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AGREE ABSTRACTS

- MOLECULAR HOMOLOGY BETWEEN ALPHA-DEFENSIN AND SCRUB TYPHUS RICKETTSIA ORIENTIA TSUTSUGAMUSHI 56KD TYPE SPECIFIC ANTIGEN
- HIV-1 Protease Is A Metalloproteinase Containing A Copper-Binding Motif Gly His Lys (GHK) At Residues 68-70

NON AGREE ABSTRACTS

- The Scorpion Venom Model Of Aids: Scrub Typhus Rickettsia Orientia Tsutsugamushi 56kd Type Specific Antigen Has A Common Motif With HIV-1 Nef In The Alpha-defensin-like Region.
- Aids and Atherosclerosis: Homology Between Atherogenic Chicken Marek's Disease Herpes Virus and LDL Receptor
- The Scorpion Venom Model Of Aids: Feline Leukemia Virus (FeLV 61C Inducing Aids) Envelope Is Homologous To A Scorpion Venom
- Molecular Homology Between RANTES, MIP 1alpha, MIP 1beta Chemokines, HIV-1,-2 SIV Envelope GP120 V2 Loop And Scorpion Venom Tityus TS-VI

Toulon 2004 : Abstracts

13th International Symposium on HIV & Emerging Infectious Diseases

6 abstracts for Toulon :

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2 AGREE ABSTRACTS

Poster's form MOLECULAR HOMOLOGY BETWEEN ALPHA-DEFENSIN

AND SCRUB TYPHUS RICKETTSIA ORIENTIA TSUTSUGAMUSHI 56KD

TYPE SPECIFIC ANTIGEN

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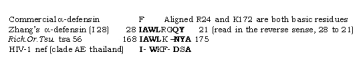
1) Zhang L.(2002) discovered an a-defensin isotype [differing by isoleucine 28 (Ileu 28 or I 28), instead of phenylalanine (Phe or F) in classical commercial a-defensin] as the natural protective factor against HIV-1 in long-term nonprogressors remaining a life without treatment.
2) Watt G (2000, 2001) remarked a beneficial effect of sera from scrub typhus Rickettsia (Orientia Tsutsugamushi) [Rick.Or.Tsu.]-infected HIV-1+ patients on HIV-1 replication, suggesting a protective cross-reactive antibody.
3) Tran M.K.G. described a molecular homology between Nef and a -defensin (Warsaw Conf., Poland, 2003), then between Nef and Rick.Or.Tsu. 56 Kd type specific antigen (tsa 56) (this Toulon Conf., 2004) centered on the common tetrapeptide GIRY. It is noteworthy that Zhang's a-defensin variant (I 28) is 20 times more protective against HIV-1 than commercial a-defensin (F 28), pointing to an important role for this isoleucine 28 residue.

METHODS:

We compared the amino acid sequence and tridimensional (3D) structure of a-defensin (I 28) and Rick.Or.Tsu. tsa 56.

RESULTS:



DISCUSSION AND CONCLUSION:

Rick.Or.Tsu tsa 56 is a perfect molecular mimicry of Zhang's a -defensin on the tetrapeptide IAWL, with a significant homology spanning 8 residues, suggesting that protection may be mediated by a cross-reactive antibody against HIV Nef sequence IWKFDSA. The trilogy (Nef, Zhang's a -defensin and Rick.Or.Tsu tsa 56) defines 2 homologous linear epitopes (centered respectively on IAWL and GIRY) located in proximity in a 3D space. For clade B and Thailand clade AE, vaccines with these Nef epitopes, or an anatoxine with Rick.Or.Tsu tsa 56, and passive immunotherapy (sera, monoclonal antibodies, Fab, Fv,É) could be designed as an interesting anti-HIV-1 therapy, as this Nef region is relatively conserved inside each clade.

Lengthy Version

HIV-1 Protease Is A Metalloproteinase Containing A Copper-Binding Motif Gly His Lys (GHK) At Residues 68-70

INTRODUCTION:

Antiproteases are very efficient molecules, however they rapidly induce cross-reactive chemoresistence with occurrence of multiple mutations (L10FIRV, K20MR, L24I, D30N, V32I, L33F, M36I, M46IL, I47V, G48V, I50V, I54VML, L63APQ, A71TV, G73SA, V77I, V82AFTS, I84V, N88DS, L90M), rendering their long term efficacy problematic.

METHODS:

We undertook a systematic screening of the complete amino acid sequence of HIV-1 protease, looking for some specific motifs which could have escaped to previous investigators.

RESULTS:

There is a classical typical copper-binding motif Glycine Histidine Lysine (Gly His Lys, or GHK) [K stems for Lysine] (Pickart L, 1980) at HIV-1 protease residues 68-70. For example, GHK is found in collagen I sequence, and released after proteolysis as a copper tripeptide (Maquart F.X., 1988). This 68-GHK-70, located far from the catalytic site, classified HIV-1 protease as a member of metalloproteinase family, with 2 symmetrical coppers. The function of copper seems important: Only rarely His 69 is mutated to Tyrosine (Tyr or Y) (treatment by lopinavir) and even then, the replacement of His by Tyr could be non functional, because both residues bind copper, although the copper affinity for His is higher. As HIV-1 Gag contains also GHK, and is the target of HIV-1 protease, it may be that copper, as a metal bridge, could contribute to gag

proteolysis.

DISCUSSION AND CONCLUSION:

A chemical design of new anti-proteases generation must take in account the chelation by the motif 68-GHK-70 of the 2 symmetrical coppers in protease dimer, to enhance efficacy and perhaps avoid chemoresistence, as far as copper is necessary for HIV-1 functional enzymatic activity. As a metalloproteinase, HIV-1 protease may be attacked by adequate antiprotease simultaneously at this copper Achilles' heel, what has never been done until now.

4 NON AGREE ABSTRACTS

The Scorpion Venom Model Of Aids:
Scrub Typhus Rickettsia Orientia Tsutsugamushi 56kd Type Specific Antigen Has A Common Motif With HIV-1 Nef In The Alpha-defensin-like Region

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INTRODUCTION:

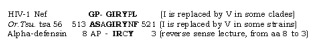
Watt G. (2001, 2000) found in Thailand that scrub typhus rickettsial infection by Orientia Tsutsugamushi (Or.Tsu.) was beneficial for HIV-1+ patients, by a cross-reactive immunity involving antibodies to a common epitope between HIV-1 and Or.Tsu. Elsewhere, HIV-1 Nef was found mimicking a member of the scorpion venom family: Alpha-defensin (Tran M.K.G., E.A.C.S. Warsaw Eur. Conf., 2003), the natural protective protein in long-term nonprogressors (Zhang L., 2002). We tried to determine precisely this protective cross-reactive epitope.

METHODS:

Comparison of amino acid (aa) sequences between HIV-1 proteins (Los Alamos databanks) and Or.Tsu. surface proteins [56 kD type specific antigen (tsa 56)].

RESULTS:

We found a common motif GIRY (or GVRY) between clade E Thailand HIV-1 Nef and Or.Tsu. tsa 56 (513-521):



P and S are commonly found on the tip of a loop; L and F are hydrophobic semi-conserved, A and G are space providing aa. The length is 9 aa, which is significant. Interestingly, this epitope is located exactly in the Nef region which mimicks a -defensin (Tran MKG, Warsaw 2003), suggesting a crucial functional role. A second epitope is published in this Toulon conference (Tran MKG, 2004).

DISCUSSION AND CONCLUSION:

A protective specific vaccine or immunotherapy (serotherapy, monoclonal antibodies or Fab, etc...) strategy may be developed on the basis of a homology between Thailand HIV-1 Nef and Or.Tsu. tsa 56 centered on the GIRY (or GVRY), with a better fitness between the corresponding HIV-1 Nef and Or.Tsu. strains than a blind serotherapy (as did Watt G. in 2001). The relatively conserved Nef sequence may be presented by heat shock proteins to dendritic cells (Srivastava P, 2002). This also confirms our scorpion venom model of AIDS and the efficacy of Tacrine.

Aids and Atherosclerosis: Homology Between Atherogenic Chicken Marek's Disease Herpes Virus and LDL Receptor

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INTRODUCTION:

Hypercholesterolemic, hypertriglyceridemic, diabetic, lipodystrophic AIDS patients are particularly prone to atherosclerosis, WHO's first cause of mortality in the world. Atherosclerosis may be of viral herpetic origin: Paterson (1950) discovered a link between Marek's disease virus (MDV) a poultry herpesvirus and coronary sclerosis in chickens. Fabricant CG (1973) found cholesterol crystals in cell cultures infected by a feline herpesvirus and in 1975 submitted chickens to a diet without cholesterol but infected by MDV: They developed an atherosclerosis of aortic, celiac, gastric, mesenteric and coronary arteries with cholesterol deposition and

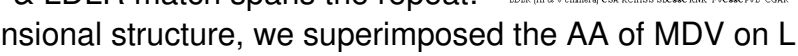
spumous cells. Chicken (Influenza, poliomyelitis) viruses may be transmitted to humans. MDV p53 inhibitor Meq induced a clonal arterial smooth muscle cell proliferation, coupled with an accumulation of phospholipids, free fatty acid, cholesterol and cholesterol esters. We try to elucidate MDV role in cholesterol deposition.

METHODS:

Amino acid (AA) sequence comparison and tri-dimensional structure superimposition.

RESULTS:

We found in MDV genome a 132 base pair, 40 AA long, repeated about 8 fold in some strains. A similar ~ 8 fold repetition of a 42 AA sequence occurs in LDL (or bad) cholesterol receptor (LDLR). In genetic familial hypercholesterolemia & Watanabe rabbit model, mutations occurred precisely in the LDLR. MDV & LDLR match spans the repeat:



In the LDLR flower tri-dimensional structure, we superimposed the AA of MDV on LDLR, by centering on cysteines C (C bridges ss).

DISCUSSION AND CONCLUSION:

MDV contains a viral LDLR, present during infection in the arterial (i.e. coronary) plaque, which captured and retained the bad LDL cholesterol in situ (MDV antigens were detected in arteries) provoking a fatty accumulation initiating atherosclerosis. Alimentary chickens must be analyzed for their safety (MDV absence) to avoid atherosclerosis, especially in AIDS. Anti-herpetics [i.e. propolis, better than aciclovir (Vinograd N, 2000)] and a vaccine (which exists for poultry) may be developed against MDV.

The Scorpion Venom Model Of Aids: Feline Leukemia Virus (FeLV 61C Inducing Aids) Envelope Is Homologous To A Scorpion Venom

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INTRODUCTION:

Retrovirus-induced AIDS has long-standing precedent in Feline Leukemia Virus (FeLV)-associated immunodepression (designated as FeLV-AIDS), occurring in cats with some isolates of FeLV. More cats die from the cytosuppressive consequences of FeLV infections (AIDS and bone marrow aplasia) than from leukemia itself. AIDS in cats is characterized by progressive weight loss, intractable diarrhea, lymphoid hyperplasia, lymphopenia, opportunistic infections (bacterial rhinitis, pneumonia, necrotizing stomatitis). Sequencing of the retrovirus envelope reveals a difference of 6 residues (sequence NVKHGA) between the fatal AIDS-inducing strain (FeLV 61C) and the benign strain (FeLV 61E) (Overbaugh J., Science, 1988: 906). Our objective is to understand why this strain 61C was so pathogenic conducing to fulgurant lethal AIDS.

METHODS:

Amino acid sequences comparison.

RESULTS:

We discovered that only AIDS-inducing strain 61C, but not benign strain 61E, could be aligned with a scorpion venom toxin from Centruroides sculpturatus Ewing (CsE). In the case of the benign strain 1E, the hexapeptide NVKHGA insertion after SPT disrupted completely the alignment:

AIDS-inducing FeLV 61C **DLC W E SPTGYP- PSKYGC**
CsE scorpion venom **DLC WCE TPT- YPLPNKS -C**
Benign FeLV 61E SPT *NVKHGA* GYPPSKYGC

A more extended alignment is found if chimeras of scorpion venoms and FeLV envelope are considered.

DISCUSSION AND CONCLUSION:

In cats, FeLV can kill by a fulgurant fatal AIDS. The AIDS inducing strain 61C differs from the benign strain 61E by an hexapeptide deletion ; this deletion permitted to align 61C with a scorpion venom, whereas 61E could not. Thus the concept of scorpion venom of AIDS (Tran MKG, 1989 ; Werner T., 1991) is found not only for HIV-1, but also for a lymphocytotropic leukemia virus in cats. Tacrine, which modifies the scorpion venom receptor (voltage dependent Na+ channel), may be tried and be beneficial in cat AIDS.

Molecular Homology Between RANTES, MIP 1alpha, MIP 1beta Chemokines HIV-1,-2 SIV Envelope GP120 V2 Loop And Scorpion Venom Tityus TS-VI

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INTRODUCTION:

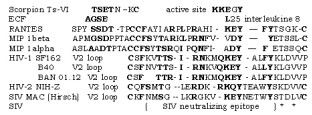
As chemokines (RANTES, MIP 1alpha, MIP 1beta) were implicated in AIDS physiopathology, we analyzed them in the context of scorpion venom model of AIDS. We try to analyze RANTES, MIP 1alpha, MIP 1beta mechanism of action.

METHODS:

The amino acid sequences of RANTES, MIP 1alpha, MIP 1beta were compared to those of eosinophilic chemotactic factor (ECF), scorpion toxins and HIV Los Alamos databanks.

RESULTS:

HIV envelope gp 120 V2 loop is a scorpion venom; the tri-dimensional structures of RANTES and scorpion venom were similar with one alpha-helix and 3 beta-strands in common. The RANTES active site residue Y 27 is homologous to scorpion venom Y 5. The best fit was with Tityus Serrulatus Ts-VI, a scorpion venom inducing a generalized allergy in mice. Asterisks * are HIV-1 RF escape mutant Y177, T179.



DISCUSSION AND CONCLUSION:

RANTES, MIP 1alpha, MIP 1beta chemokines were homologous to HIV-1,-2 SIV envelope V2 loop, as well as to scorpion venom Tityus serrulatus Ts-VI (which induced, like RANTES, an allergy).Thus RANTES can be integrated a larger concept of the scorpion venom model of AIDS (i.e. V3 loop, gp41, Nef; scorpion receptor voltage-dependent Na+ sodium channel; and the drug Tacrine, a modifier of Na+ channel).