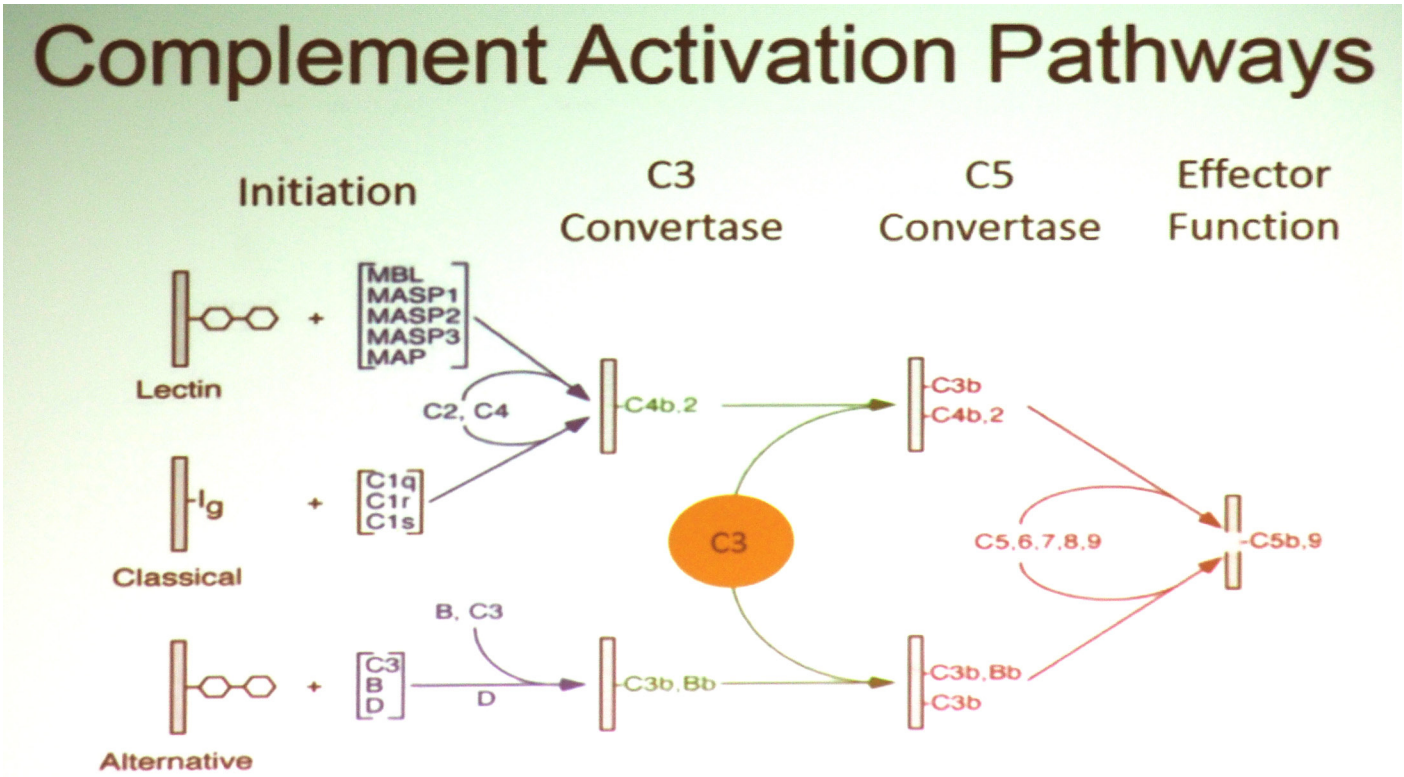
Discussed methodology for improving processing of antivenom for European viper bites, based on the Zagreb equine F(ab)2 product. Previously this was a 2 step process, but a new simultaneous purification process has been developed, with use of reduced temperatures yielding increased yields. The new process is faster, though with slightly lower efficacy.

North American Society of Toxinology Symposium

Cobra Venom Factor: A Lead Venom Component for the Development of a Biologic for the Treatment of Complement-mediated Diseases

Carl-Wilhelm Vogel. University of Hawaii at Manoa, Honolulu, Hawaii.

Prof. Vogel discussed his work on cobra venom factor (CVF) as a tool in understanding and managing complement mediated diseases. He detailed the range of such diseases and the complement path-



way. C'3 is central in all pathways. CVF is a complement activator found in cobra venoms (notably *N. naja* & *N. kaouthia*) and is "identical" to C'3 structurally, but has a far longer half life (7hrs versus 1.5 mins). It works in the fluid phase and rapidly depletes circulating C'3, which remains depleted for days until replenished by the liver. His aim is to develop humanised CVF (hCVF) to treat humans diseases by blocking C' activation through C'3 depletion. Preliminary studies in mice looking at myocardial infarction have shown encouraging reductions in infarct size. In myasthenia gravis this therapy protects the NMJ thereby preventing paralysis and it can reduce macular degeneration. So far no toxicity has been observed from hCVF therapy in short term in vivo studies. In mice hCVF has only minor immunogenicity and does not appear to cause problems with normal haemostasis.

Combined animal and human data in support of effectiveness of antivenom against M. fulvius neurotoxicity

Leslie Boyer. University of Arizona, Tucson, Arizona, USA.

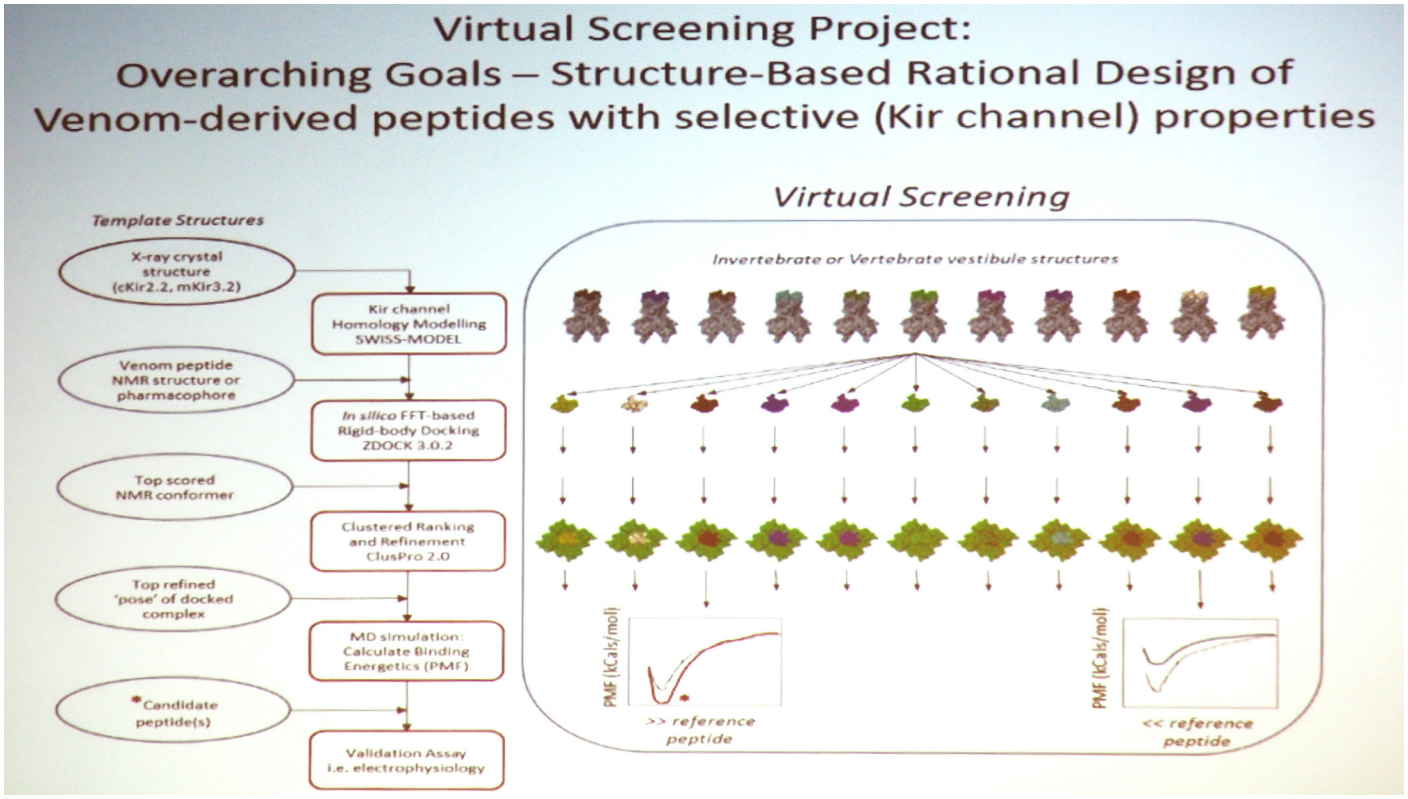
Dr. Boyer detailed the problems with coral snake envenoming in the US, associated with the potent presynaptic neurotoxicity of *Micrurus fulvius* (and *M. tener*) venom, which, untreated can cause death due to respiratory paralysis in 5-60 hrs post-bite. In the pre-AV era mortality was about 15%, but since AV became available in 1967, mortality has dropped dramatically. However, this AV never underwent a clinical trial, but any new AV, to replace the increasingly unavailable current AV, will require full clinical trials. Given there are only about 75 cases/yr it is likely uneconomic to undertake such a process using standard FDA guidelines. Use of an historic control may assist. 2 linked studies have been undertaken using a new Inosan F(ab')2 AV, the first in humans using a 5 vial initial dose with an endpoint of survival/death and a target of 55 cases over 4 years. Problems with accessing cases resulted in the trial only enrolling 26 cases because of competition with remaining stocks of the previous AV product. Measured venom levels did not show a relationship with the clinical level of envenoming. Vomiting was the most common sign of envenoming in the human trial and most patients responded to the initial dose. The conclusion was that the new AV was effective, though there was insufficient data for this to be definitively conclusive. The second trial used a large animal model (sheep), designed to mimic human envenoming, with lymph duct cannulation and collection of lymph prior to it reaching the bloodstream via the thoracic duct. This study showed that most venom travels via the lymphatic system and is only released into the circulation slowly over hours. AV reaches the lymph very rapidly, in about 6 min and binds 72% of venom in the lymph even before venom can reach the circulation.

The Neutralization of Snake Venom Metalloproteases using a novel disintegrin antibody
Elda Sánchez. Texas A&M University-Kingsville, Kingsville, Texas, USA.

Dr. Sanchez provided an introduction to her department and it's activities, including the extensive live snake collection. Thematic areas covered in her dept. are (1) toxins as molecular targets, (2) evolutionary biology of venom & snakes, (3)antivenom therapy, (4)pathophysiology of envenoming. Her dept. is particularly interested in disintegrins and their role in envenoming, with a view to treatment possibilities which may be useful in a pre-hospital setting and also the development of tightly targetted AV based on Ab that target single classes of toxins. Dr. Sanchez discussed the role and activity of disintegrins and the cloning of *Crotalus scutulatus scutulatus* type-B disintegrins, which were used to develop polyclonal rabbit Ab. These Ab recognised disintegrins and metalloproteinase type P-II & P-III from this venom and can neutralise their activity. It wasn't clear how this might progress into a clinical application at this time.

Validation of computational models for tertiapin-blocked neuronal Kir3.2 channels
Craig A. Doupnik. University of South Florida College of Medicine, Tampa, Florida, USA

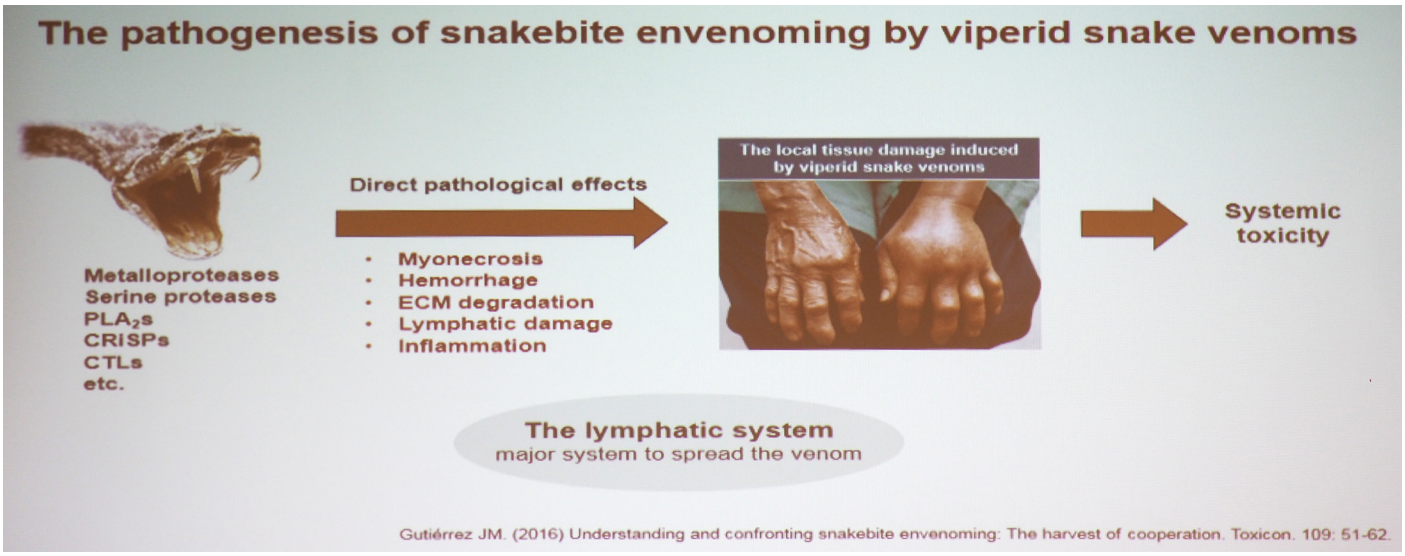
Dr. Doupnik presented a rather complex paper on virtual screening with an overarching goal of structure based rational design of venom derived peptides with selective (Kir channel; inward-rectifying K channels) properties. These Kir channels are expressed in the nervous system and regulate activity. A 21AA peptide toxin, Tertiapin, from honey bee, *Apis mellifera* venom, appears to be one of the few specific blockers for Kir channels, with nanomolar affinity. By developing models of Tertiapin docking to Kir channels to examine pore interactions greater understanding of pore function is possible. This may allow development of novel Tertiapin variant peptides with highly selective Kir channel blocking activity.



The acute effects of snake venom CRiSP toxins on blood and lymphatic endothelial cell permeability: new insights into the pathophysiology of snakebite

Montamas Suntravat. Texas A&M University-Kingsville, Kingsville, Texas, USA.

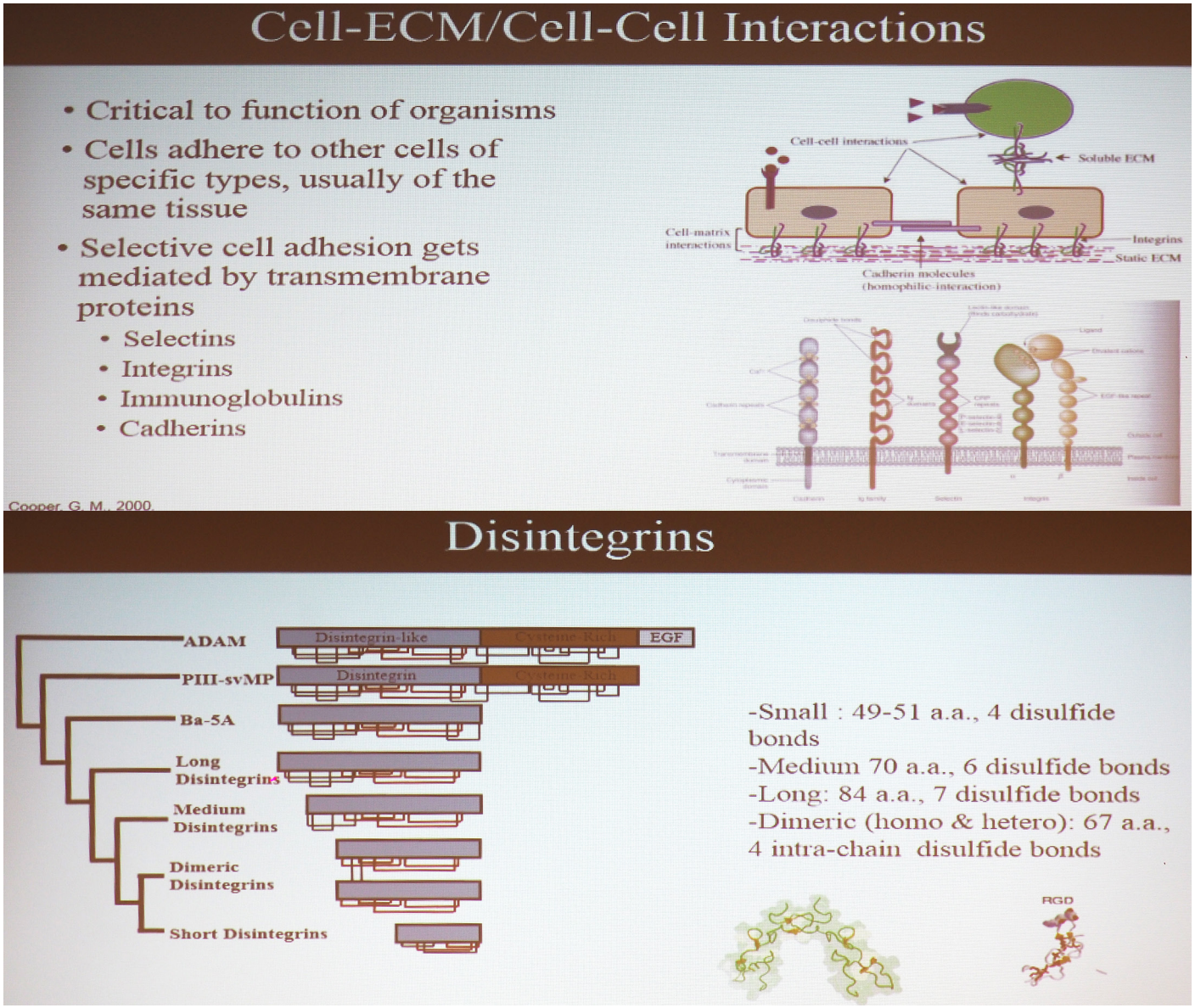
Dr. Suntravat discussed the effects of viperid venoms in envenoming and the key role of lymphatic transport in moving venom to the systemic circulation. She then focussed on CRiSPs (Cysteine Rich Secretory Proteins) which are part of the CAP superfamily, listing examples from a wide range of venomous sources. She hypothesised that CRiSPs may flush larger toxins into the lymphatic system and promote their rapid transport to the circulation, affecting endothelial cell function and promoting vascular permeability. Her research concentrated on the effect of CRiSPs on vascular and lymphatic endothelial cells. Sh purified CRiSPs from *Crotalus adamanteus*, *C. horridus*, *C. atrox*, *C. scultulatus* & *Agkistrodon piscivorus* venom. Css CRiSP induced IL-6 production by endothelial cells, leading to increased vascular permeability. Thus the role of CRiSP in increased vascular permeability in envenoming may be an indirect effect.



Novel Applications for Snake Venom Disintegrins

Jacob Galan. Texas A&M University-Kingsville, Kingsville, Texas, USA.

Dr Galan detailed the role of disintegrins in cell-cell interactions, covering ground discussed by previous speakers, before presenting his own research looking at antidotes to disintegrin-type venom actions and understanding structure-function relationships, plus designing molecular probes for cell imaging and studies on signalling protein pathways disturbed by disintegrins. A central aim is to develop a low-cost universal therapy against envenoming by snakes, focussing on inhibition/neutralisation of metalloproteinases. He also discussed use of nanoparticles. It wasn't clear if this work had progressed to a conclusion.



The genome and transcriptome of the Indian cobra.
Sekar Seshagiri. Genentech USA.

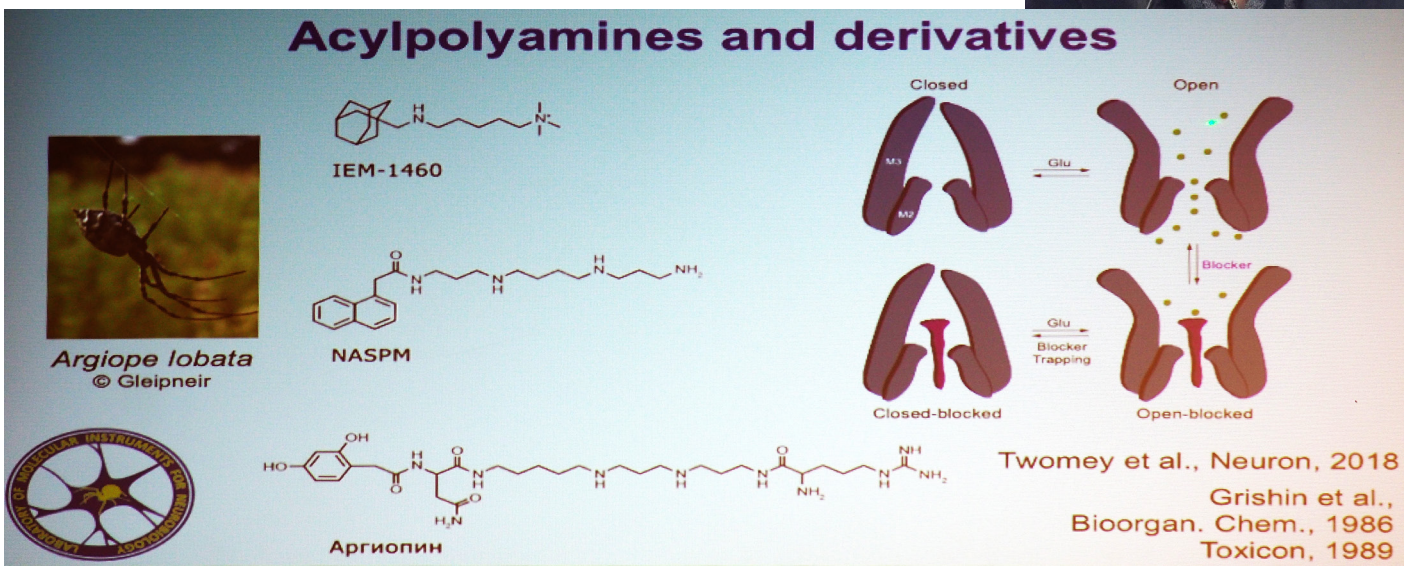
This was an extra presentation. Dr. Seshagri first discussed the history of Genentech, founded in 1976 by Herbert Boyer & Bob Swanson. He then moved to the Indian cobra, *Naja naja* and compared it to previous snake genome efforts. *N naja* genome was measured at 1.48 to 1.78 Gpb genome length. He discussed different methodologies (short read vs long read) and the new Bionano technology, followed by great detail on the read results. He argued that hybrid de novo genome assembly can produce super scaffolds with high contiguity, approaching chromosome-arm length contiguity, claiming that their N. naja genome assembly is about 100x more contiguous than the next best assembled snake genome. A high degree of genome annotation is possible. This high quality assembly reveals clustering of venom gene families on single scaffolds. By providing a catalogue of full-length expressed venom gland genes in combination with short-read data, it may be possible to support antivenom generation/characterisation.

Toxins as Biochemical Tools

Mechanism of Glutamate Receptor Block by Acylpolyamines

Alexander Vassilevski. Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Moscow, Russian Federation.

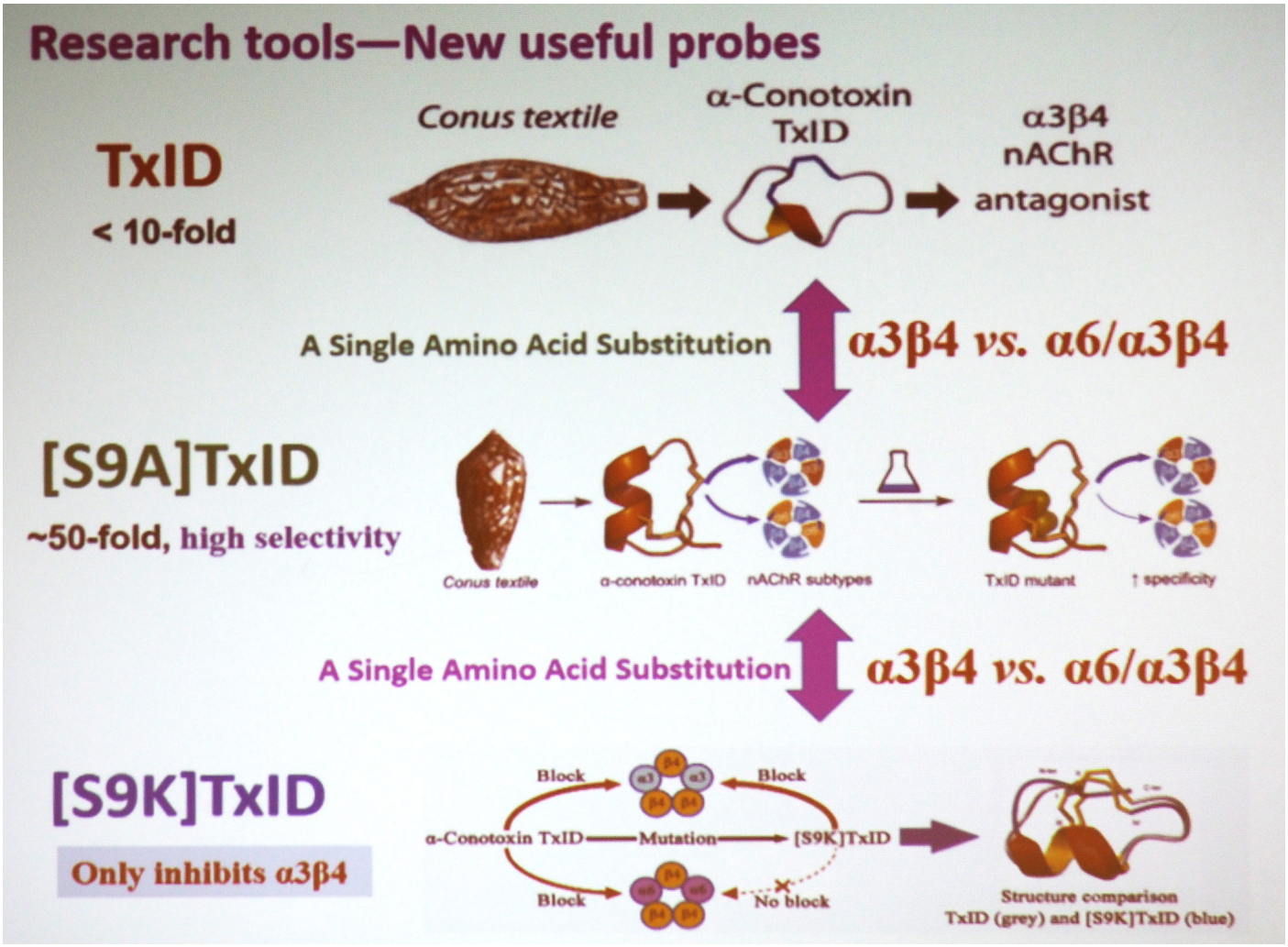
Dr. Vasilevski's presentation was rescheduled to an earlier slot in the congress. Glutamate is a CNS synapse neurotransmitter, with specific receptors in several subtypes. A number of compounds, including toxins (e.g. kainic acid, domaic acid) and acylpolyamines can block glutamate activity. The channel is opened, the blocker enters, then it closes the channel with the blocker inside. There are similarities with K+ channels. Acylpolyamine hydrophobic heads and tails uniquely match pore architecture and electrostatics with the tails resembling permeant cations. There are potential drug leads within this toxin group.



α-Conotoxin TxID and its Mutants Targeting α3β4 nAChR Subtype

Sulan Luo. Hainan University, Haikou Hainan, China.

Prof. Luo Discussed her work on alpha conotoxins and their interaction with nicotinic acetylcholine receptors (nAChRs). These receptors are pentameric and membrane bound with many subtypes based on differing pentameric composition. The α3ß4 receptors are of particular interest because of their role in pain, addiction, cancer and obesity. The α-conotoxin TxID blocks the α3ß4 receptors. It is a 15AA peptide with 2 DS bonds. By further modification of this toxin it has been possible to increase selectivity for α3ß4 subtypes with the S9K variant being absolutely selective, so the best tool for discriminating from other nAChRs. Prof. Luo noted that smoking is now a major problem in China with around 2,000 deaths/day from smoking-related diseases, a figure which is predicted to rise to 8,000/day by 2050 unless interventions are successful. She speculated that these highly specific contotoxins may have a role in treating smoking addiction.



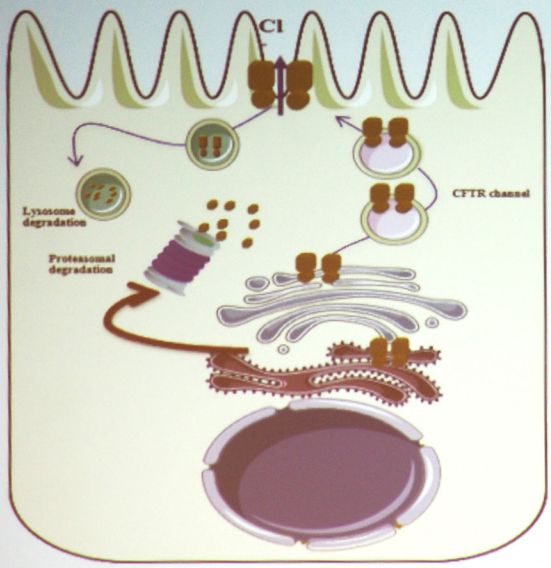
Toxins as Pharmacological Tools

Snake venom PLA2 as a ligand and modulator of various protein targets (hCFTR, hFXa, nAChR): mechanism of action and therapeutic potential

Grazyna Faure. Institut Pasteur, Paris , France.

Dr. Faure detailed her work with Crotoxin sourced from *Crotalus durissus terrificus* venom, a toxin with 2 subunits (CA & CB). The CB subunit is PLA2-based. The cystic fibrosis transmembrane conductance regulator (CFTR) hydrates and purges lung mucus; the dysfunction of this mechanism is involved in Cystic Fibrosis, accounting for the severe and potentially fatal respiratory complications of this disease. The CB subunit of Crotoxin forms a specific complex with CFTR, increasing Cl- channel current and acts as a corrector of the ΔF508 abnormality in cystic fibrosis CFTR. The binding interface has been identified by molecular docking. CB prevents formation of the complex between keratin 8 and ΔF508-CFTR, thereby acting as a corrector and a potentiator. This may provide new drug leads in treatment of cystic fibrosis. Dr. Faure then discussed pentameric ligand-gated ion channels (pLGIC). These are allosteric membrane proteins. GLIC/AChBP are protein targets of CB and CB is a ligand for some pLGIC. Studies of these interactions indicates PLA2 is a new regulator for GLIC proton-gated channels and CB is a powerful tool capable of arresting GLIC in specific conformational states, allowing study of PLA2-receptor interactions at a molecular level. Lastly, Dr. Faure discussed the anticoagulant effect of CB, which interacts with human Factor Xa which inhibits the formation of the prothrombinase complex, thereby inhibiting thrombin formation. Her studies on the interaction between CB and FXa may lead to novel non-competitive FXa inhibitors.

CFTR trafficking in epithelial cells

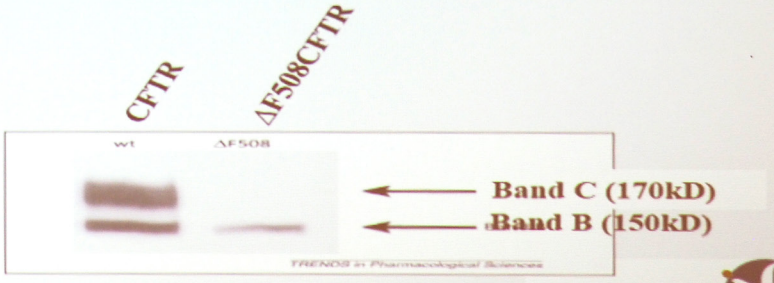


In WT-CFTR cells :

25% reaches plasma membrane

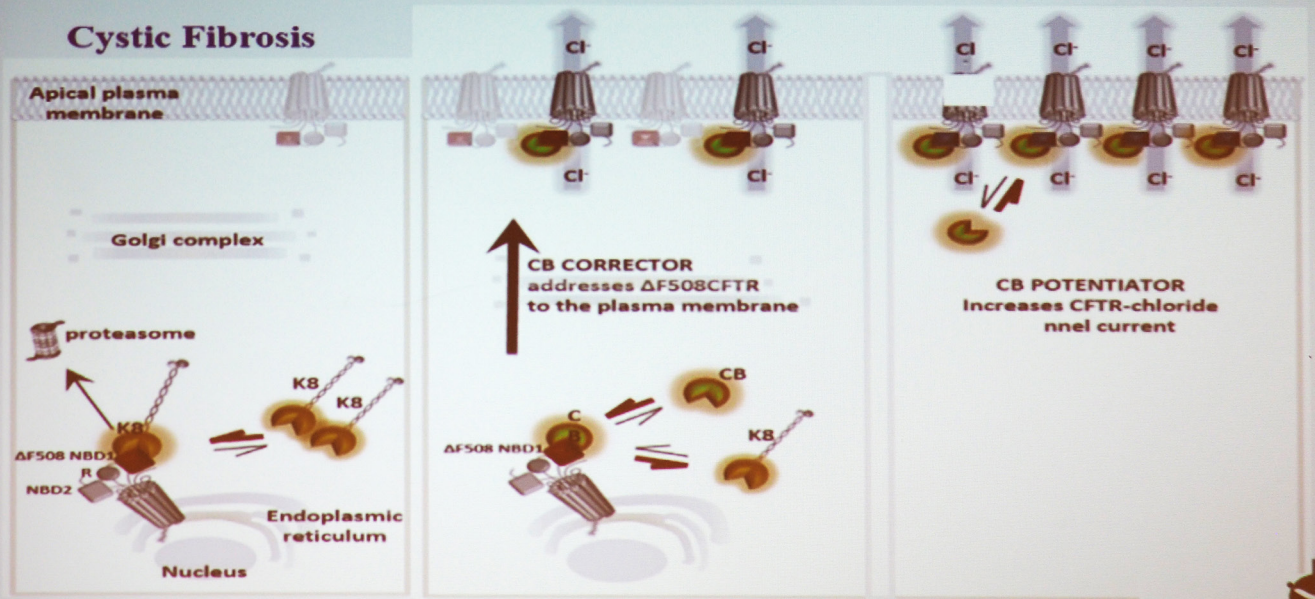
In ΔF508-CFTR cells :

only 1% reaches plasma membrane



Institut Pasteur

CB prevents formation of the complex keratin 8 /ΔF508CFTR allowing escape of mutated CFTR from degradation



Faure et al., Edelman (2016) J Mol Biol 428, 2898-2915

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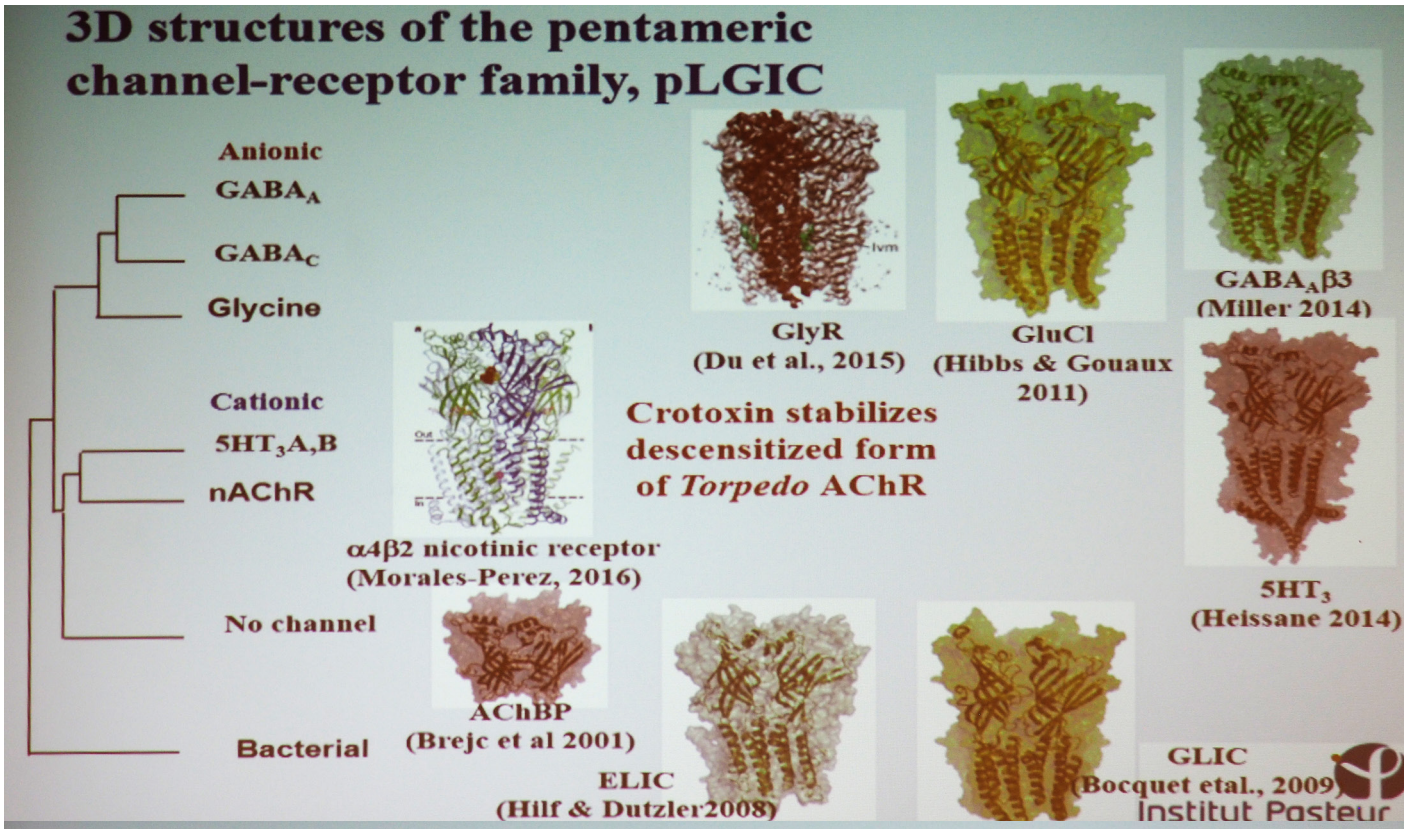
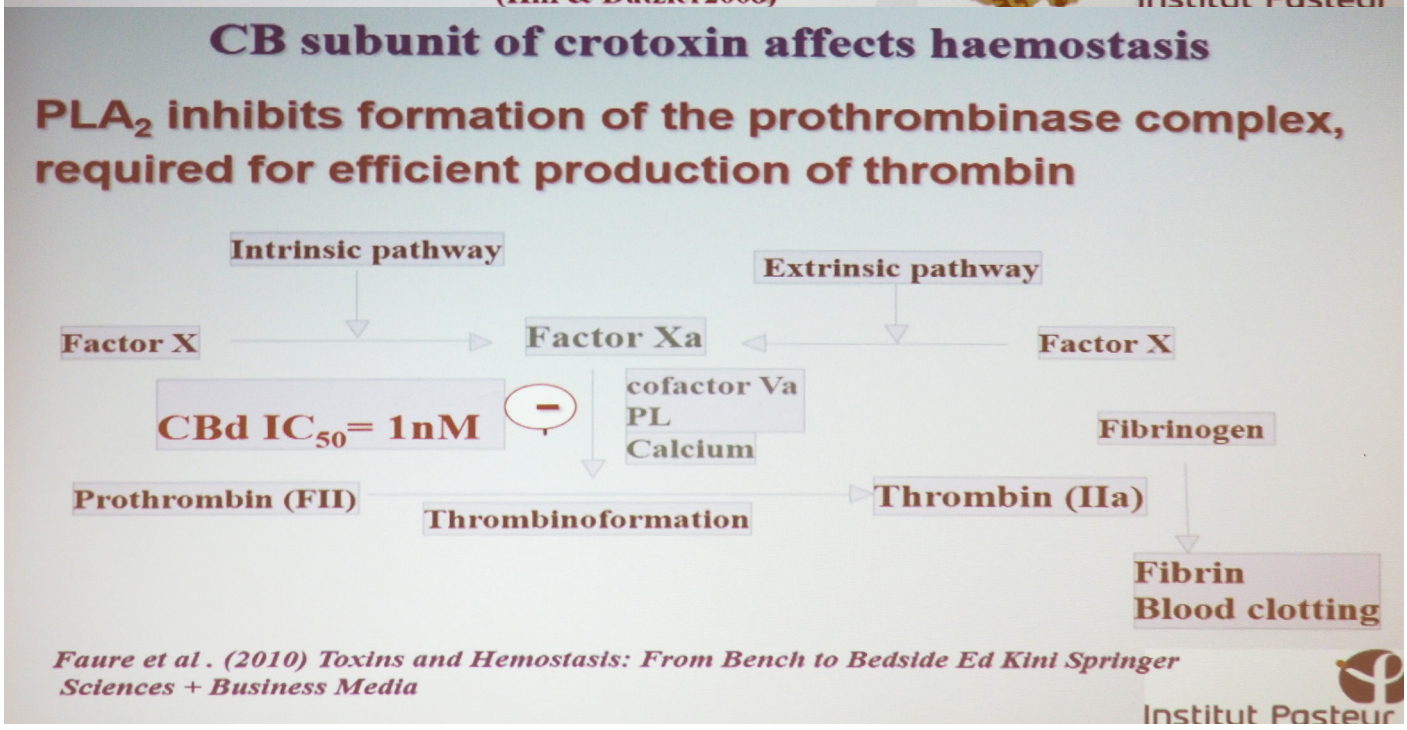
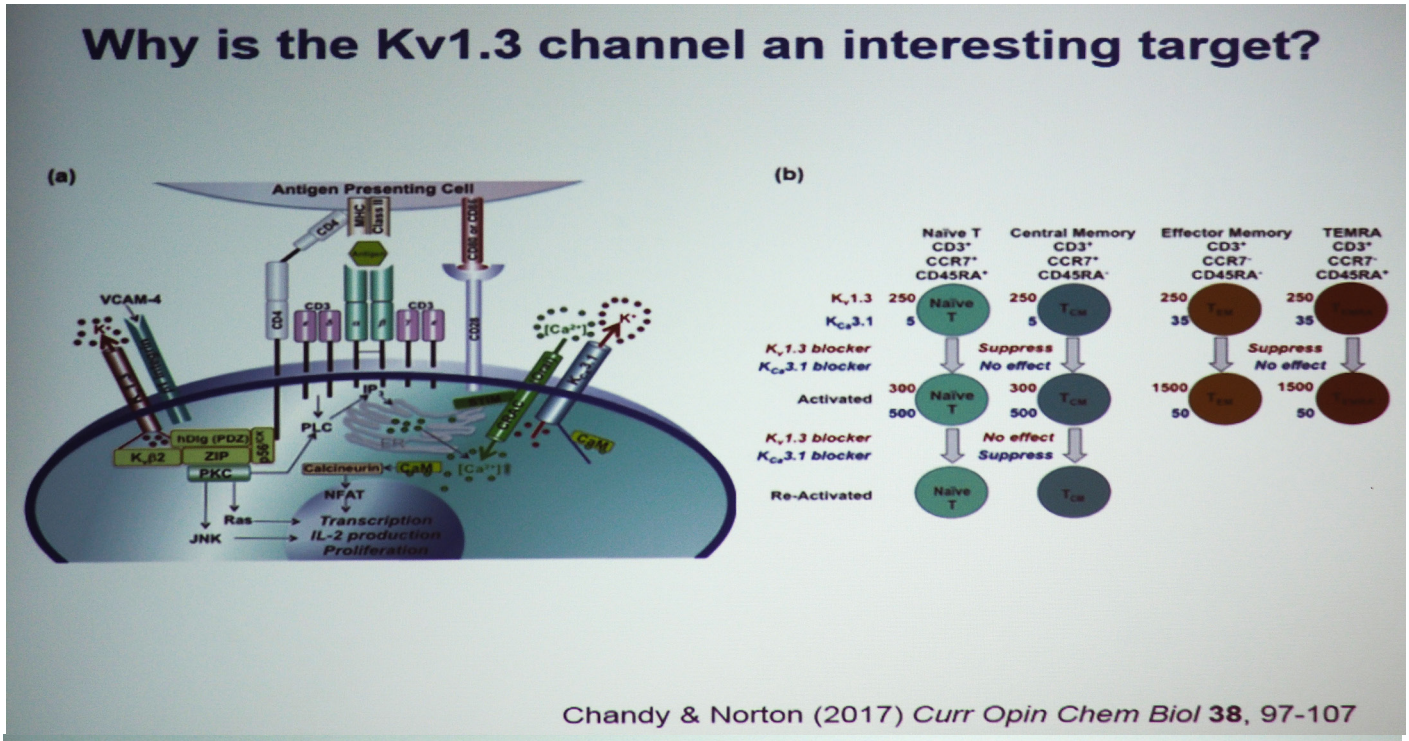




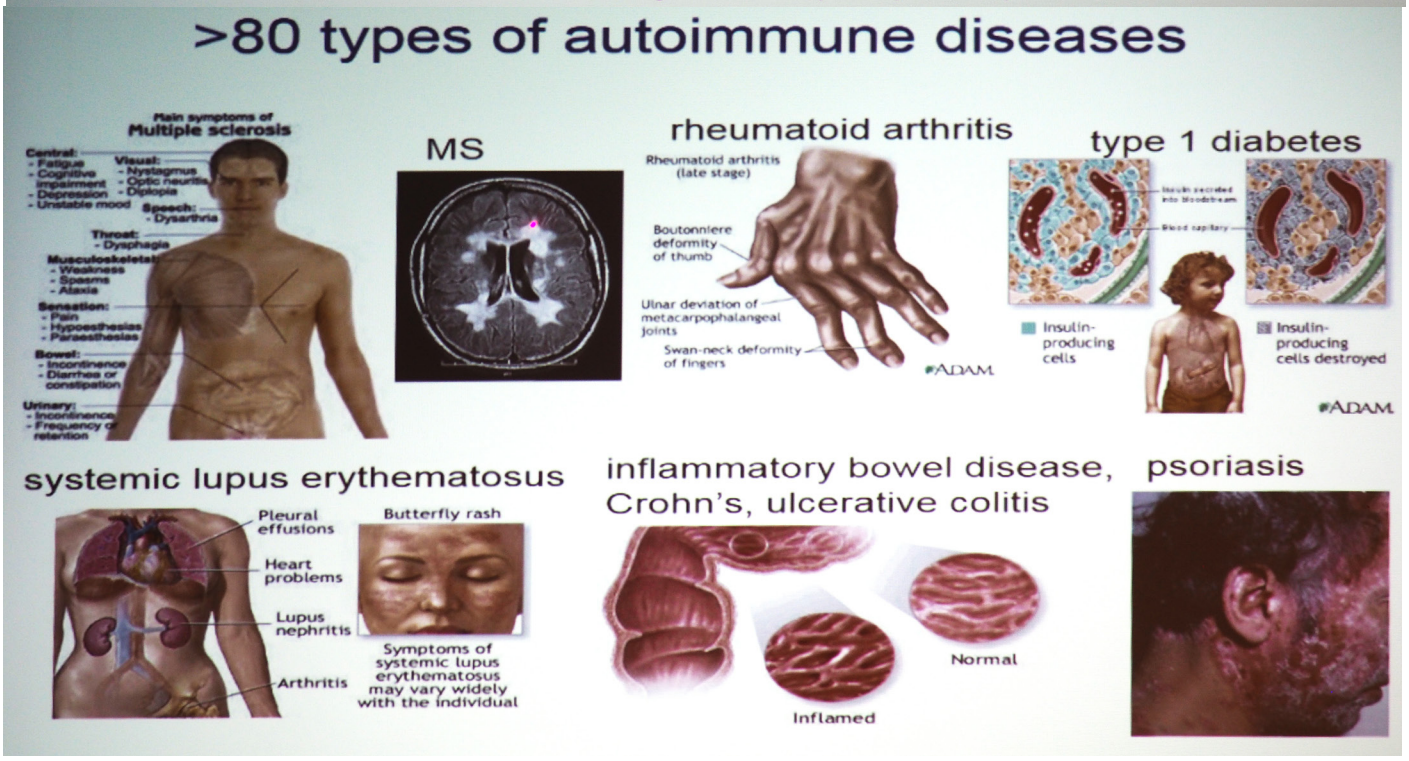
Sea anemone peptides: therapeutic leads, pharmacological tools and new folds

Raymond S. Norton. Monash University, Parkville, Australia.

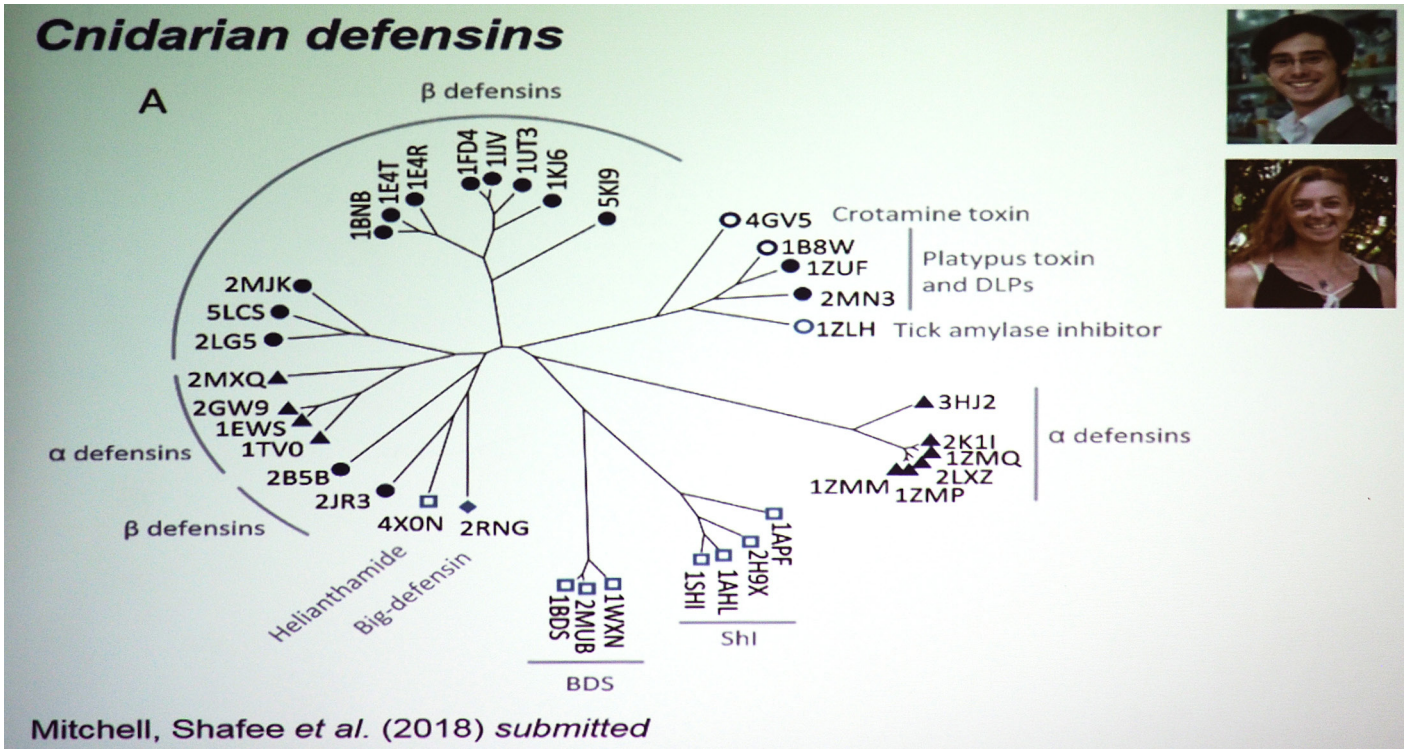
Prof. Norton discussed sea anemone toxins, specifically the ShK toxins (from *Stichodactyla helianthus*, found in the Caribbean) as Kv1.3 blockers. Kv1.3 is involved in TEM lymphocyte activation and these cells cause tissue injury in autoimmune diseases, therefore Kv1.3 blockers are potential therapeutic agents for this large group of diseases, including multiple sclerosis, psoriasis, rheumatoid arthritis, glomerulonephritis, atopic dermatitis, inflammatory bowel disease etc. A number of these ShK Kv1.3 toxins and their analogues have been examined as potential drug leads. ShK-170 is highly selective for Kv1.3 and ShK 192 (186) has entered preclinical trials. The immunomodulation is selective and does not affect the normal immune response to



Chandy & Norton (2017) *Curr Opin Chem Biol* **38**, 97-107



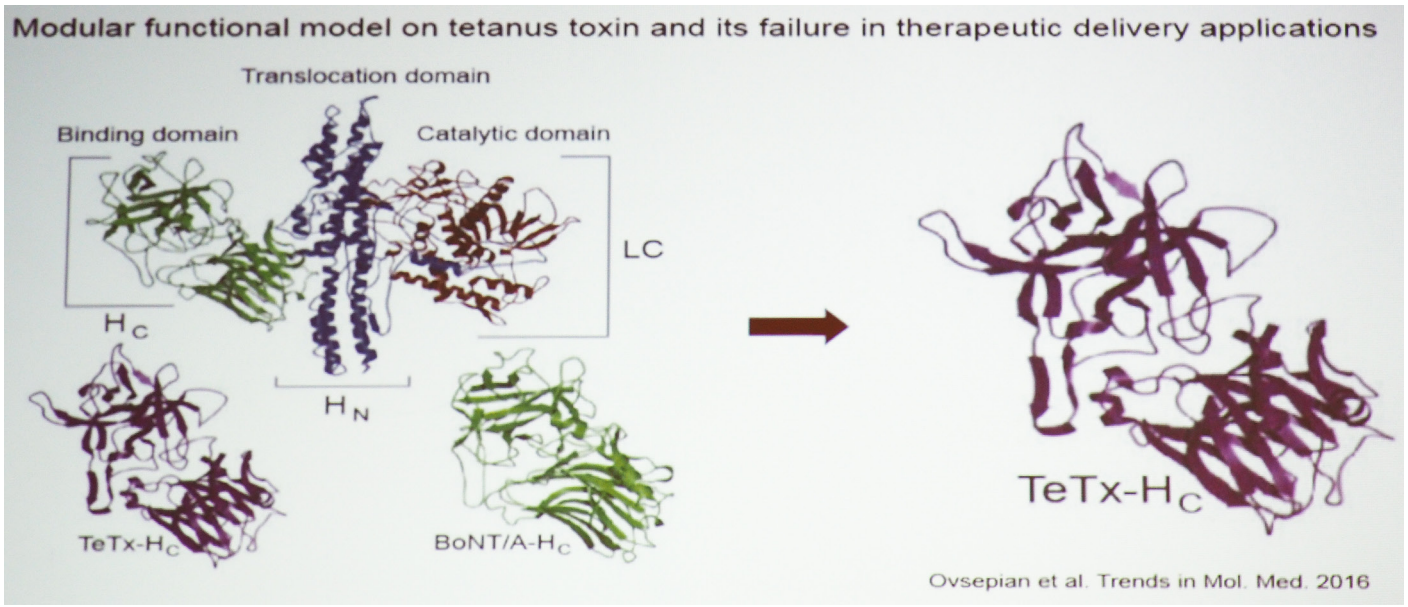
infection plus has a long half life (1 week). The clinical trial of Dalazatide (ShK 186) has been successful in treating psoriasis and is awaiting phase 2 trials. New ShK analogues are being sought, including from other sources such as scorpion venom. Over 3,300 ShK domains are known. New indications for treatment may provide new fields for drug lead searches. An interesting new area is ShK type toxins found in parasitic worms and the possibility that these may have therapeutic uses because some worm infestations are associated with reduced symptoms in autoimmune disease. So far work K channel blockers appear to be less potent than anemone ShK toxins. Another area of new interest are cnidarian defensins.



Detoxified Tetanus Toxin (TETIM) – A Superb Nano-Carrier for Retro-axonal Gene Delivery to Motor Neurons in Bypass of Blood Brain Barriers

Saak Ovsepian. Technical University Munich, Munich, Germany.

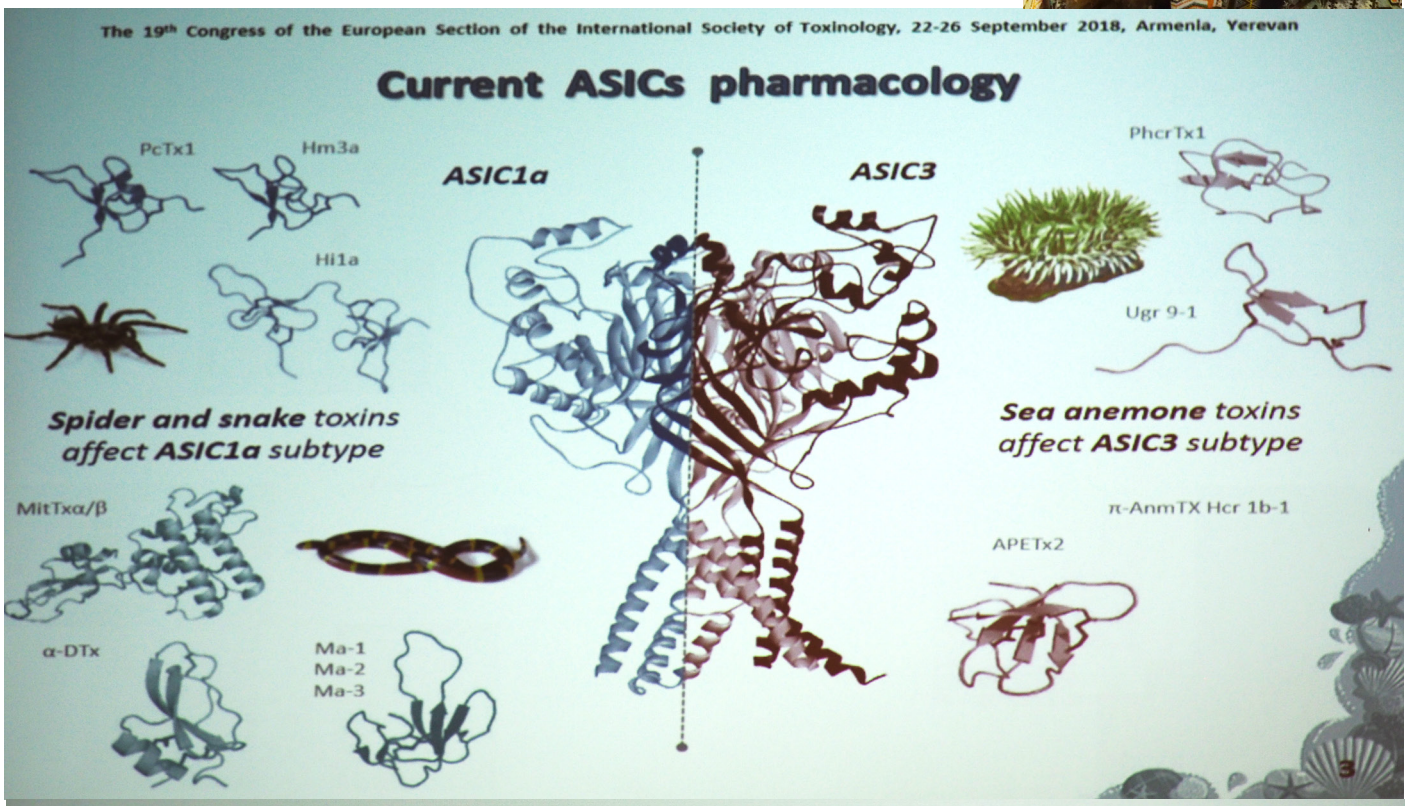
Dr. Ovsepian first noted the global impact of tetanus (toxin), with 182 deaths per day (7.5 deaths/hr), with highest rates in Africa, South Asia and in parts of South America. Like botulinum, toxin tetanus toxin targets the snare complex of axons (specifically VAMP I/II for TeTx). However, like BoTx, TeTx may have therapeutic uses in controlled settings, such as management of muscle spasms. Research has centered on ways of delivering a modified TeTx across the blood brain barrier to the CNS which has proved difficult to achieve. By combining with a core streptavidin gene, a new peptide has been created which appears to be a powerful new delivery tool for other pharmaceuticals to reach the CNS by crossing the BBB.

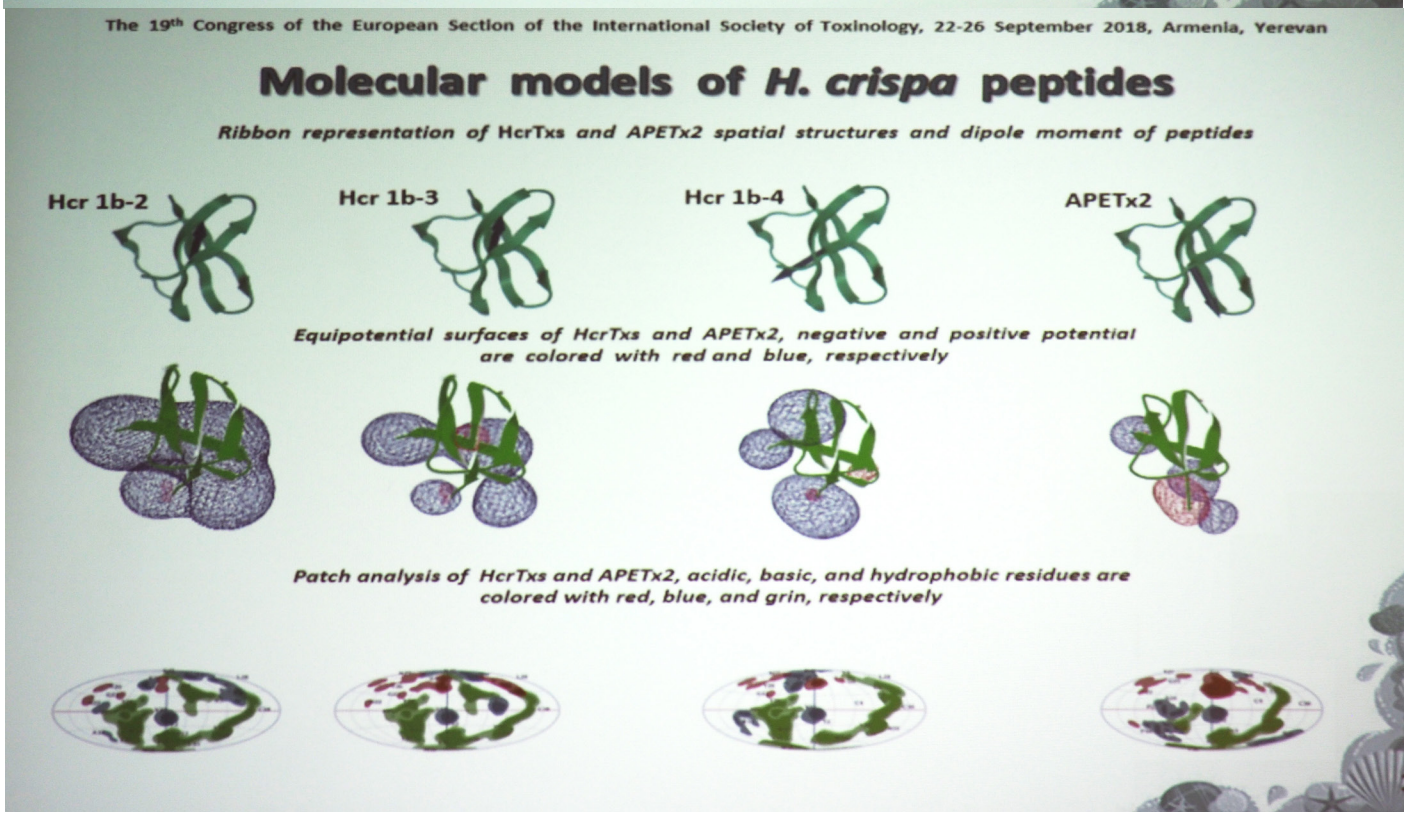


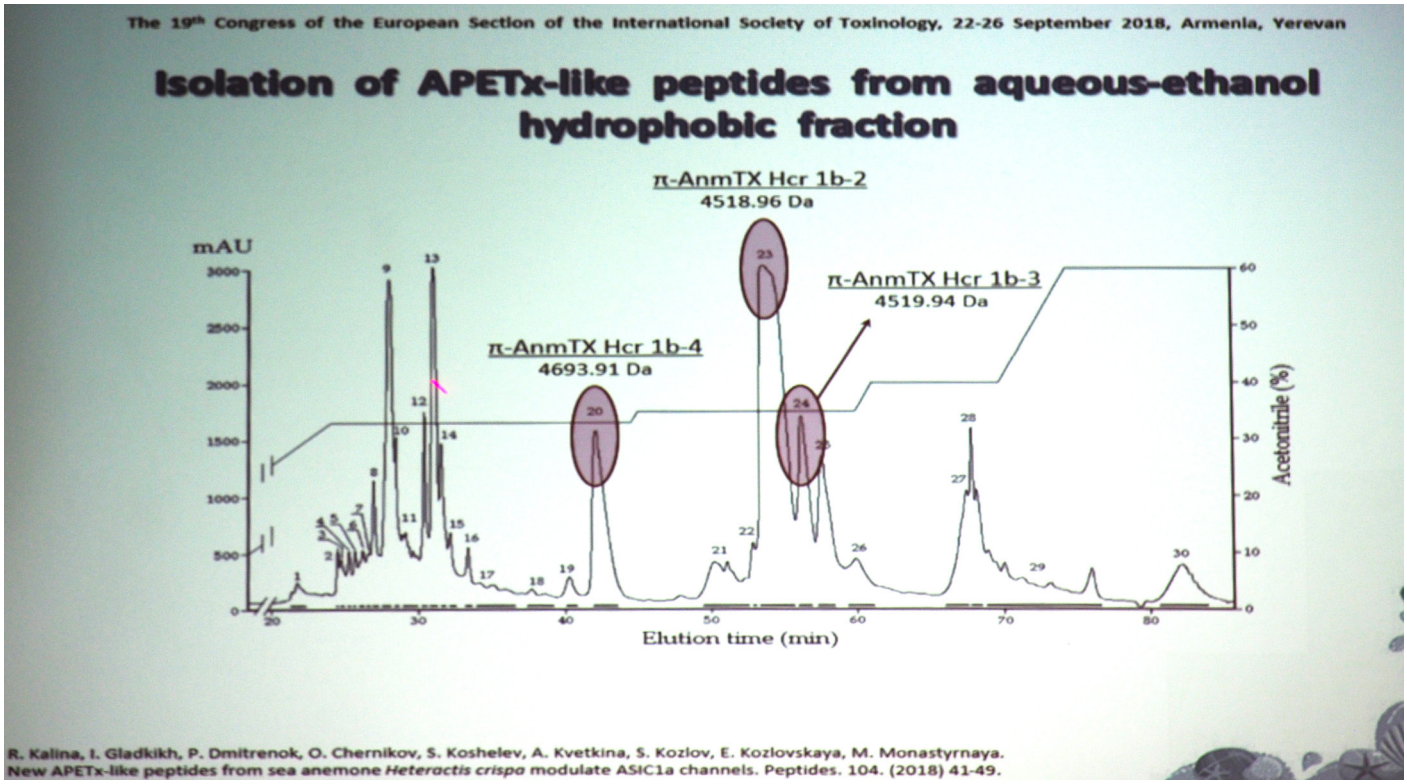
Sea anemone Heteractis crispa produces a pool of peptides active on ASIC channels

Irina Gladkikh. Elyakov Pacific Institute of Bioorganic Chemistry, Vladivostok, Russian Federation.

Dr. Gladkikh presented work on Acid Sensing Ion (ASIC) channel toxins isolated from the anemone *Heteractis crispa*. Anemone toxins target ASIC3 subtype, unlike spider and snake toxins that target ASIC1a subtype. Toxins were isolated using polychrome-C and RP-HPLC and subsequently sequenced. Key AA residues involved with ASIC3 were determined. Hcr 1b-2 and Hcr 1b-3 are the first peptides able to inhibit both ASIC1a and ASIC3 and Hcr 1b-4 is the first potentiator of homomeric ASIC3 channels. She hypothesised that the interaction surface of Hcr 1b-4 is distinct from Hcr 1b-2 and Hcr 1b-3.







Toxicity and microglia activity in murine induced by Macrovipera lebetina obtusa venom with inhibited enzymatic activity

Armen Voskanyan, Orbeli Institute of Physiology of NAS, Yerevan, Armenia.

Dr. Voskanyon detailed a study of *Macrovipera lebetina obtusa* venom, in particular focussing on toxicity and effects in the CNS, using a mouse model to examine microglial cell effects. When PLA2 and metalloproteinase activity of the venom was inhibited there was a decreased effect on these cells, suggesting the importance of toxin enzymatic actions in toxicity. However, inhibiting PLA2 activity had less effect on haemorrhagic activity of the venom. He concluded that both PLA2 and SVMP toxins, respectively 15% & 30% of the venom, are important in overall toxicity (LD50), with decreased toxicity evident when either or both classes of toxins are inhibited.

Student Short Presentations (a number of these were also represented as posters)

Mechanisms underpinning the permanent muscle damage induced by snake venom metalloprotease.

Harry F. Williams. School of Pharmacy, University ofReading, Reading, UK.

Harry presented studies on a PIII metalloproteinase from *Crotalus atrox* (CAMP) and a cardiotoxin I from Naja pallida (CTX) as causes of muscle damage following snake envenoming. CAMP causes necrosis, reduces blood supply, prolongs macrophage infiltration, destroys the basement membrane, reduces satellite cell function and remains in the muscle for >10 days. He suggested that the 2 key actions were basement membrane damage and reduction in blood supply, with other effects being secondary.

New Kunitz-peptide of Heteractis crispa with a propeptide in the precursor structure interacts with serine proteases and exhibit neuroprotective activity

Aleksandra Kvetkina. Elyakov Pacific Institute of Bioorganic Chemistry, Vladivostok, Russian Federation.

Aleksandra presented her work on anemone toxins, with discovery and purification of a new Kunitz-type peptide, HCIQ2c1. She detailed the purification process and molecular cloning of the toxin and its interactions with/inhibition of serine proteases (trypsin & α-chymotrypsin), comparing this new toxin with previously known similar toxins. The toxin does not affect K+ channels of type 1.

Harnessing human monoclonal antibodies for neutralisation of dendrotoxins in a murine model

Cecilie Knudsen. Technical University of Denmark, Lyngby, Denmark.

Cecilie discussed her work developing new methodologies for antivenom production using molecular biology techniques to produce multiple monoclonal Ab, rather than the traditional polyclonal Ab AV raised in large animals. This method first isolates targets for venom, then identifies and purifies specific toxins which are then used for specific Ab production leading to Ab expression using bacteria. She worked on black mamba venom, specifically 3-finger toxins and dendrotoxins. Studies with mice showed good survival with venom-Ab premix testing.

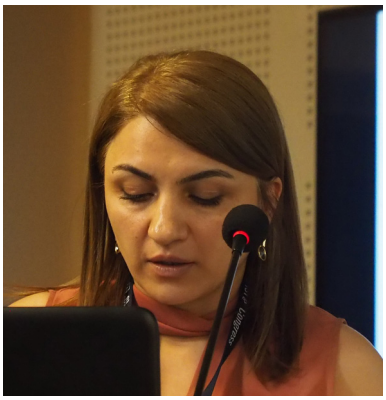
Cardiovascular collapse induced by Echis ocellatus venom: an in vivo and in vitro examination

Rahini Ragavan. Faculty of Medicine, Nursing and Health Sciences, Monash University, Australia.

Rahini hypothesised that carpet viper (*Echis ocellatus*) venom causes cardiovascular collapse in a similar mechanism to Australian brown snakes, testing this in an animal model looking at hypotension. Administering Eo venom caused complete collapse which was not modified by providing respiratory support (unlike Russell's viper venom), but on mixing Eo and brown snake venom, the rate of collapse was markedly reduced (not seen with Dr + Pt venom). Priming with low dose venom (either Eo or Pt) also showed marked reduction in collapse. Her conclusion was that release of depletable endogenous mediators (histamine, bradykinin etc) may be involved in the collapse. The situation is clearly different for Russell's viper, where provision of respiratory support can mitigate collapse.

Assessment of toxicity of hydroponics Stevia rebaudiana Bertoni: Biochemical approaches

Armine Isoyan. Neuroendocrine Relationships Lab, Orbeli Institute of Physiology,Yerevan, Armenia



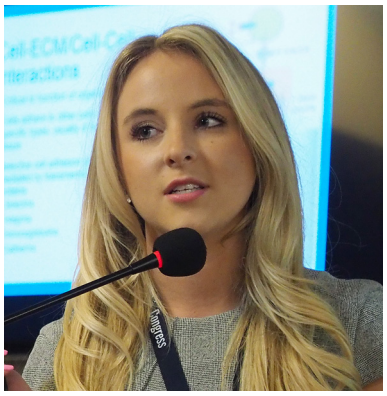
Armine presented work on toxins in the plant Stevia, looking at the composition of leaves varying by plant substrate (eg soil versus hydroponics). This then morphed into a discussion on aflatoxins.

Brazilian Bothrops diporus, in fact a lineage of Bothrops pubescens: Mitogenomic, Venomic and
Ontogenetic studies

Jessica Matos Kleiz Ferreira. Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Jessica presented a study on 2 closely related species of *Bothrops* (*B. diporus* and *B. pubescens*), part of the *B. neuwiedi* group, using a venomics and ontogenetic approach. *B diporus* undergoes ontogenetic change in venom composition, as does *B. pubescens*. The 2 venoms are so similar that it suggests they may be the same species, supported by examination of their mitogenomes which are more similar than 2 populations of another species, *B. jararaca*, the conclusion being that *B. diporus* is a lineage of *B. pubescens*.

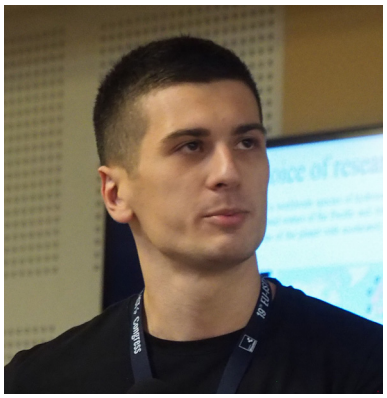
C-type lectin, hellercetin, negatively regulates melanoma cell adhesion and increases permeability



Shelby Szteiter. Texas A&M University-Kingsville, Kingsville, Texas, USA.

Shelby spent most of her presentation on a background to cell-cell interactions and the role of C-type lectins which can inhibit these interactions. She then documented purification of Hellericetin from *Crotalus oreganus helleri* venom using a one-step cation exchange column. This lectin toxin showed strong inhibition of ristocetin action on platelets, but no action against collagen or ADP. The toxin is not cytotoxic, but does affect specific melanoma cell lines.

Venom of Jellyfish Gonionemus Vertens Contains Components against Various Types of Cellular
Receptors



Sergey Kozlovskii. Elyakov Pacific Institute of Bioorganic Chemistry, Vladivostok, Russian Federation.

Sergey studied jellyfish “mucus”, isolating fractions using gel filtration and used a crab neurotoxicity assay, a mouse neuroblastoma cell assay for cytotoxicity a Torpedo assay for nAChR binding, assessing potency of fractions. Fraction I was further separated using RP HPLC and these fractions assessed for nAChR activity. Fraction I also had the highest cytotoxic and lethal potency.

Snake’s and arthropod’s venom-induced pain-like behavior

Lilya Parseghyan. Orbeli Institute of Physiology of NAS RA, Yerevan, Armenia.

Lilya’s study looked at pain effects of snake venom examining the nociceptive behaviour of mice and the anti-nociceptive effects of N-acyl amides and selected analgesics. Mice had venom injected into the hind paw and behaviour including tail withdrawal and “biting/licking” was recorded. *Macrovipera lebetina obtusa* venom was used. PLA2 venom components were considered most important in pain causation, but pain did not cause the mouse to seek escape. Cannabinoids may reduce pain as does cobra venom and standard analgesics. Scorpion venom similarly causes pain and may be of value in scaring off predators.

Antinociceptive effect induced by a PnPP-19 derivative: new insights into venom peptides targeting opioid receptors

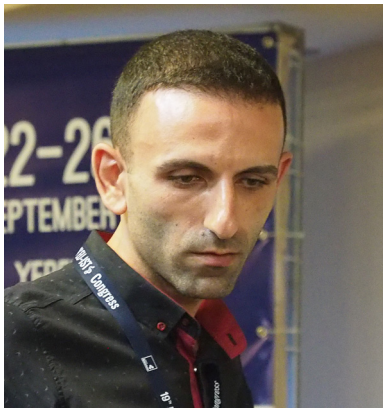
Ana Cristina Nogueira Freitas. Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Ana studied the anti-nociceptive activity of a fraction of *Phoneutria nigriventer* venom, PnPP-19 (19AA) against the pain inducing and erectile activities of another toxin from the same venom, PnTx2-6 (48AA). PnPP-19 induces an anti-nociceptive effect through direct activation of opioid receptors and inhibition of endogenous opioid agonist degradation. It also improves erectile function and can be applied topically. This may lead to a new class of pharmaceuticals.

This paper won the award for best student presentation.

Effect of hydroponic Teucrium polium in ovariectomized rats

Karen Simonyan. Neuroendocrine Relationships Lab, Orbeli Institute of Physiology, Yerevan, Armenia



Karen worked with *Teucrium polium* which is a plant whose extracts can cause excitotoxicity in the CNS. Active compounds include a phenylpropanoid glycosides (verbascoside, poliumosaide, teupolioside) and flavinoids. Excitotoxicity causes brain atrophy with neuronal loss with microglial activation and chronic inflammation.

Phoneutria nigriventer spider toxin PnTx2-1 (δ-Ctenitoxin-Pn1a) is a modulator of sodium channel gating

Steve Peigneur. University of Leuven (KU Leuven), Leuven, Belgium.

Steve studied specific toxins from *Phoneutria nigriventer*, specifically toxin PnTx2-1 activity against Nav channels, which was found to specifically modulate the cardiac Nav channel with reduction of Na conductance and enhanced recovery after activation.

Ana Cristina Nogueira Freitas from the Universidade Federal de Minas Gerais, Belo Horizonte, Brazil receiving her award for the best student oral presentation, from Prof. Naira Ayvazyan, Congress Chairperson.

Prof. Naira Ayvazyan with the student presenters.

Congress Social Program

Congress Cheese and Wine evening, with traditional dancing

Congress Dinner with a live show including a small orchestra, followed by popular singers and dancing, then a live dance/theatre presentation about Armenian history, and then the official Congress celebratory cake.








Report on the 2018 GRC on Venom Evolution, Function & Biomedical Applications

Mandë Holford, Hunter College and CUNY Graduate Center, New York, USA
Ray Norton, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia

The inaugural Gordon Research Conference on Venom Evolution, Function & Biomedical Applications was held August 5-10, 2018, in West Dover, Vermont. One hundred and six attendees from 22 countries participated in the meeting, which encompassed a full week of cutting-edge science discussions. The meeting sessions were focused on how to advance venom research to best incorporate ecological and evolutionary hypotheses about venomous organisms into the efficient identification and characterization of new agents that could be used as tools to enhance fundamental knowledge about ligand-receptor interactions (in particular, for ion channels and transporters), and in some cases developed as therapeutics for treating human disorders. While the number of participants was slightly lower than anticipated, the conference itself was a huge success scientifically, bringing together as it did participants from very diverse backgrounds to discuss recent progress and future prospects.

The evaluations received from attendees were glowing, with several highlighting the diversity of speakers, the high level of scientific content, and the congenial atmosphere. Attendees found both the presentations and the ensuing discussion stimulating and thought provoking. Specifically, attendees enjoyed the following aspects:

- The opportunity for students and early career researchers to interact extensively with leaders in the field, such as David Julius, Baldomero Olivera and the conference chairs and vice chairs.
- The integration of disparate topics to establish common methods and strategies.
- The assemblage of different backgrounds in both chemistry and biology to identify key trends and highlight opportunities for breakthroughs, for example with novel analgesic compounds and molecular targets.

There was a palpable excitement for the next meeting, and, we have received a number of emails from participants expressing their enthusiasm for this GRC and their desire to see it continue in future. Pleasingly, approval has been received recently from the GRC organization for the next meeting to be held in 2020, again in Vermont.

Our GRC received excellent publicity, being featured on the front cover of Science magazine February 2018 Gordon Conference Issue. The chairs and co-chairs of this GRC also co-authored a short perspective, Venoms to the rescue: Insights into the evolutionary biology of venoms are leading to therapeutic advances, which is part of a Science special issue, Technologies Transforming Biology (Holford et. al. Science 361, 842-844). We hope that this will further publicize both the GRC and the rapidly developing venom field, and in turn enhance interest in and participation in future conferences. Additionally, Toxins, a well-regarded journal in the venom field, will publish a special issue of the journal featuring contributions from several investigators who participated at this Venom GRC (in accordance with the GRC no publication policy). This will further promote the venom field and serve to foster interest in the next GRC on this topic. Discussions will be initiated with the venom research community to establish a network to facilitate the sharing of resources among research groups in this field to expedite the identification and characterization of therapeutically interesting venom-derived peptides that can be prime leads for addressing high profile therapeutic issues, such as the discovery and development of non-addictive pain therapies and the treatment of autoimmune diseases.

Relationship to IST

One challenge faced by this inaugural meeting, in our view, was its potential overlap with research covered at annual meetings of the International Society on Toxinology (IST). Prior to the GRC, we believe that it was unclear to many in the broader venoms and toxins community just how our GRC would differ from these IST meetings. Now that the GRC has been held, however, that distinction is clear to those who participated, and indeed, this distinction was a common observation made by many at the GRC. We are therefore confident that this message will now be disseminated to the venoms and toxins community, and will contribute to higher participation in future GRCs in this series.

Future opportunities

As noted, approval has been received already for a second GRC in the USA in 2020, which will be co-chaired by Ashlee Rowe and Glenn King. Beyond that, we anticipate holding this meeting biennially in Europe (Italy/Spain) and Asia (Hong Kong) in order to facilitate participation of several potential attendees and attract a number of new participants. The venue choices reflect comments received from the 2018 participants, as well as from potential invited speakers/discussion leaders from Europe, for whom the timing and location prevented their attendance because of family vacation commitments. We also anticipate that a future conference in Asia would attract a number of new participants from China in particular, given the considerable activity in this field in that country. In summary, given the overwhelmingly positive response of our inaugural Venom GRC, the follow-up publications in Science and Toxins, and the acquired knowledge by the chairs (who had not previously chaired a GRC), we are confident that the 2020 and future meetings will provide a vibrant and stimulating forum for discussion that nicely complements the excellent annual conferences run by IST.

In addition, with venom research being recognized recently by the World Economic Forum as a future frontier of research, (https://www.weforum.org/agenda/2018/11/frontiers-of-science-research-global-future-councils-2018/), the venom field will continue to grow, and we expect that this GRC and future IST meetings will attract a diverse audience of scientists from both the academic and private sectors.

Southwest Venoms

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ponerine@dakotacom.net

CATALOGUE OF INSECT VENOMS (2012-2013)

Prices in U.S. dollars. All venoms are pure venoms (not venom sac or apparatus homogenates) collected according to the methods of Schmidt (1986. *In*: Venoms of the Hymenoptera [T. Piek, ed.], pp. 425-508. Academic Press: London.).

Prod. No.	VENOM	(LD_{50} mg/kg, mice)	VENOM PRICE 1 mg	5 mg	25 mg	100 mg
	SOCIAL WASPS	(LD_{50})				
	Yellowjackets -- *Vespula*					
W-10	*V. pensylvanica*	(6.4)	50	225	1000	*
W-19	other species**		*			
	Hornets -- *Vespa*					
W-20	*V. mandarinia*	(4.1)	50	225	1000	*
W-21	*V. tropica*	(2.8)	50	225	1000	*
W-29	others **		*			
	Paper wasps -- *Polistes*					
W-30	*P. comanchus navajoe*	(5)	40	180	800	*
W-31	*P. flavus*	(3.8)	40	180	800	*
W-32	*P. canadensis*	(2.5)	50	225	*	
W-33	*P. erythrocephalis*	(1.5)	50	225	*	
W-39	*Polistes* sp. as available**		30	135	600	2100
	New World Polybiine wasps					
W-40	*Brachygastra mellifica*	(1.5)	60	270	1200	*
W-50	*Synoeca septentrionalis*	(2.7)	60	270	1200	*
W-60	*Parachartergus fraternus*	(5)	70	300	1400	*
W-70	*Polybia sericea*	(6)	80	350	*	
W-71	*P. simillima*	(4.1)	80	350	*	
W-72	*P. occidentalis*	(5)	100	*		
W-80	*Agelaia myrmecophila*	(5.6)	140	*		
	Old World Polybiine wasps					
W-90	*Belonogaster juncea colonialis*	(3)	80	350	*	
	SOCIAL BEES					
	Honey bees -- *Apis*					
B-10	*A. mellifera*	(2.8)	20	90	400	1400
B-11	*A. mellifera* Africanized bees	(2.8)	20	90	400	1400
B-12	*A. mellifera* queens		40	180	800	2800
B-13	*A. dorsata*	(2.8)	50	225	1000	3500
B-14	*A. cerana*	(3.1)	55	245	*	
B-19	others (*A. flo*rea, etc.)**		*			
	Bumble bees -- *Bombus*					
B-20	*B. sonorus*	(12)	50	225	1000	*
B-21	*B. impatiens*	(12)	50	225	*	
B-29	other species**		30	*		

Prod. No.	VENOM	(LD_{50} mg/kg, mice)	VENOM PRICE 1 mg	5 mg	25 mg	100 mg
	ANTS -- FORMICIDAE	(LD_{50})				
	Pogonomyrmex -- harvester ants					
A-10	*P. barbatus*	(0.6)	50	225	1000	3500
A-11	*P. maricopa*	(0.12)	60	270	1200	4200
A-12	*P. occidentalis*	(0.5)	70	315	1400	*
A-13	*P. rugosus*	(0.7)	50	225	1000	3500
A-15	*P. desertorum*	(0.7)	160	*		
A-19	*Pogonomyrmex* sp. as available		45	200	900	3200
	Myrmecia -- bull ants					
A-20	*M. gulosa*	(0.18)	60	270	1200	4200
A-21	*M. tarsata*	(0.18)	60	270	1200	*
A-22	*M. browningi*	(0.18)	70	315	*	
A-23	*M. rufinodis*	(0.35)	70	315	*	
A-24	*M. simillima*	(0.21)	70	315	*	
A-25	*M. pilosula*	(5.7)	100	*		
A-30	*Pachycondyla (Neoponera) villosa*	(7.5)	60	270	*	
A-31	*P. (Neoponera.) apicalis*	(>16)	70	*		
A-32	P. *crassinoda*	(2.8)	80	*		
A-33	*P. (Megaponera) foetens* (Metabele ant)	(130)	70	315	*	
A-34	*P. (Paltothyreus) tarsatus* (stink ant)	(64)	50	225	1000	3500
A-35	*P. (Bothroponera) strigulosa*	(9)	70	*		
A-36	*Termitopone commutata*	(10)	70	315	1400	*
A-40	*Platythyrea lamellosa*	(11)	70	315	*	
A-50	*Diacamma* sp.**	(35)	100	450	*	
A-60	*Dinoponera gigantea*	(11)	60	270	1200	4200
A-70	*Paraponera clavata* (bullet ant)	(6.0)	60	270	1200	4200
A-80	*Ectatomma tuberculatum*	(1)	60	270	*	
A-81	*E. quadridens*	(17)	60	270	*	
A-90	*Odontomachus* sp.**	(33)	60	275	*	
A-110	*Tetraponera* sp**	(.35)	140	600	*	
A-120	*Streblognathus aethiopicus*	(8.0)	80	360	*	
	SOLITARY WASPS AND BEES					
	Spider wasps -- Pompilidae					
SW-10	*Pepsis* sp.**	(65)	60	270	1200	4200
	Mutillid wasps -- Mutillidae					
SW-20	*Dasymutilla* sp.**	(71)	70	315	1400	*
SW-39	Other wasps (Scoliidae, Tiphiidae, Sphecidae, Eumenidae, etc.)**		*			
	Carpenter bees -- *Xylocopa*					
SB-10	*X. californica*	(21)	50	225	1000	*
SB-11	*X. veripuncta*	(33)	55	245	*	
SB-20	*Proxylocopa rufa*	(11)	100	450	*	
SB-39	Other bees**		*			

*Inquire for prices and availability.
**Available species provided; exact determinations usually included.

Natural Toxins Research Center (NTRC)

Texas A&M University Kingsville

Venom Quality Guarantee

Authenticity of Species • Purity of Venom
Maximum Biological Activity • Our Venom is Never Pooled

Snake venoms contain important molecules which are valuable for researching the treatments of strokes, heart attacks, and cancer.

The Natural Toxins Research Center (NTRC) at Texas A&M University-Kingsville is dedicated to providing high quality snake products for biomedical research. We are committed to the procurement and distribution of venoms, venom fractions and tissue for biomedical research. Venoms from the same species can be different, and therefore extracted venoms are never pooled. Each vial contains venom from a single snake, and venoms of the same species are never mixed. The vials are labeled with the snakes' scientific and common names, ID tag number and sex. The ID tag number can be traced back to the NTRC Internet Database (ntrc.tamuk.edu/cgi-bin/serpentarium/snake.query) for additional information about each snake.

(A) - neurotoxic venom
(B) - non-neurotoxic venom
****Subject to availability***

Southern Copperhead - *Agkistrodon contortrix contortrix*	$75.00/1g	$50.63/500mg			
Broad-Banded Copperhead - *Agkistrodon contortrix laticinctus*	$100.00/1g	$67.50/500mg			
Northern Copperhead - *Agkistrodon contortrix mokasen*	$50.00/1g	$33.75/500mg			
Trans-Pecos Copperhead - *Agkistrodon contortrix pictigaster*	$75.00/1g	$50.63/500mg			
Florida Cottonmouth - *Agkistrodon piscivorus conanti*	$60.00/1g	$40.50/500mg			
Western Cottonmouth - *Agkistrodon piscivorus leucostoma*	$56.00/1g	$37.80/500mg			
Eastern Diamondback Rattlesnake - *Crotalus adamanteus*	$50.00/1g	$33.75/500mg			
Western Diamondback Rattlesnake - *Crotalus atrox*	$45.00/1g	$30.38/500mg			
Sonoran Sidewinder - *Crotalus cerastes cercobombus*	$125.00/1g	$84.38/500mg			
Timber Rattlesnake - *Crotalus horridus*	$70.00/1g	$47.25/500mg			
Mottled Rock Rattlesnake - *Crotalus lepidus lepidus*	$125.00/1g	$84.38/500mg			
Blacktail Rattlesnake - *Crotalus molossus molossus*	$400.00/1g	$270.00/500mg	$72.90/100mg	$49.21/50mg	
Great Basin Rattlesnake - *Crotalus oreganus lutosus*	$125.00/1g	$84.38/500mg			
Grand Canyon Rattlesnake - *Crotalus oreganus abyssus*	$250.00/1g	$168.75/500mg	$45.56/100mg	$30.75/50mg	
Texas Coral Snake - *Mircrurus tener tener*	$2000.00/1g				
Florida Coral Snake - *Mircrurus fulvius*	$1800.00/1g				
Southern Pacific Rattlesnake - *Crotalus oreganus helleri*	$400.00/1g	$270.00/500mg	$72.90/100mg	$49.21/50mg	
Northern Pacific Rattlesnake - *Crotalus oreganus oreganus*	$400.00/1g	$270.00/500mg	$72.90/100mg	$49.21/50mg	
Mohave Rattlesnake - *Crotalus scutulatus scutulatus (A)*	$250.00/1g	$168.75/500mg	$45.56/100mg	$30.75/50mg	
Mohave Rattlesnake - *Crotalus scutulatus scutulatus (B)*	$1000.00/1g	$675.00/500mg	$182.25/100mg	$123.02/50mg	$33.22/10mg
Prairie Rattlesnake - *Crotalus viridis viridis*	$70.00/1g	$47.25/500mg			
Red Spitting Cobra - *Naja pallida*	$100.00/1g	$67.50/500mg			
Desert Massasauga - *Sistrurus catenatus edwardsii*	$1000.00/1g	$675.00/500mg	$182.25/100mg	$123.02/50m	$33.22/10mg
Western Massasauga - *Sistrurus catenatus tergeminus*	$1000.00/1g	$675.00/500mg	$182.25/100mg	$123.02/50mg	$33.22/10mg
Bushmaster - *Lachesis muta muta*	$2000.00/1g	$1350.00/500mg	$364.50/100mg	$246.04/50mg	$66.43/10mg

Venom is collected under stringent laboratory conditions using disposable labwear for each extraction. Venom is collected in new, non-reusable plastic cups with parafilm coverings. Snakes are allowed to bite into the parafilm diaphragm and the venom glands are not massaged. Immediately following collection, each venom sample is clarified by centrifugation at 500 x g for 5 minutes to remove cellular debris and frozen at -90º C until lyophilized.

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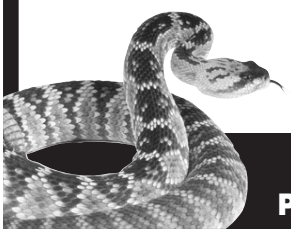

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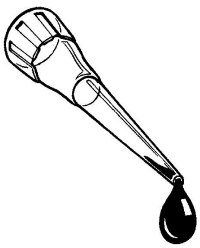

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Snakes

Scientific name	Price(US$)/200mg	Price(US$)/gm
Acanthophis antarcticus	$170	$745
Acanthophis praelongus	$210	$845
Agkistrodon billineatus	$50	$200
Austrelaps superbus	$400	$1,600
Austrelaps labialis	$700	$3,000
Bitis arietans	$70	$300
Bitis rhinoceros	$75	$340
Bitis nasicornis	$75	$340
Bothriechis schlegelii	$200	$850
Crotalus adamanteus	$100	$450
Crotalus unicolor	$200	$900
Crotalus vegrandis	$160	$700
Hoplocephalus stephensii	$220	$900
Hoplocephalus bitorquatus	$220	$900
Naja kaouthia	$60	$250
Naja melanoleuca	$50	$200
Naja mossambica	$60	$250
Naja siamensis	$60	$250
Notechis ater humphreysi	$350	$1,600
Notechis ater niger	$350	$1,600
Notechis ater serventyi	$350	$1,600
Notechis scutatus	$300	$1,445
Ophiophagus hannah	$200	$850
Oxyuranus microlepidotus	$300	$1,300
Oxyuranus scutellatus	$260	$1,250
Oxyuranus scutellatus canni	$400	$1,500
Pseudechis australis	$110	$520
Pseudechis butleri	$160	$700
Pseudechis colletti	$110	$500
Pseudechis guttatus	$110	$500
Pseudechis porphyriacus	$140	$650
Pseudechis papuanus	$288	$1,380
Pseudonaja affinis	$800	$3,900
Pseudonaja aspidorhyncha	$800	$3,990
Pseudonaja inframacula	$800	$3,990
Pseudonaja nuchalis	$800	$3,990
Pseudonaja textilis	$760	$3,700
Tropidechis carinatus	$300	$1,500

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Latrodectus hasseltii	$500/50 sac contents.	

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Pure bee venom (*Apis mellifera*)	250mg	$58
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	(6-10gm)	$116/gm
	(60gm and over)	$95/gm

Amphibian Venoms

Bufo marinus	$95/200mg	$450/gm

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Naja nigricollis (Ghana)	$205.00
Naja h. annulifera	$125.00
Naja kaouthia	$205.00
Naja naja (Pakistan)	$250.00
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Fone (55) 14 9731 2436
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Slade, KY 40376

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- DNA samples in the form of scale clippings available; please inquire about tissue samples
- Other venoms available upon request; contact us for more information.
- CITES permits available for all CITES listed species. Extra cost for permits.
- KRZ makes every effort to stay current regarding nomenclature and taxonomy. Our listing reflects current trends, with former names in parentheses. If you have any questions, feel free to contact us.

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VENOM PRICE LIST

Crotalidae

Species Name	**Price (US$) Per Gram**
Agkistrodon bilineatus	$300.00
Agkistrodon contortrix (fmr. A. c. contortrix, A. c. mokasen)	$150.00
Agkistrodon laticinctus (fmr. A. c. laticinctus, A. c. phaeogaster, A. c. pictogaster)	$150.00
Agkistrodon leucostoma	$75.00
Agkistrodon piscivorous	$75.00
Bothrops alternatus	$200.00
Bothrops atrox (Columbia origin)	$250.00
Bothrops atrox (Surinam origin)	$250.00
Bothrops moojeni	$250.00
Calloselasma rhodostoma	$200.00
Crotalus adamanteus	$120.00
Crotalus atrox	$120.00
Crotalus durissus durissus	$200.00
Crotalus durissus terrificus	$225.00
Crotalus horridus	$150.00
Crotalus scutulatus scutulatus	$175.00
Crotalus viridis viridis	$100.00
Protobothrops flavoviridis	$200.00
Sisturus catenatus tergeminus	$300.00

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Helodermatidae

Species Name	**Price (US$) Per Gram**
Heloderma horridum	$600.00
Heloderma suspectum	$600.00

Viperidae

Species Name	**Price (US$) Per Gram**
Bitis arietans	$225.00
Bitis gabonica	$225.00
Bitis rhinoceros	$225.00
Deinagkistrodon acutus	$300.00
Echis carinatus sochureki	$400.00
Echis pyramidium	$400.00

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Elapidae

Species Name	**Price (US$) Per Gram**
Dendroaspis angusticeps	$450.00
Dendroaspis polylepis	$500.00
Naja annulifera	$80.00
Naja haje	$80.00
Naja kaouthia	$100.00
Naja kaouthia (Suphan province)	$100.00
Naja melanoleuca	$150.00
Naja mossambica	$100.00
Naja naja (India origin)	$150.00
Naja naja (Pakistan origin)	$150.00
Naja nigricollis nigricollis	$80.00
Naja nivea	$150.00
Naja pallida	$100.00
Naja philippinensis	$300.00
Naja samarensis	$300.00
Naja siamensis	$80.00
Ophiophagus hannah	$120.00
Oxyuranus scutellatus scutellatus	$500.00
Pseudechis colletti	$320.00

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