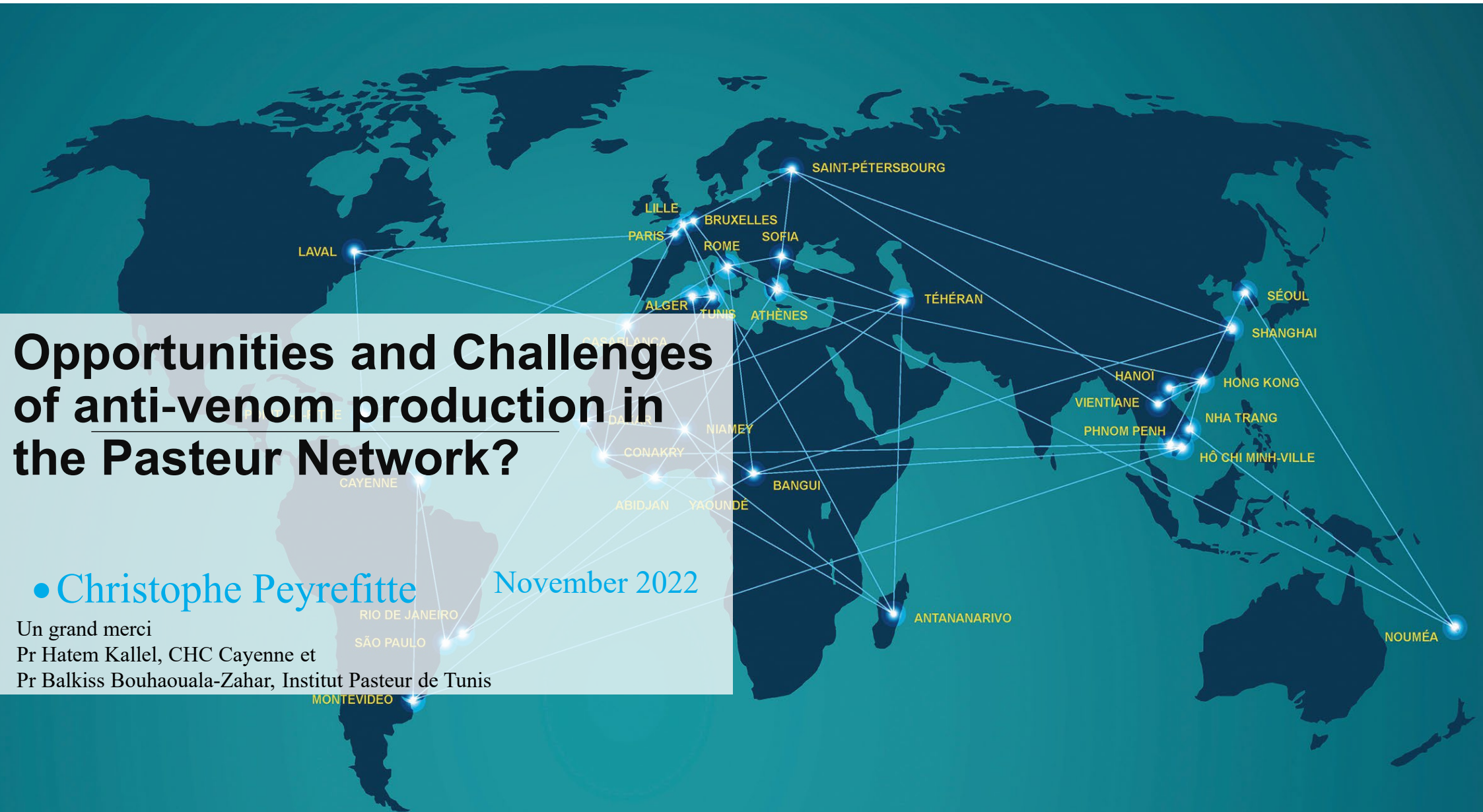


Opportunities and Challenges of anti-venom production in the Pasteur Network?

• **Christophe Peyrefitte** November 2022

Un grand merci
Pr Hatem Kallel, CHC Cayenne et
Pr Balkiss Bouhaouala-Zahar, Institut Pasteur de Tunis





**+ 2.5 million cases
of envenoming
every year**



**causing an estimated
81'000 to 138'000
deaths**

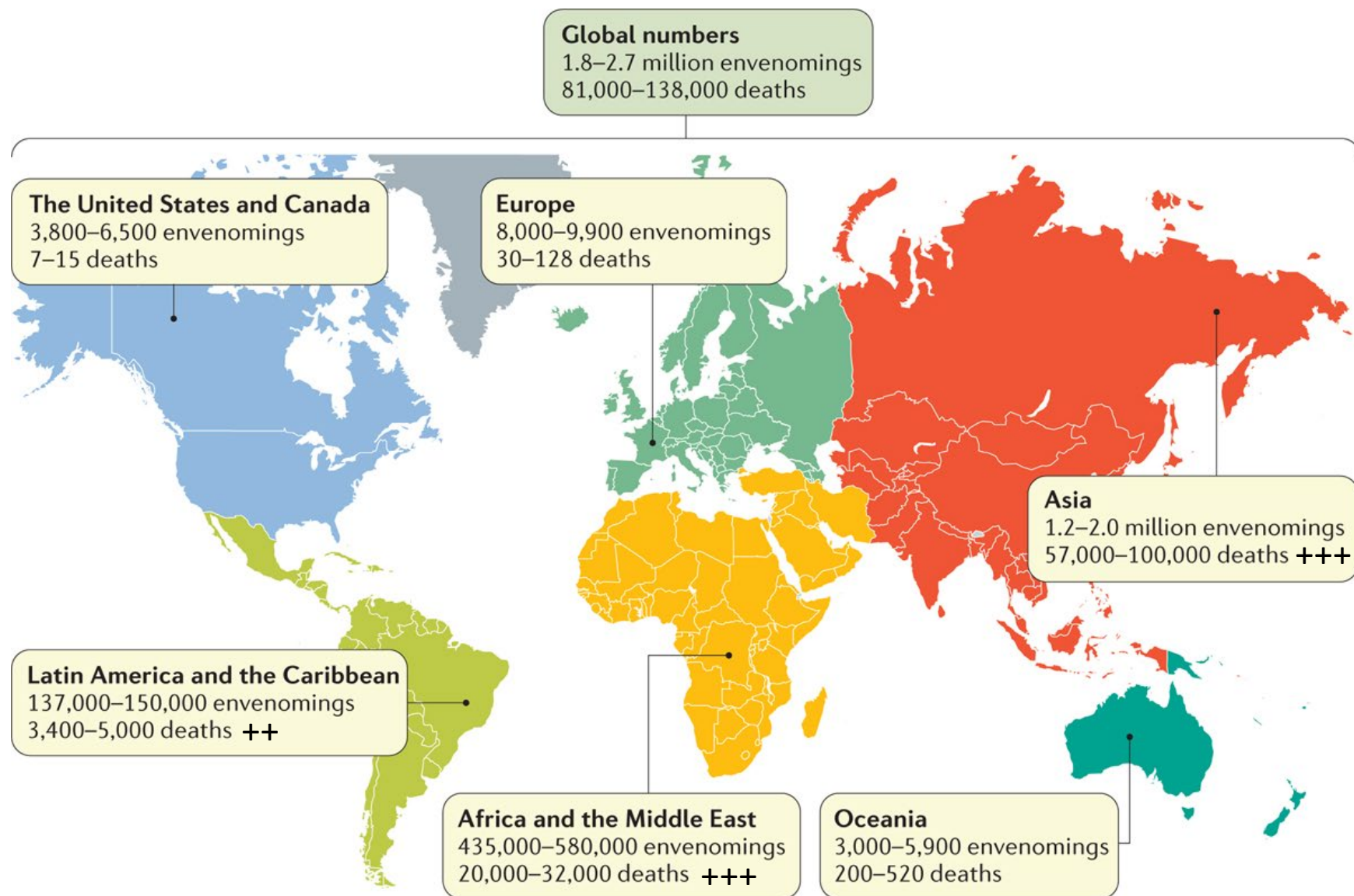


**3x more amputations
and permanent
disabilities**



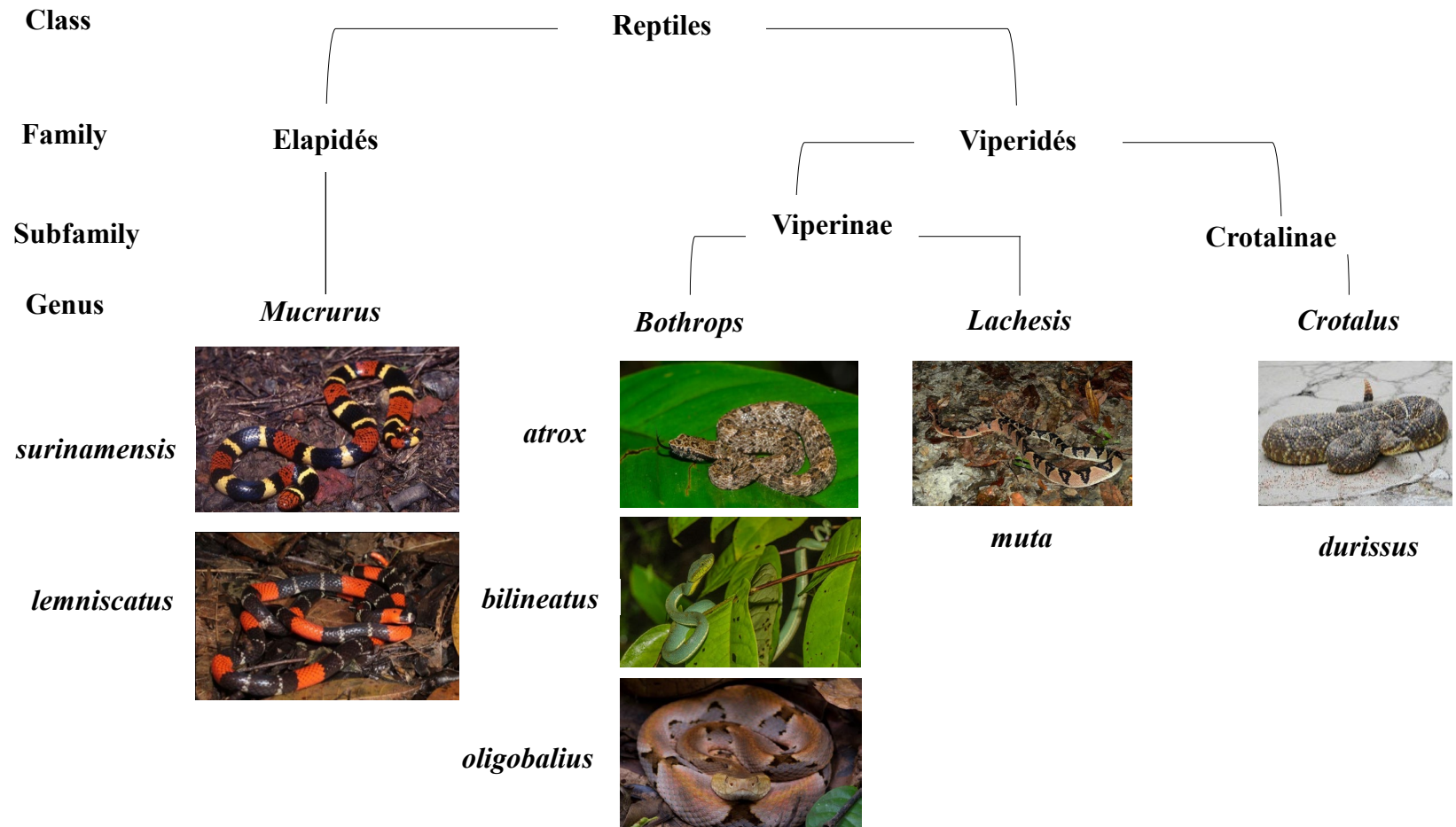
≈ meningitis or measles (NTDs)

Geographical distribution of the estimated number of snakebite envenomings and deaths



Nature Reviews | Disease Primers

Poisonous snakes in French Guiana



VENOMOUS SNAKE PROFILE

COMMON NAME: **Common lancehead**

SCIENTIFIC NAME: ***Bothrops atrox***

FAMILY: **Viperidae**

OTHER COMMON NAMES: **Caiçaca, Equis, Fer-de-lance, Jaracara-do-rabo-branco, Jaracara do norte, Jergón de la selva, Labarri, Labarriayre, Mapanare, Nenenenca, Yoperojobobo**

Category 1: Highest medical importance
Category 2: Secondary medical importance

MEDICAL TREATMENT: **Medical treatment should be sought immediately**
VENOM ACTIVITY: **Not available**
ANTIVENOMS: **URL**

HUMAN POPULATION WITHIN SNAKE SPECIES RANGE: **30,282,634**

0.38% OF WORLD POPULATION

COUNTRIES: **Bolivia (Plurinational State of), Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, Venezuela (Bolivarian Republic of)**

Production date: 2021-09-14
Credits: NTD & DNA Departments, WHO
<https://www.who.int/snakebite>

World Health Organization

VENOMOUS SNAKE PROFILE

COMMON NAME: **Two-striped forest-pitviper**

SCIENTIFIC NAME: ***Bothrops bilineatus***

FAMILY: **Viperidae**

OTHER COMMON NAMES: **Aramambo, Cobra-papagaio, Cobra-verde, Green labaria, Jaracara-verde, Loro machacuy, Mapanare-verde, Vibora lora**

Category 1: Highest medical importance
Category 2: Secondary medical importance

MEDICAL TREATMENT: **Medical treatment should be sought immediately**
VENOM ACTIVITY: **Not available**
ANTIVENOMS: **URL**

HUMAN POPULATION WITHIN SNAKE SPECIES RANGE: **30,983,569**

0.39% OF WORLD POPULATION

COUNTRIES: **Bolivia (Plurinational State of), Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, Venezuela (Bolivarian Republic of)**

Production date: 2021-09-14
Credits: NTD & DNA Departments, WHO
<https://www.who.int/snakebite>

World Health Organization

VENOMOUS SNAKE PROFILE

COMMON NAME: **Bushmaster**

SCIENTIFIC NAME: ***Lachesis muta***

FAMILY: **Viperidae**

OTHER COMMON NAMES: **Amazonian bushmaster, Atlantic coastal bushmaster, Bosmeester, Cascabel púa, Cascabel puga, Cofasi, Couanacounche, Cuanira, Ipolipo, Mapepi, Motolo, Mute rattler, Pico-de-jaca, Pine, Shushupe, Surucucú, Surucucú-de-fogo, Surucútinga,**

Category 1: Highest medical importance
Category 2: Secondary medical importance

MEDICAL TREATMENT: **Medical treatment should be sought immediately**
VENOM ACTIVITY: **Not available**
ANTIVENOMS: **URL**

HUMAN POPULATION WITHIN SNAKE SPECIES RANGE: **77,677,014**

0.98% OF WORLD POPULATION

COUNTRIES: **Bolivia (Plurinational State of), Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, Trinidad and Tobago, Venezuela (Bolivarian Republic of)**

Production date: 2021-09-14
Credits: NTD & DNA Departments, WHO
<https://www.who.int/snakebite>

World Health Organization

VENOMOUS SNAKE PROFILE

COMMON NAME: **South American rattlesnake**

SCIENTIFIC NAME: ***Crotalus durissus***

FAMILY: **Viperidae**

OTHER COMMON NAMES: **Amaru, Asakamio, Cascabel, Cascavel, Ma'ara, Maracá, Maracabóia, Palla, Sak-kah-sak, Saka sneki**

Category 1: Highest medical importance
Category 2: Secondary medical importance

MEDICAL TREATMENT: **Medical treatment should be sought immediately**
VENOM ACTIVITY: **Not available**
ANTIVENOMS: **URL**

HUMAN POPULATION WITHIN SNAKE SPECIES RANGE: **303,173,012**

3.84% OF WORLD POPULATION

COUNTRIES: **Argentina, Aruba, Bolivia (Plurinational State of), Brazil, Colombia, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela (Bolivarian Republic of)**

Production date: 2021-09-14
Credits: NTD & DNA Departments, WHO
<https://www.who.int/snakebite>

World Health Organization

New species even in 2021?

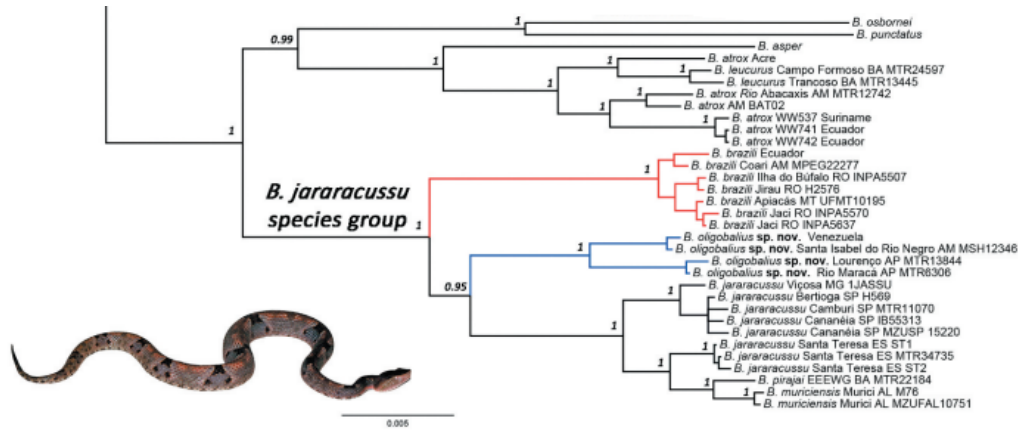
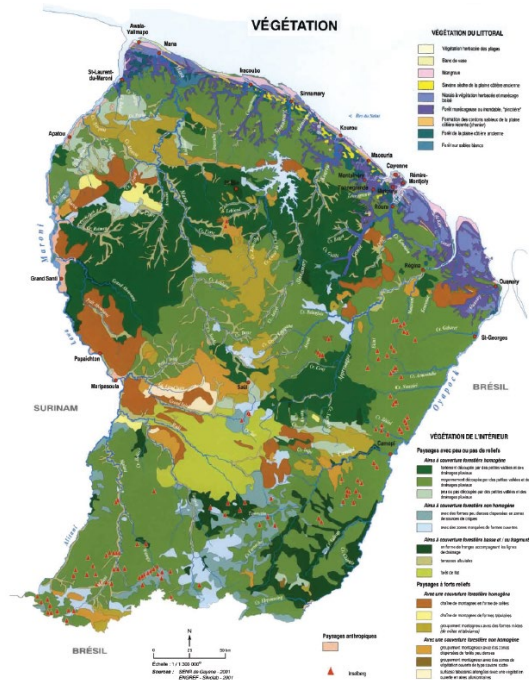


Figure 1. Phylogenetic relationships within *Bothrops* highlighting the placement of *B. oligobalius* sp. nov. (blue) and *B. brazili* (red) in the *jararacussu* species group. Posterior probabilities are shown above nodes. Scale bar indicates substitutions per site. Photo: *B. oligobalius* sp. nov. from French Guiana, by Maël Dewynter.



Dal Vechio et al. J of Natural History (2021)
Pr Hatem Kallel

6 | Pasteur Network Presentation | November 2022



VENOMOUS SNAKE PROFILE

COMMON NAME:
Brazil's lancehead

SCIENTIFIC NAME:
Bothrops brazili

FAMILY:
Viperidae

OTHER COMMON NAMES:
Jararaca-vermelha, Jergon-shushupe, Kalakunaro, Mapanare, Rabo de ratón, Southern Velvety Lancehead, Surucucu-vermelha falsa

COUNTRIES:
Bolivia (Plurinational State of), Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, Venezuela (Bolivian Republic of)

HUMAN POPULATION WITHIN SNAKE SPECIES RANGE:
15,745,318

0.20% OF WORLD POPULATION

MEDICAL TREATMENT:
Medical treatment should be sought immediately

VENOM ACTIVITY:
Not available

ANTIVENOMS:
URL

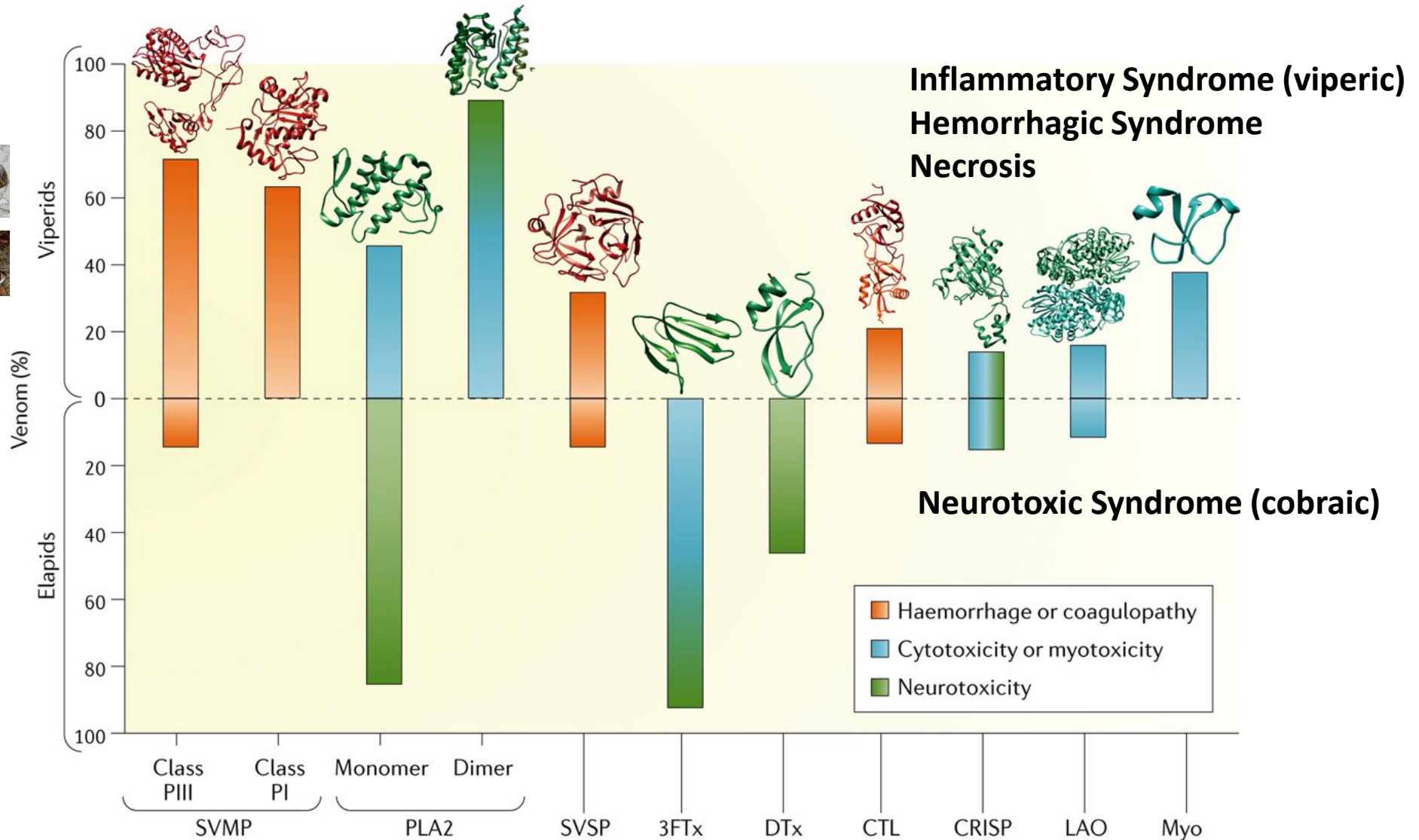
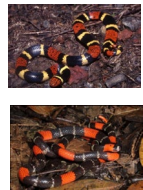
Category 1: Highest medical importance
Category 2: Secondary medical importance

Production date: 2021-09-14
Credits: NTD & DNA Departments, WHO
<https://www.who.int/snakebite>

World Health Organization



Toxin levels in the venom of viperids and elapids

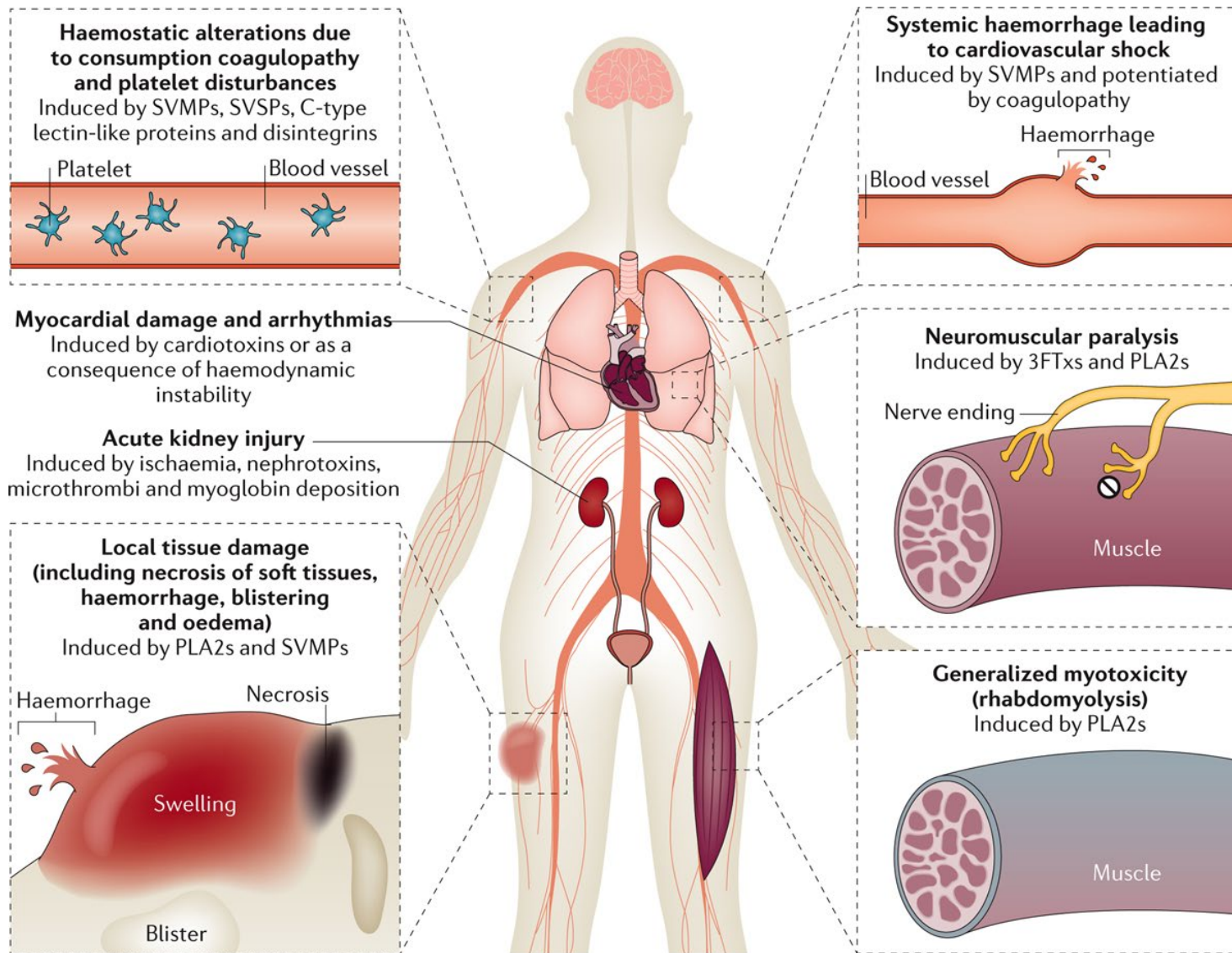


SVMP : snake venom metalloprotease
 PL : phospholipase, including PLA₂ and PLB
 SVSP : snake venom serine protease
 CLEC : C-type lectin, including CLEC-like
 LAO : L-amino acid oxidase
 3FTx : three-fingered neurotoxins

Nature Reviews | Disease Primers

Gutiérrez, J. M. *et al.* (2017) Snakebite envenoming
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2017.63

Action of snake venom toxins on different body systems



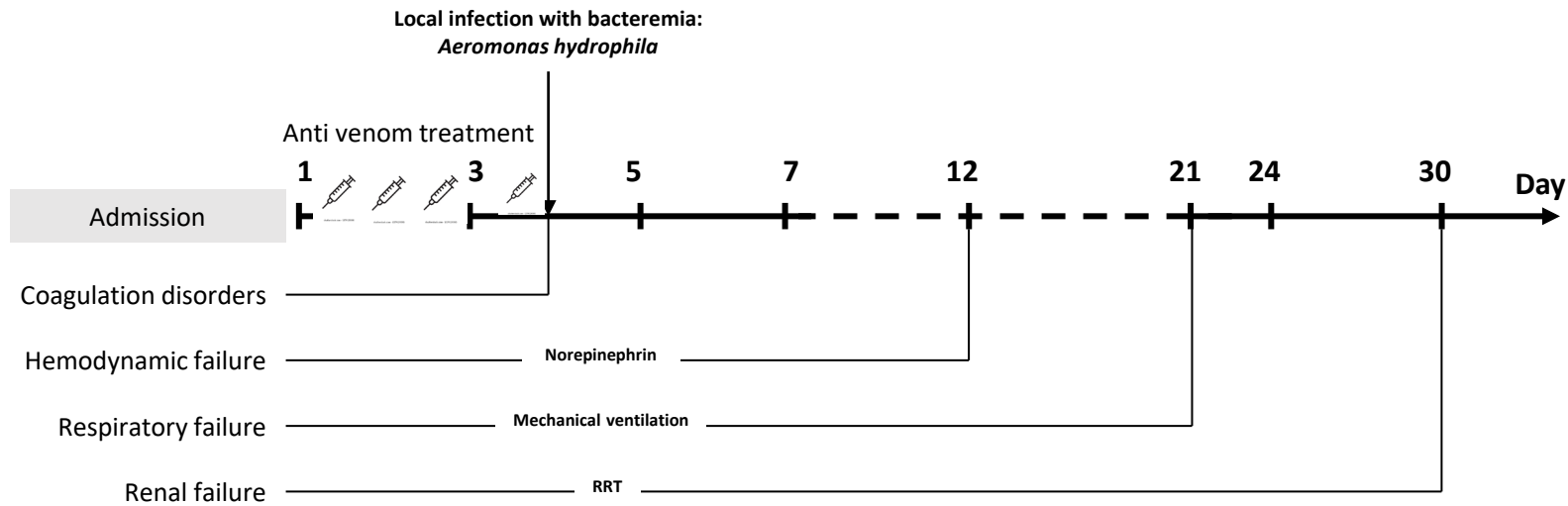
Intrinsic toxicity

SVMP : snake venom metalloprotease
 PL : phospholipase, including PLA₂ and PLB
 SVSP : snake venom serine protease
 CLEC : C-type lectin, including CLEC-like
 LAAO : L-amino acid oxidase
 3FTx : three-fingered neurotoxins

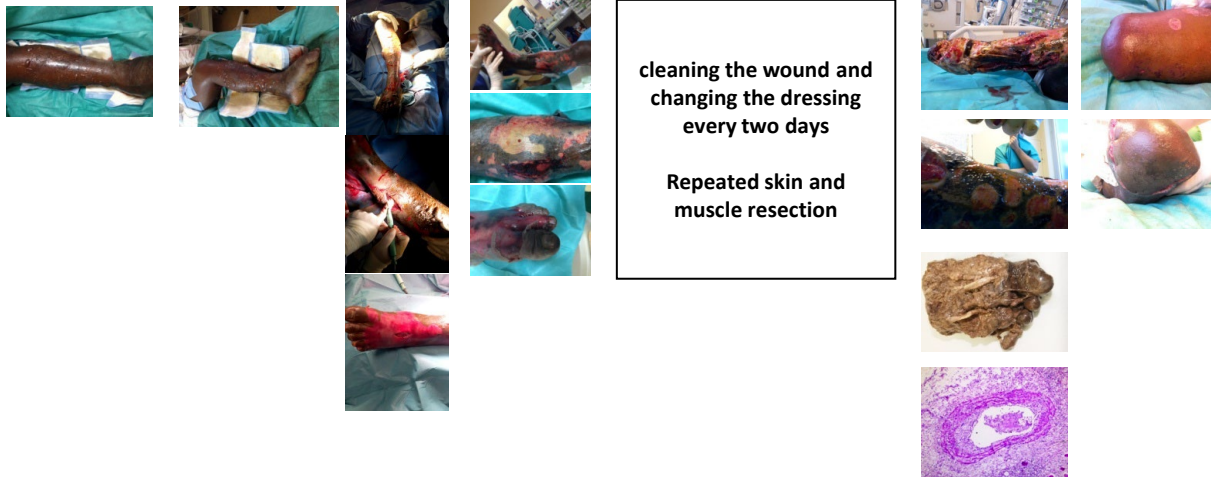
Nature Reviews | Disease Primers

Gutiérrez, J. M. *et al.* (2017) Snakebite envenoming
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2017.63

The treatment is a race against time



Cutaneous lesions

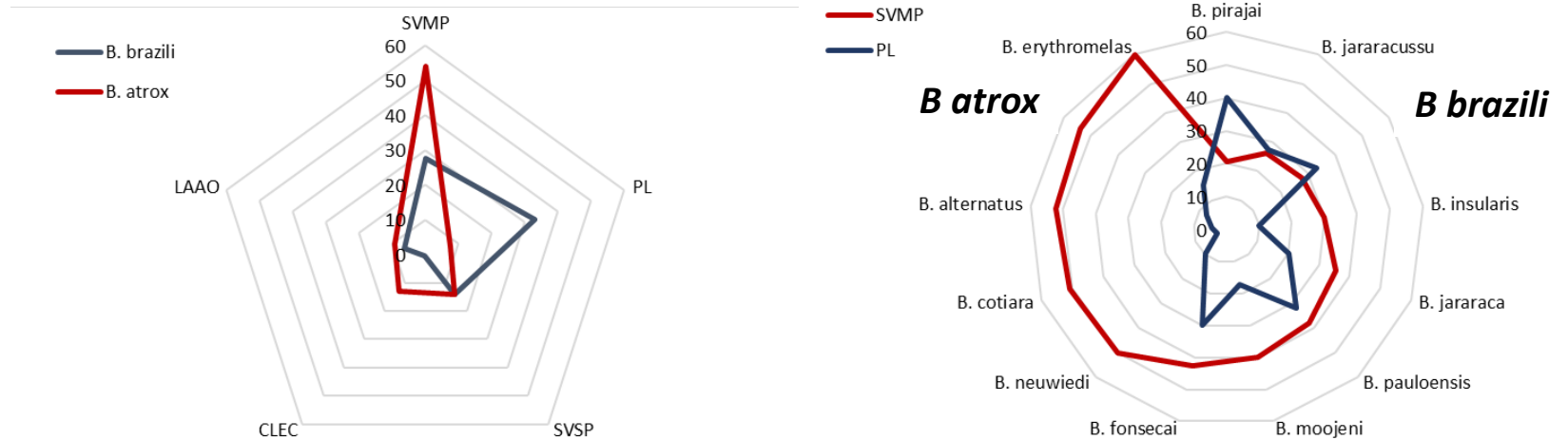


Similarities in the venom

Heterogeneous mixtures of proteins, peptides and organic and inorganic substances

To confine, immobilize and digest their preys,

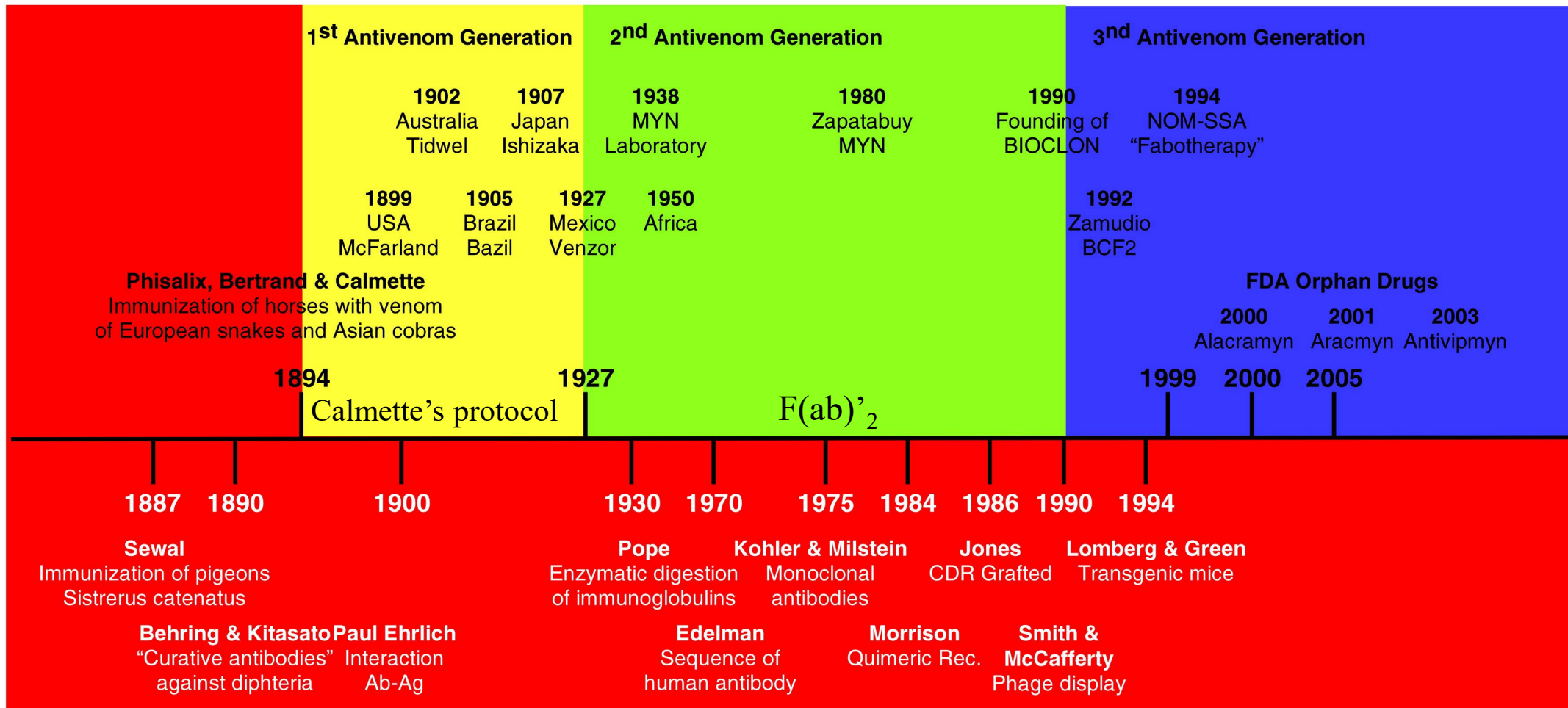
To protect against predators.



SVMP : snake venom metalloprotease
 PL : phospholipase, including PLA₂ and PLB
 SVSP : snake venom serine protease
 CLEC : C-type lectin, including CLEC-like
 LAAO : L-amino acid oxidase

Mamede et al. Toxicon (2020)

Antivenom treatment development



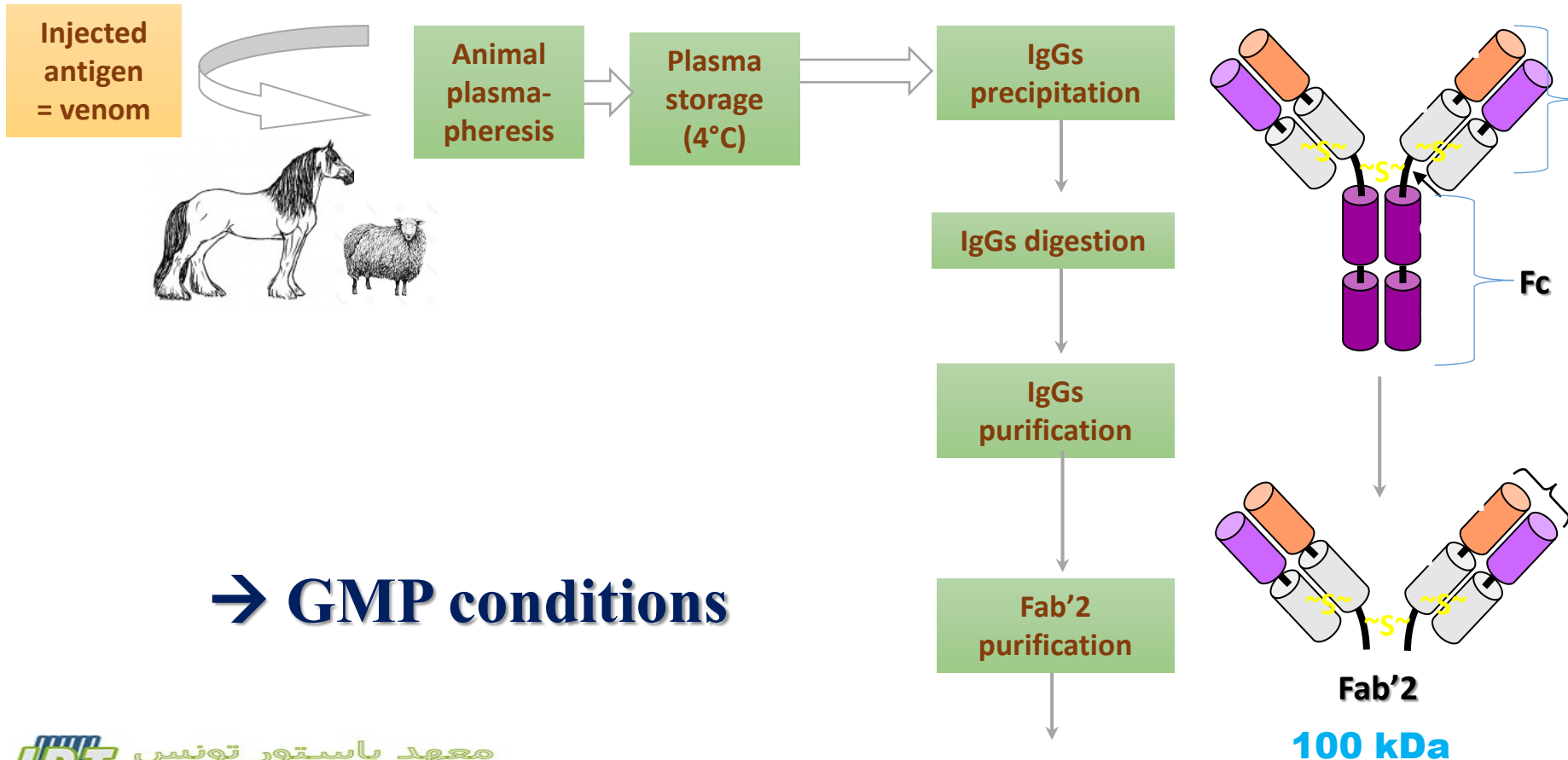
1st generation : decantation then centrifugation; precipitation

2nd generation : Digestion then purification F(ab)'₂

3rd generation : lyophilisation, recombinant

Espino-solis et al. J of Proteomics (2009)

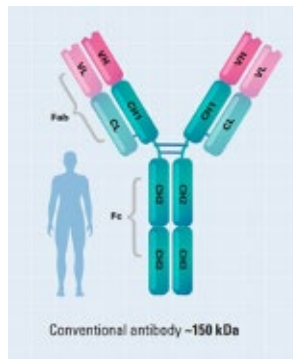
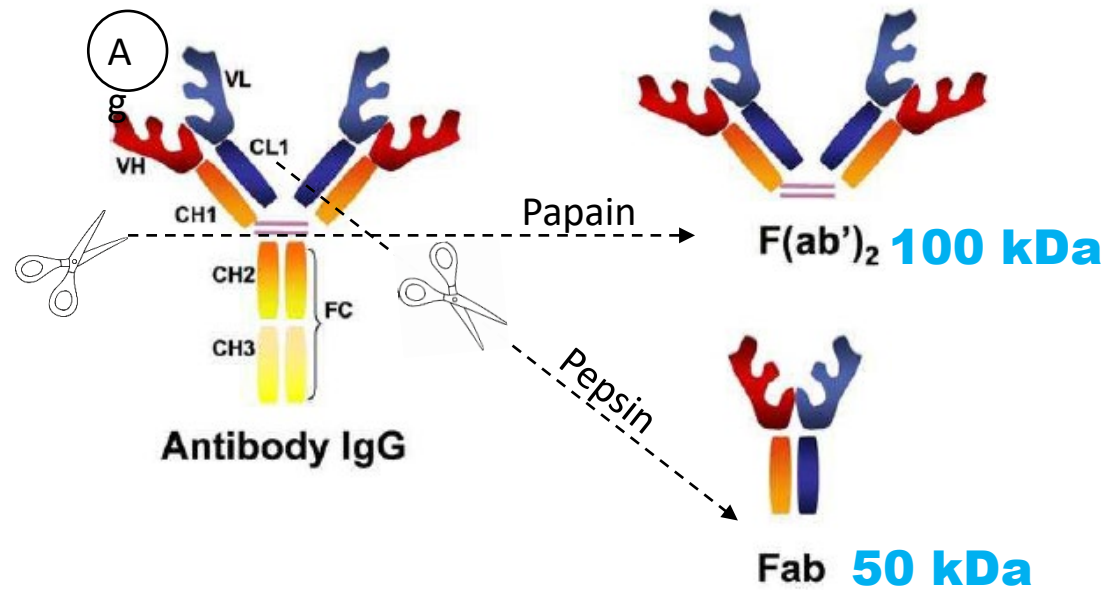
Fab'2-based antivenom preparation process



IPT معهد باستور تونس
Institut Pasteur de Tunisie

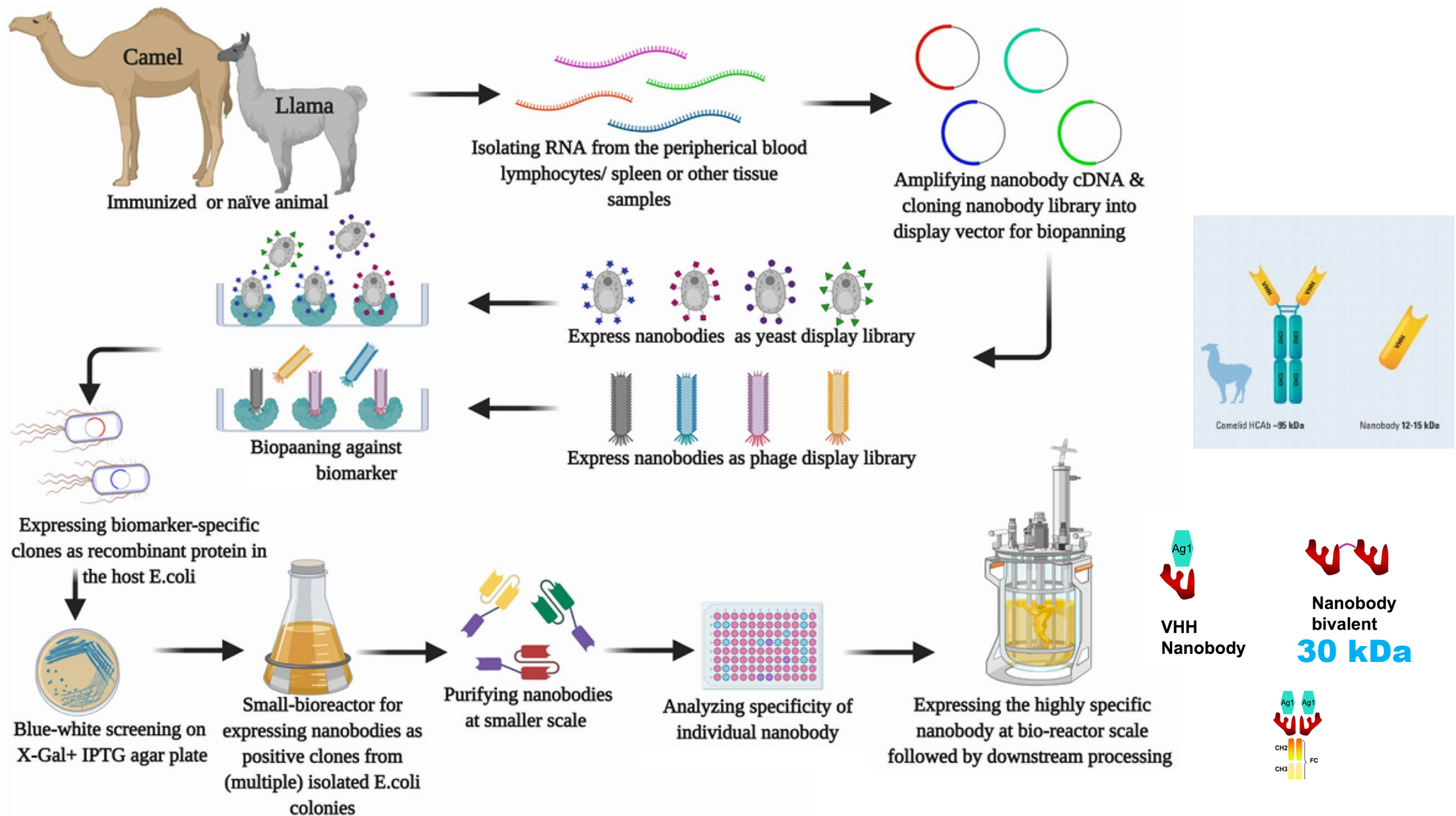


Fab'2-based antivenom preparation process



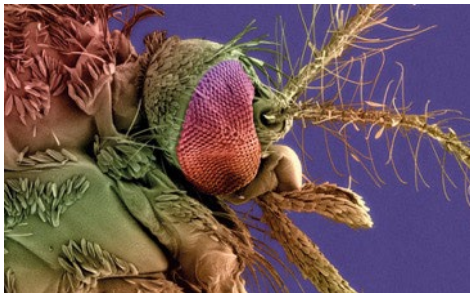
Espino-solis et al. J of Proteomics (2009)

Next generation : antigen-specific nanobody



Does it fit into the PN?

A scientific and humanistic community to serve public health worldwide in fighting mainly infectious diseases



Biomedical research

- pathogen, vectors, reservoir, transmission
- low income countries
- emergence



Public health

- preparedness
- outbreak investigation
- diagnostic and surveillance



Training and career development

- international courses
- mobility programmes
- career development



Innovation and technological expertise

- innovative research
- high-tech platforms
- biobanking
- sequencing

Does it fit into the PN?

PASTEUR NETWORK TO WORK ON 4 MAIN LINES

**Preparedness &
Disease Intelligence**

**Grand
Challenges**

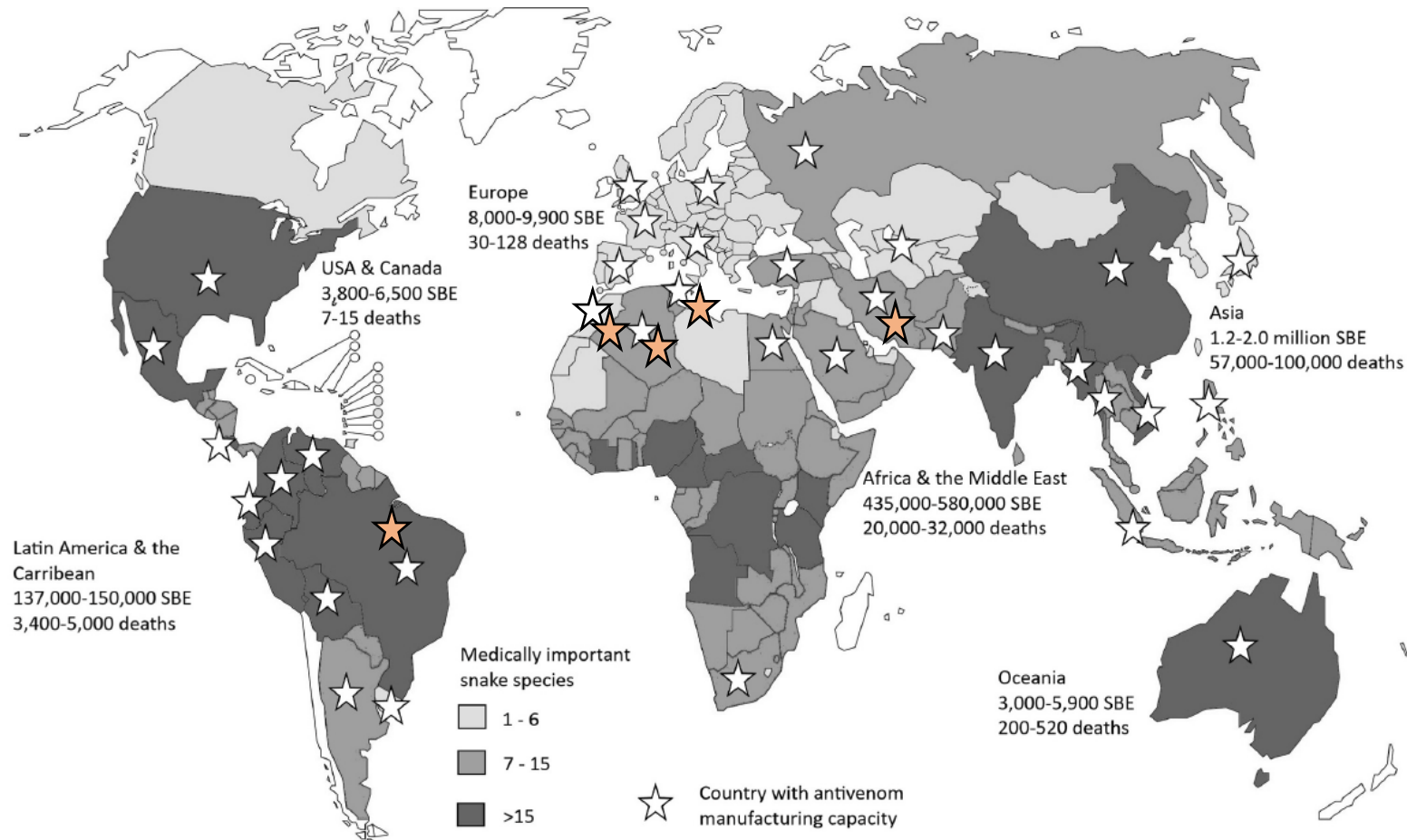
**DTV
manufacturing**

**“ERASMUS”
Mobility**

Boldness and Ambition

Antivenom manufacturing capacities ☆

Pasteur Network antivenom manufacturing capacities ★

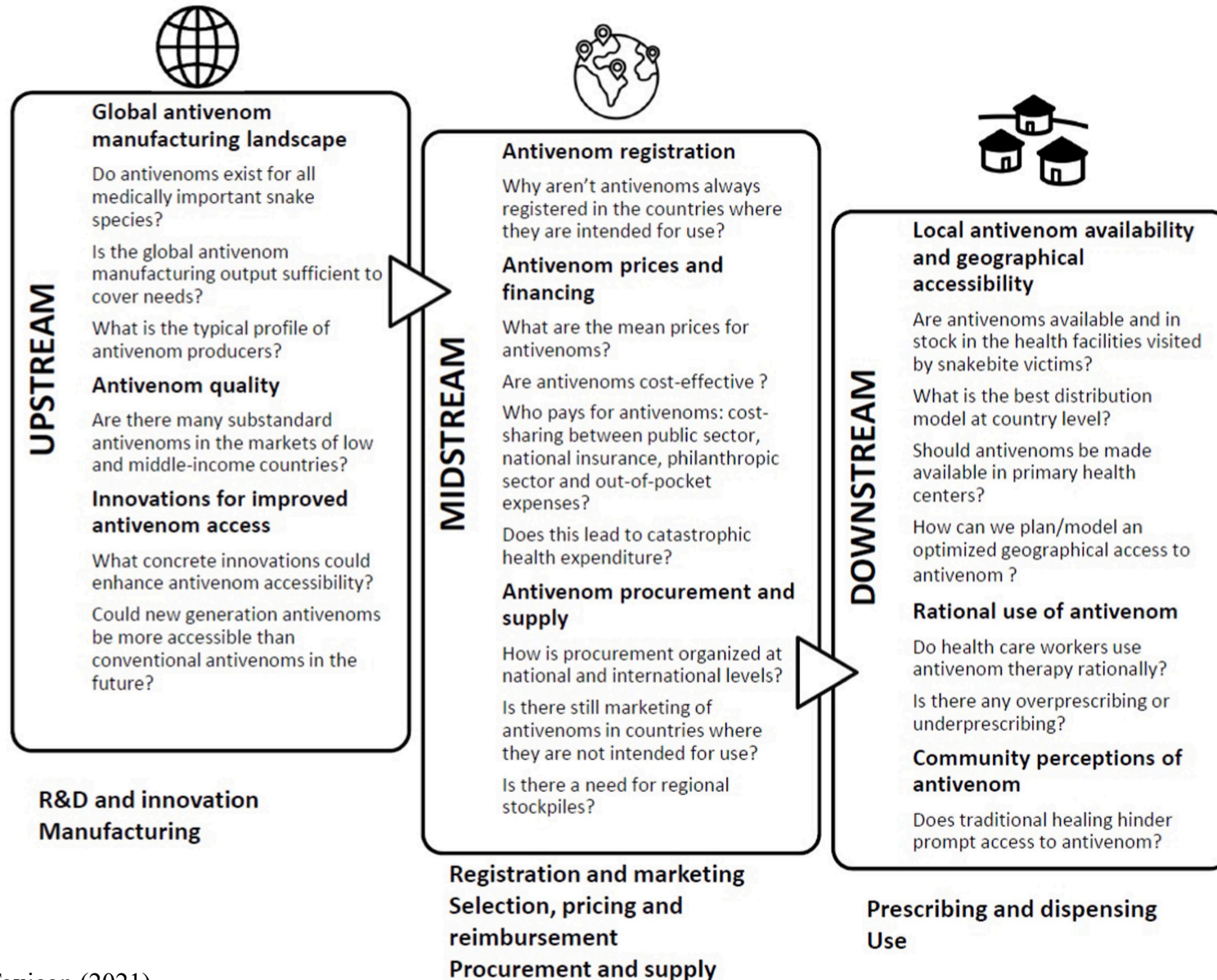


J. Potet et al.

The cost of antivenom has a major impact on accessibility and affordability

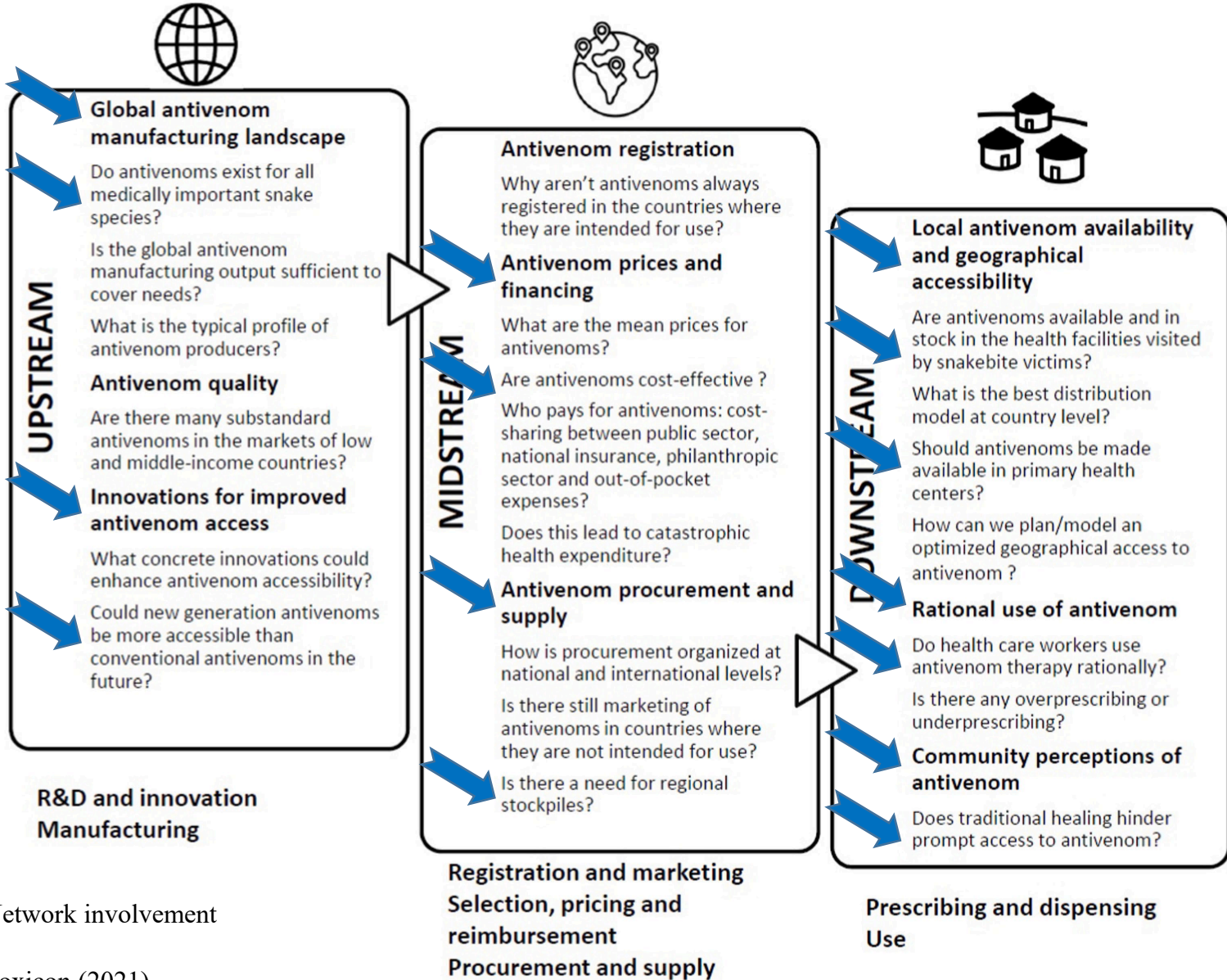
Even if antivenoms are among the most cost-effective interventions in developing countries

Potential access barriers



Potet et al. Toxicon (2021)

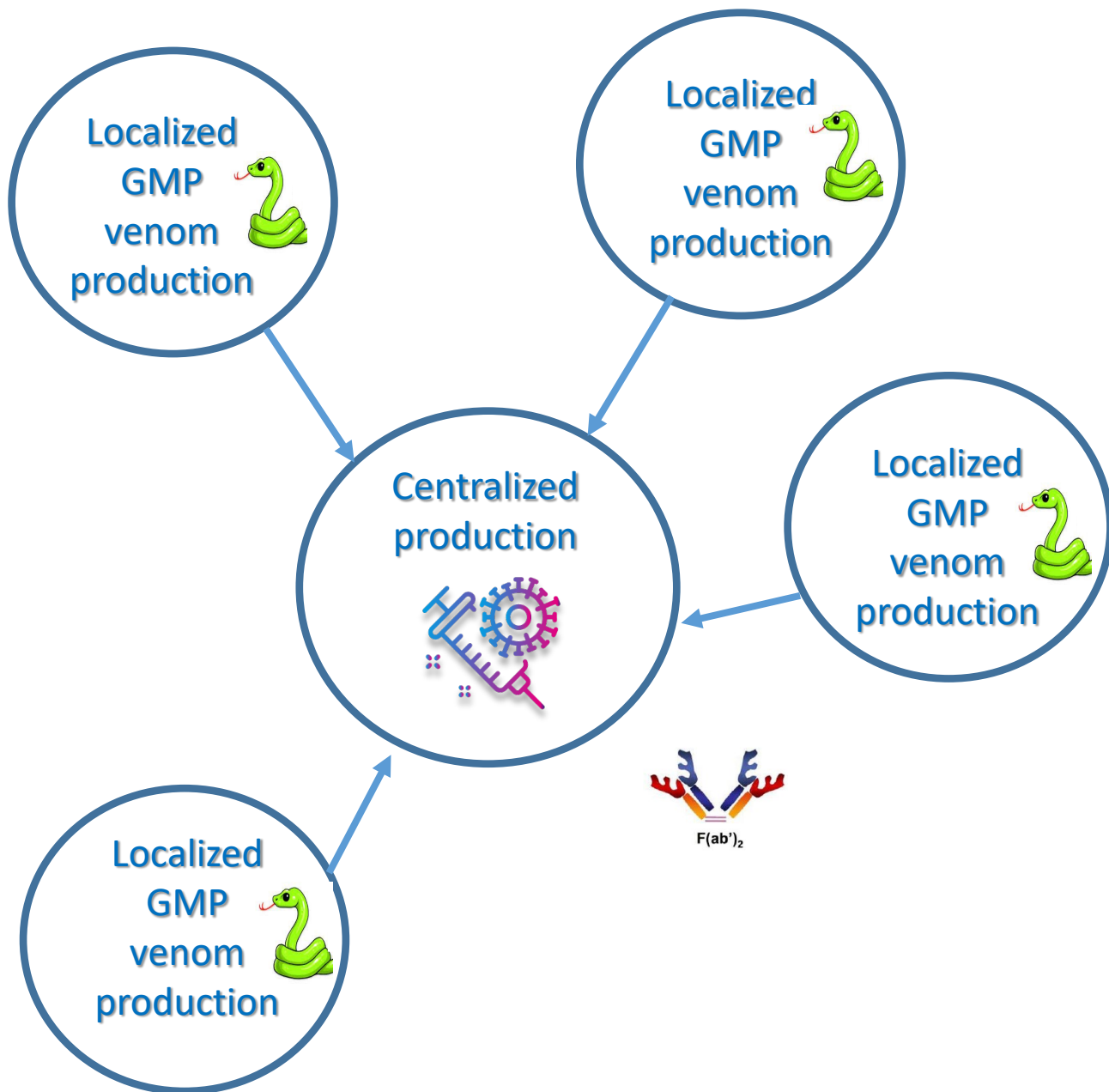
Pasteur Network potential involvement



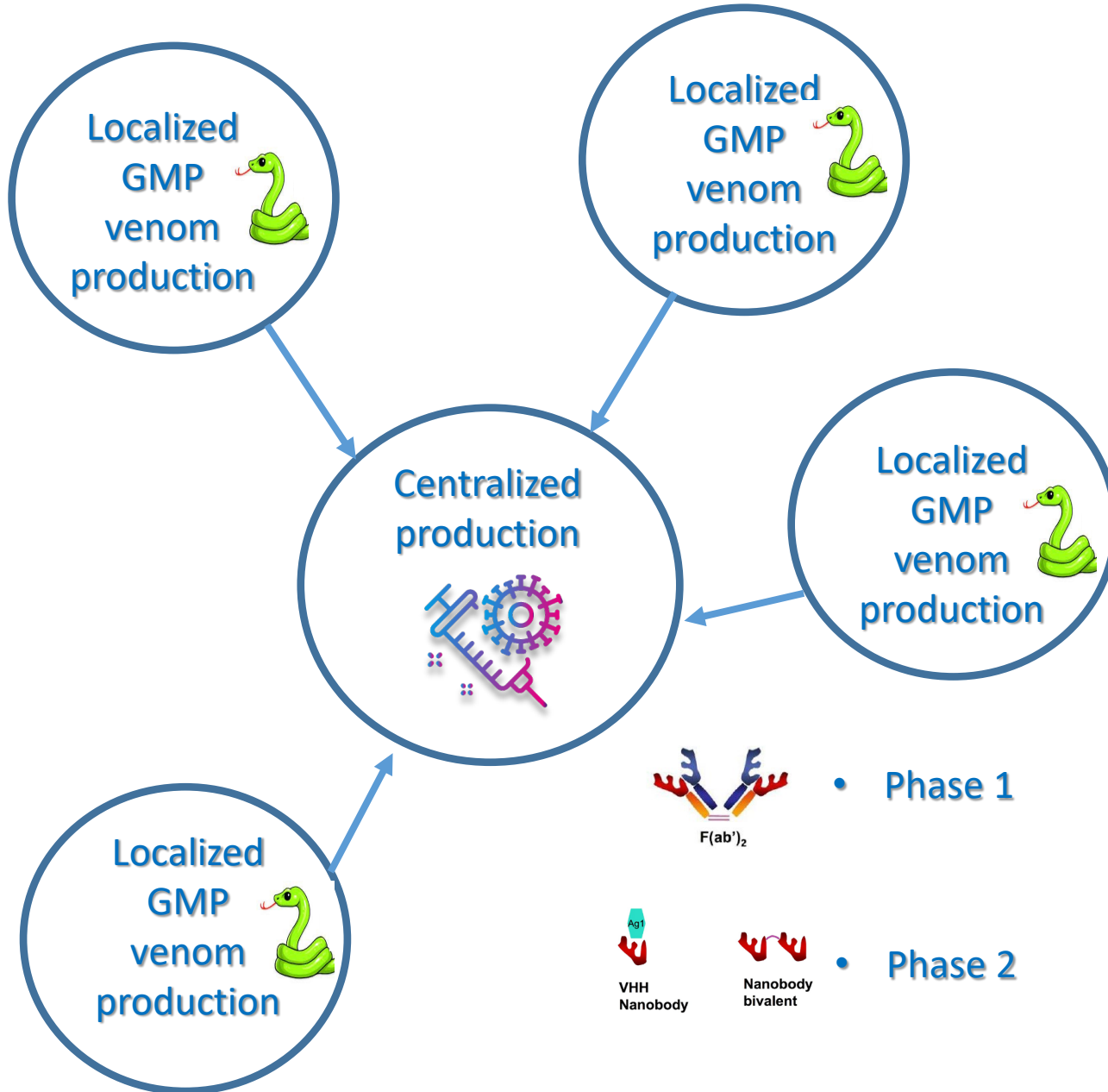
➔ Pasteur Network involvement

Potet et al. Toxicon (2021)

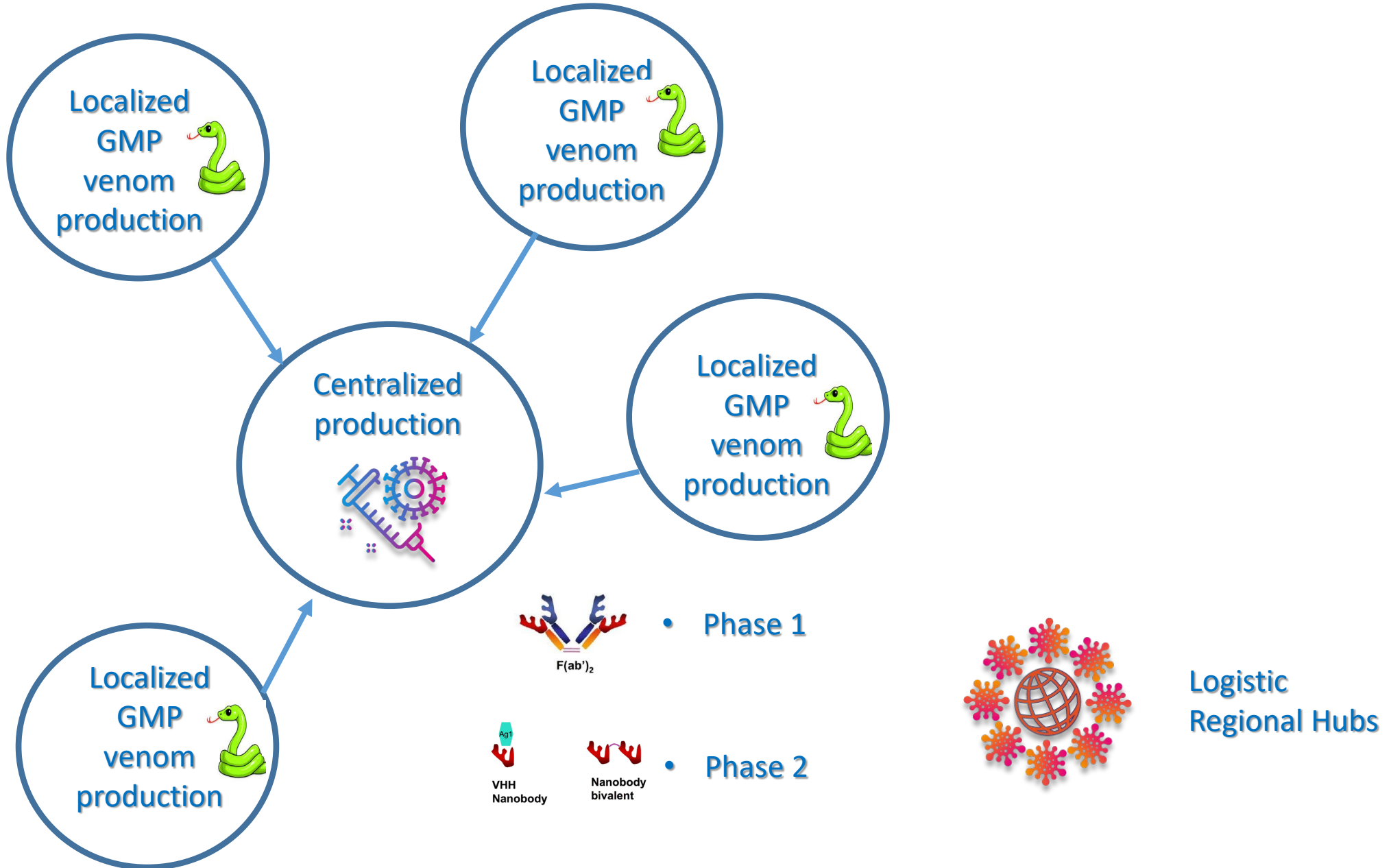
A dynamical & interconnected Pasteur network workflow



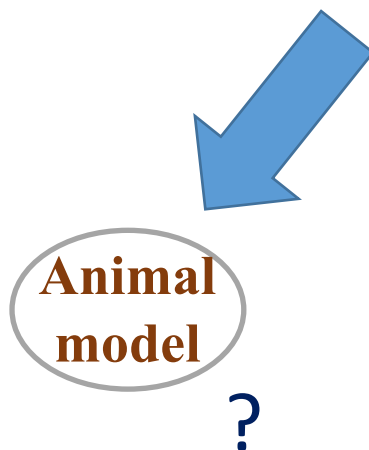
A dynamical & interconnected Pasteur network workflow



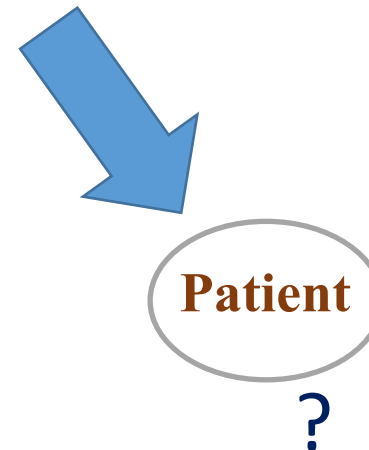
A dynamical & interconnected Pasteur network workflow



Pasteur Network Specific Research?



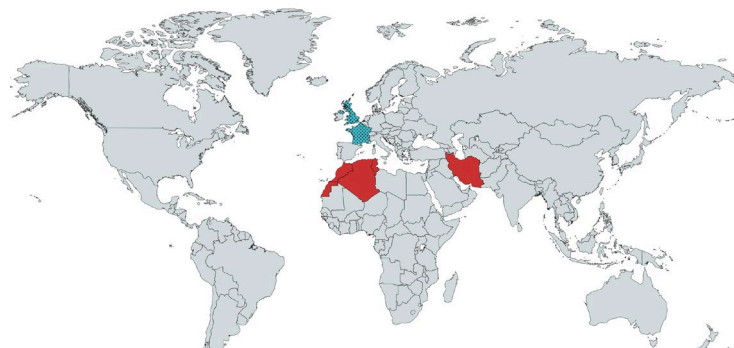
- 1. Specificity
- 2. Neutralizing capacity
- 3. Binding affinity
- 4. Epidemiology of the venom composition



- 1. Clinical trials
- 2. Regional Multi centric
- 3. Toxicology
- 4. Immunology
- 5. Phase 1, 2, 3, 4

Strategy option 3

Expand the next generation of anti-cobra-venom IPs initiative in LMI countries 'COBRA-NGaV' ?



Wellcome Trust proposal:

Discovering and Developing New Treatments for Snakebite

(BIOMEDICAL SCIENCE RESEARCH)

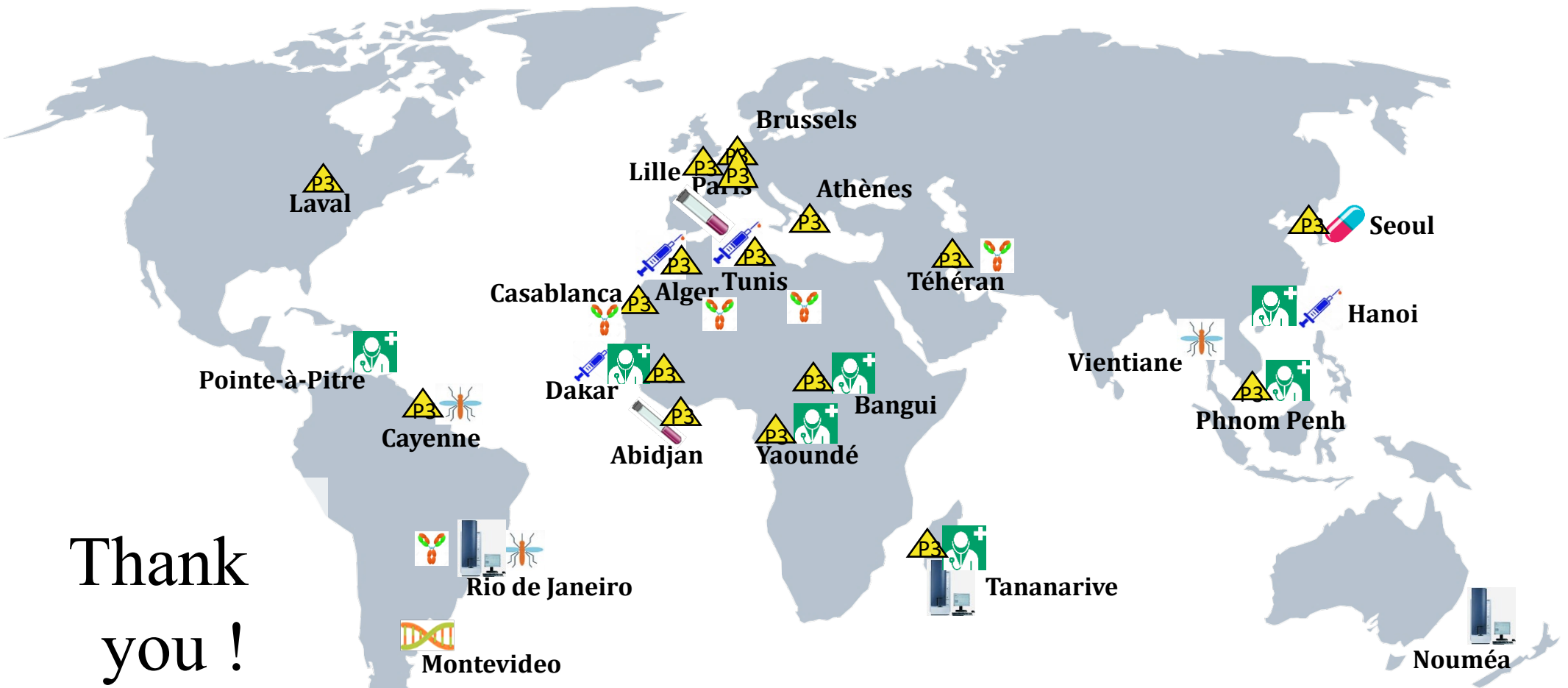
<https://wellcome.org/grant-funding/schemes/snakebite-grants>



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Institut Pasteur de Tunisie

24

A Living Network of Platforms and Hubs



Thank
you !

- Clinical research
- Vectopole
- Laboratory P3

- Malditoff
- Vaccine production unit
- Biobanking

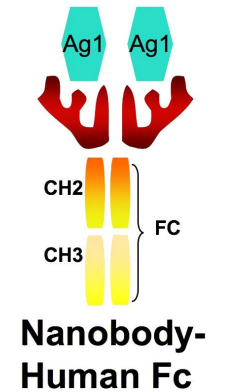
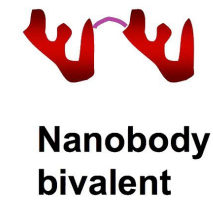
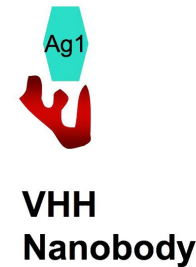
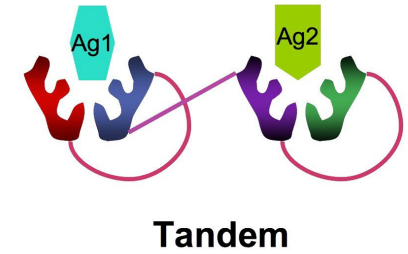
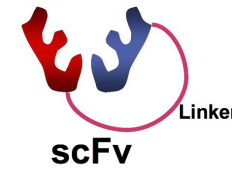
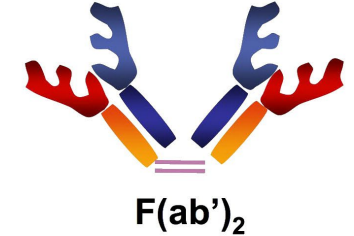
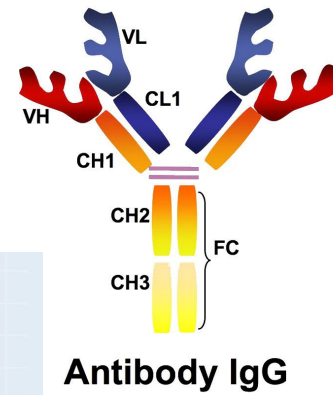
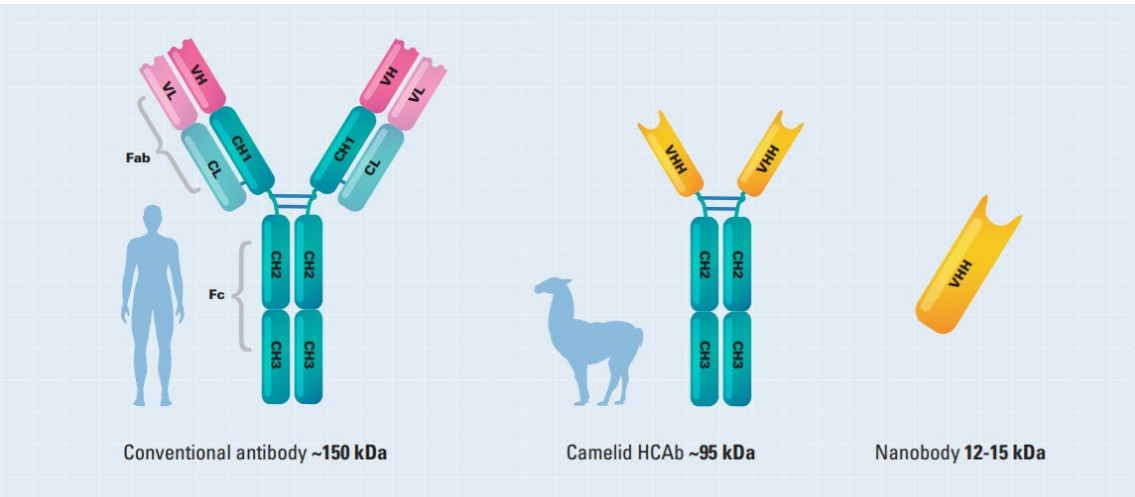
- Antivenom production unit
- Proteomic structural biology
- Drug screening



Thank you !

Antidotes against venomous animals: State of the art and perspectives

G.P. Espino-Solis, L. Riaño-Umbarila, B. Becerril, L.D. Possani*



Physiopathologie

PLA2s or PLA2 homologues (Myotoxins) :

Altérations cytoplasmique des myocytes (Myonecrose)

Altération de l'intégrité endothéliale (Hémorragie par rhexis)

Hydrolyse enzymatique de la membrane basale de la paroi vasculaire

Inflammation +++

Snake venom metalloproteinases (SVMPs) :

Atteinte microvasculaire (Syndrome hémorragique)

Destruction de la matrice proteique extra-cellulaire (décollement cutané, lyse cutanée, nécrose ...)

Hématotoxicité +++

Hyaluronidases :

Destruction de la matrice proteique extra-cellulaire (décollement cutané, lyse cutanée, nécrose ...)

Gutierrez et al. Nature (2017)

Resiere et al. Toxicon (2018)

Moreira et al. Toxins (2021) Pr Hatem Kallel

