The scorpion toxin model of AIDS : The concept of voltage-dependent sodium channel as a receptor of HIV-1.

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Ce concept de vaccin reprend le brevet de Biosantech –E.Loret sur la protéine Tat mutée (http://www.positifs.org/fr/publications/our-publications/242-c104-bis-hiv-therapeutic-vaccine-biosantech-erwann-loret-unjustifiable-attacks.html) pour lequel il explique le mécanisme d'action et identifie dans la glycoproteine gp41 un site conservé pour toutes les souches de VIH. Un nouveau vaccin comportant la protéine Tat mutée du brevet Biosantech et le site conservé de la gp41 qui est une toxine de scorpion apportera une vraie réponse prophylactique et thérapeutique.

This vaccine concept is based on Biosantech-E.Loret's patent on mutated Tat protein (http://www.positifs.org/fr/publications/our-publications/242-c104-bis-hiv-therapeutic-vaccine-biosantech-erwann-loret-unjustifiable-attacks.html) for which it explains the mechanism of action and identifies in glycoprotein gp41 a site preserved for all strains of HIV. A new vaccine comprising the Biosantech patent mutant Tat protein and the conserved site of gp41 which is a scorpion toxin will provide a true prophylactic and therapeutic response.

Tat Oyi vaccine cysteine-rich domain: Molecular homology with Conus Consors toxin CcTx and scorpion Leiurus Quinquestriatus Hebraeus alpha-like toxin Lqh3.
Tat Oyi vaccine, based on spontaneous retro-seroconversion of 23/25 Gaboneses, obtained significant results: Retro-seroconversion in a macaque and 2 beginnings of retroseroconversion
in 2 patients and 10 indetectable DNA patients after 3 years. Tat Oyi has 2 crucial mutations: C22S and F98E (which creates a 97-PE-98 motif with a cis-bond Pro-Glu). Protective IgM of innate immunity, possibly explaining natural chimpanzee AIDS resistance, are directed against 2 epitopes (Rodman TC 1992, 1993, 2001 ; Nicoli F, 2016):

the basic region and the cysteine-rich domain, also targeted by IgG. Protection of Thaï AIDS vaccine was conferred by a conotoxine-like HIV-1 V2 loop (Tran GMK, 2013). We searched cysteine-rich toxins (conus, scorpion) binding to voltage-gated sodium (Nav) channel in Tat by amino acid (AA) sequences and tridimensional (3D) structures comparison.
Results : 1°) Tat Oyi (9-42) is homologous to Conus consors CcTx 1-APWLVPSQIPTTCCGYNPGTMCPSCMCTNTC-32.
2°) Tat Oyi (39-44) is aligned with Lqh3 37-CG**F**KVGHGLA-46, Tat (35-QC**H**L/F-32) with Lqh3/Bom4/Bot1 63-EKC**H**F-67 ; Tat Oyi 29-R**K**C**Y**CNNS-22 with Lqh3/Bom4 14-H**H**C**FP**NSYC-22; Tat Oyi 96-D**PE**D-99 with 8-Q**PE**N-11 (OcyTx1 11-D**PE**D-14).
All the Lqh 3 active site AA (**P**9, **E**10, **H**15, **F**17, **F**39, **L**45, **H**66) are found in Tat Oyi (**P**97, **E**98, **K**28, **L**32, **F**38, **L**43, **H**13).
Tat Oyi residues **K**28, **L**32, **F**38, **L**43, **H**13 are almost 100% conserved in all Tat. (**H**13 replaced **H** 33 in 3D structure).
3°) TAT group O chimera (mainly O.CM.96.CMA102) has the COOH-terminus **YHC**S**KDSCN**C**CTRISGQ*YC** matching with AaH2/Boma6d/Bot2 14-**YHC**G**KNS**Y**CNEECTKLGE**SG**YC**-35.
Conclusions : Tat Oyi vaccine mechanism of action is a molecular homology with ligands of Nav channel (Conus CcTx and scorpion Lqh3); five Tat conserved AAs in all HIV-1 strains are implicated in Tat Oyi protection, by a partial cross-reactivity. This therapeutic vaccine is promising for a rapid development of prophylactic vaccine, as in rabies vaccine.

Envelope gp41 contains toxins of Androctonus Crassicauda : A cross-reactive vaccine
There is a scorpion toxin, mainly Androctonus Crassicauda (A.Cra, AC), in HIV-1 envelope gp41. We found in 2002 (13th ISHEID Conf, Toulon, France) scorpion toxin active sites **W**38, **R2** an **Y**5: HIV-1/2 /SIV gp41 chimera 662-A/E F/L N/D Q/KWASL**W**/FGN-672
α-toxinAc2/AaH2/Amm5, 8/Bot3/Lqh2 /Lqq5 A/E46,F/L15,N/D44, 37-Q**W**ASPYGN-44
HIV-1 gp41 MSD (Membrane Spanning Domain)…VNR 706-V**R**QG**Y**SPLSFQT-719
Scorpion α-toxinAc2/Bot9/Css2/Cn2,3 signal peptide…VES 1-V**R**DG**Y**-PVSLNT-10
The hydrophobic gp41 MSD corresponds exactly to the scorpion toxin signal peptide.
We completed here with α-toxin **Y**14, the α-helix 21-29, **GXC** motif and COOH-terminus :
HIV-1 B.US.WEAU160 gp41 791-EALKY-CWNLLQYWSQELKN-809
α-toxinAc4/A.Cra3/CsEV3/Ts5/AahIT1 10-DGCK**YgC**WNLLEYCTNECKD-29
HIV-1/HIV-2 824-EWTDRv**C**EIVQ**G**A**C**R-838
Scorpion Lqq5 28-E**C**TEK-CgELN**G**Y**C**Q-42
HIV-1 gp41 (in retro-inverso : from 737 to 729) 737-TGEP**R**DPG**R**-729
BmKM8 /α-toxinAc1, 4 COOH-terminus 54-S(R,E)I**K**DPG**K**-62
Gp41 COOH-terminal tail is exposed to the surface by carbohydrates (750-NGS-753, 816-NAT-818) and the Kennedy epitope 728-745.
Gp41 **SWSNKS** « 3S » is a potential therapeutic AIDS vaccine (Vieillard V, 2008):

Scorpion chimera COOH-terminus **C**KLA**C**Y-SVP-WNPTWS- RSNT**C**GKK
HIV-1/CPZ.cd90.ant gp41 ectodomain 598-**C**-KLV**C**YtSVPdWVP**SWSNKS**QTCAKN-624
It could be interesting to vaccinate with the 5 toxins (α-toxin Ac1, 2, 3, 4 /A.Cra3) of Androctonus Crassicauda venom, as it is highly cross-reactive with Old World scorpions, (as α-toxin Ac2 contains all the active site **R**/**K**2, **Y**5, **Y**14, **W**38, **P**41, **K**58, **R**/**K** 62); corresponding HIV-1 gp41 **R**/**K**707, **Y**710, **Y**795, **W**666, **L**/i669 **R**733, **R**729 are conserved; gp120 V3 loop **R**/**H**322, **R**/**Q**326 are only highly conserved. HIV-1 gp41 662-E**L**DQ/K**W**AS**L**-669 (entry fusion inhibitor T-20, enfurvitide), the target of 2F5 antibody, neutralizes primary isolates of African, Asian, American and European HIV-1 strains (**L**663, **W**666, **L**669 are conserved). In HIV-1 patients, the level of this antibody is very low. In HIV-1 gp41, α-toxin Ac2 is incomplete, as its COOH-terminus 48-CYKLPD**H**VRT**K**GPG**R**-62 is lacking and mimics HIV-1 B.US.RF gp120 V3 loop 309-CTRPN∗**R**KSIT**K**GPG**R**-326 (∗ is glycosylated NNT) (Tran GMK, 1989).
The link between TAT and gp41, 2 scorpion toxins, is Luman, a transcription factor : gp41 inhibits Luman (an inhibitor of TAT) ; Luman induces human herpes virus reactivation.
There are Androctonus toxins in Nef :
HIV-1 Nef chimera 120-YIPDWQNYT**K**GPGv**R**-134 137-YFGFCY-WKLV-146
A.Crassicauda α-TxAc2 49-YKLPDHVRT**K**GPG**R**-62, AaHIT4 34-YYGYCYfWKLA-44
α-defensin 1-4, a major natural immunity HIV-1 inhibitor in long term non progressors (Zhang L, 2003; Wu Z, 2005), is a scorpion venom family member and aligned with Nef (Tran GMK, 2003).
HIV-1 protease has a Buthus/A.Cra toxin (phylogentically, spider venom contains protease for preys digestion): BomPI, Bot2 56-VPIRIEGK-62, HIV-1 protease 11-VPIRIEGR-18, α-toxin Ac1 56-VPIK(P,D)SQ-63.
Until now no research was done on mutations of the Na+ voltage-gated channel in HIV-1 resistent patients : This could be helpful for HIV-1 cure, as observed in « the patient of Berlin » (by targeting the CCR5delta32 mutation).
Lethal Australian spider Atrax Robustus toxin active site matches with HIV-2 envelope gp120 V2 loop, in three-dimensional structure:
Spider key residues (4-KR-5, M18, K19, Y22, 23-AWY-25, Q27, C31) superimpose on HIV-2 residues (180-KK-181,M172, K173, Y183,186-AWY-188, Q190, C194).
To summarize, HIV-1 vaccine with the 5 α-toxins of scorpion A. Crassicauda (AC) venom has a broad spectrum and can protect against mainly gp41, and accessorily Nef, protease and some envelope gp120 V3 loops. A therapeutic vaccine with scorpion AC 5 attenuated α-toxins would evaluate this concept of molecular mimicry.

Ligands of Na+ voltage-gated channel are anti-HIV-1 drugs

In conclusion, HIV-1 contains many scorpion toxins, but devoid of any classical complete cysteine core structure; this means that its receptor is a sodium voltage-dependent channel and consequently HIV-1 can be inhibited by Na+ channel modifiers (vitamin B1, vegetal fatty acid omega-3, antiarythmics, local anaesthetics (procaïne), eugenol, antimalarials (quinine, chloroquine), antiepileptics, lithium, ginsenoside, tetrodotoxin. Tacrine (Fredj G, Maurisson G) was the first prototype in AIDS treatment, but was limited by its hepatotoxicity : The hydroxylated metabolite of Tacrine has the structure of grayanotoxin. Vegetal fatty acid

omega-3 has no toxicity. As Na+ channel does not mutate, no chemoresistence occur during treatment : This is a crucial advantage over drugs directed against HIV-1 proteins (reverse transcriptase, protease, integrase).