IMMUNE THERAPEUTIC VACCINE (ITV)

A FUSION INHIBITOR AND IMMUNOMODULATOR

BY

HARRY ZHABILOV

HIV infection affected predominantly the immune system. The depletion of CD4 lymphocytes is predominantly due to the tropism of HIV for CD4 bearing cells. Because CD4 cells surface molecule functions as a receptor for the virus, HIV enters the cell through a specific interaction between the V1 region of the CD4 molecule on the cell surface and a specific region within the HIV envelope glycoprotein. The binding of gp120 to CD4 results in the exposure of the trans-membrane protein gp41, facilitating virus-cell fusion and viral entry. The frequent mutability of the gp41 and gp120 surface antigens confirms the conclusion that traditional approaches for creating immunity have no success against HIV. New approaches are using gp41 and gp120 complexes with new immunomodulators which increase their immunogenicity.

Zhabilov discloses a method for isolating and preparing an inactivated pepsin fraction (IPF), under license to Immunotech Laboratories Inc. specific to the HIV/AIDS indication as Immune Therpeutic Vaccine (ITV), useful for detecting and treating HIV-1 infection and some autoimmune and viral diseases. According to preliminary trials ITV, gp41, and gp120 bound together through –alpha-1, -alpha 2 and – beta serum fractions, which when formed inside the body blocks direct HIV-CD4 contact and at the same time triggers an immune reaction.

An essential element of this approach is using combinations of known and new immuno-creators with gp41 and gp120 antigens in order to increase their immunogenicity. This approach, using ITV as an immuno-creator results in creating a complex antigen having the properties of a vaccine. The next antigen complex triggers an immune reaction model with the participation of T- lymphocytes with –gamma –delta chains on their surface.

The results of experimental trials based on a mono approach show the action and effectiveness of ITV. Immunological results (by Dr. Bouic from Synecxa Labs in South Africa) are:

1. Increase in percentages and numbers of CD8, CCR5 positive cells in the treated patients.
2. Significant decline in CD8+, CD38+ cells in the treated patients.
3. Significant increase in both the CD4+ iNFg, secreting cells in the treated patients.

All of the above immunological changes show the immunological effect of ITV. These results can open a window for the creation of preventive vaccines against some diseases such as cancer, HIV, hepatitis, genital herpes.

Theoretically, there are four different ways to assault HIV-1 in the human body:

1. To use a chemical substance or specific antibodies destroying the HIV-1 virus

2. To block cellular receptors' viral attachment capability by chemical substance or specific antibodies

3. To block a viral receptor accomplishing viral invasion by chemical, biological molecules or specific antibodies.

4. To use nonspecific immunomodulators.

The best method to eradicate infection agents is a high titer of specific antibodies. The natural history of the HIV-1 contamination and AIDS shows a poor spontaneous antibody production against HIV-1. These are not significant antibody formation in cases with pure viral antigens' application into the body of AIDS patients. This means that infected organisms have some low possibilities to recognize viral antigens. The blocking of cellular receptors by chemical molecules or specific antibodies is possible . The viral aggression uses one cellular receptor – CD4 and two co- receptors –CCR5 and CXCR4. The first step in cell entry occurs when a glycoprotein on the viral surface (gp 120) binds to surface receptors on the target cell. The next step is a new binding between HIV-1 envelope protein and cell co-receptor CCR5. Once gp120 links to both receptors, gp41 (a transmembrane viral complex) undergoes a conformational change and literally brings the viral membrane into close proximity with cell membrane. Fusion of two lipid bilayers then occurs, thus allowing intracellular entry of viral contents (1). Human Genome Sciences Inc., has a US patent which covers the DNA molecules encoding CCR5. The company has the intention of CCR5 reproduction and to find some chemical molecules or antibodies which can block these receptors because " **people who lack a functional receptor gene are resistant to infection with HIV** ". This statement is not totally correct. In fact, individuals with **two mutant alleles** for the CCR5 receptor are protected against HIV infection. Homozygosity for the 32 deletion in the CCR5 gene is associated with **relative** resistance to HIV infection.
(2) In a preliminary meta-analysis of ten cohorts, haterozygosity for the CCR5 32 deletion was associated with 32% decrease in the risk of progression to AIDS with HIV –1 infected individuals and with a 2.5-fold lower median viral load (3). Other authors did not find significant association between heterozygosity of CCR5 (4). There are two more important investigations which suppose a low – rate possibility to eradicate HIV-1 by CCR5 cellular co-receptor blocking:

1. The HIV-1 infects new host cells by changing its tropism for target cells, which have no CCR5 receptors. These CD4 negative cell types may form important viral receptors for HIV-1 (5), (6).
2. Scientists from the Scripps Research Institute demonstrated that the HIV-1 virus, mutated rapidly by using another co-receptor after CCR5 blocking (5). Their report suggests that multiple co-receptors, not only CCR5 blocking may be necessary to capitalize on this strategy of HIV-1 inhibition.

TP-5, is a synthesized derivative of Thymopoietin, a naturally occurring hormone responsible for inducing T-cell precursors to differentiate and mature. An Increase of T-cells does not mean formation of specific antibodies. These products do not show stable results in HIV infection and other viral infections treatment.

The mechanism of action for use of thymic hormones with hepatitis B or HIV/ AIDS is unknown. In a few small clinical trials HIV/AIDS patients treatment with Thymosin Alpha-1 has been reported to increase :

1. IL-2 and alpha interferon receptors on T-cells.
2. Thymic mutation of T-cells.
3. Production of IL-2 gamma interferon and alpha interferon.

Further studies shows that after stopping treatment with Thymosin alpha-1 on HIV patients, the above results start to decline. At the end the report of German researchers finish with: " Until we see the data or hear from other studies , we do not know. " The observed hormonal immunomodulators with non specific actions show in the first moment of their use against viral infections including HIV,AIDS an increase of T-4 cells, and formation of specific antibodies. After stopping treatment, the virus level increases and new mutated viral strains are formed. As a result, these hormonal medications isolated from thymus and synthesized are characterized as non specific immunomodulators. They have a direct impact in elevating immunity as a whole, though they cannot be used as specific treatment for viral diseases. They can function as a support therapy with other medications.

A study at the Instituto di Patologia Medica in Bari, Italia, reported **thymopoietin** increases T-4 cells as a non specific immunomodulator. This does not mean formation of specific antibodies against viral infections. That fact allows continuous mutation of the HIV virus. Existing homeopathic nonspecific immunomodulators, isolated from herbs and plants, do not demonstrate the formation of specific antibodies against HIV infections.

(ITV), produced by Immunotech Laboratories, Inc. **is a brand new specific protein for the treatment of HIV and other viral infections. For the first time a naturally occurring strong binding with gp41 HIV-1 envelop protein "in vitro" was demonstrated.** The laboratory results obtained from ITV treated patients have shown the following:

1. Increase in WBC after the second week of treatment
2. A Two fold increase in MHC II cell expression as well as an increase in HLA-DR receptor expression after the first week of treatment
3. Increase in gamma/delta chain expression on T-cells after the second week of the treatment and their decrease after fourth weeks
4. A drop in CD4 cell count after the second week and gradual, uninterrupted increase after the third week
5. Dramatic increase in HIV –1 RNA by PcR the second week
6. Two times increasing in IgG after the fourth week
7. Two to ten fold increases in HIV –1 antibodies after the fourth week measured by Western Blot
8. Serum conversion from p24 positive to p24 negative
9. One to two log decrease in HIV –1 RNA by PcR, becoming undetectable one month after the end of the treatment

10. Reduction of HIV-1 infected cells' population as measured by PBMC's to undetectable levels.

The results of the above blood investigation may be interpreted as:

1. Increasing in WBC shows cell stimulation by ITV
2. Increase in MHC II and HLA-DR receptor expression verifies that ITV is being recognized
3. Increasing in gamma/delta expression demonstrates activation of the T-cells antigen receptors. Gamma/delta T-cell receptors share many cell-surface with alpha/beta T-cells and are able to secret lymphokines and express cytolytic activities in response to antigen stimulation.
4. A CD4 decrease after the second week suggests cytolytic activity against CD4 HIV-1 contaminated cells. This observation provides explanation why there is an increase of the serum viral load after the third week
5. The most important result from ITV treatment is a specific anti HIV-1 antibody increase in high levels. We can assume that ITV introduced in the human body binds with a high degree of affinity to gp41 HIV-1 envelop protein and a new build-up of super-antigen elicits antibody production in sufficient quantity to eliminate the viral infection.

ITV STUDY:

Observations of immunological changes in select patients during follow up

At the outset, it must be stated that since this study is placebo-controlled and double blind, the changes reported hereunder cannot be directly linked to patients who may be receiving the active investigational compound. However, it is tempting to speculate that the immunological changes detected in the lymphocytes of these patients may be induced by ITV.

A. *Phenotypic changes in whole bloods:*

It is apparent from the follow up samples of patients when analyzed on the flow cytometer that significant and sustainable changes occur in certain subsets of lymphocytes. These changes are observed following the period of active therapy (ie. After day 51 onwards). Once detected, these changes are sustained over time. Such changes include:

a) Increase in the CD4+CD45RO+CD62L population
b) Increase in the CD4+CD45RA+CD62L population
c) Appearance of a second CD4+ population having lower CD4 intensity but no increase in SSC: this implies a second CD4 cell population. Preliminary analysis of this population in isolation does not reveal these cells to be memory or naïve cells.
d) There is a parallel increase in the absolute CD4 cell counts when this phenomenon appears.

e) Increase in the CD8+CCR5+ population also in parallel to the above-mentioned parameters.

B. Functional changes over time:

Since some functional assays are conducted, it is interesting to note the following changes (in parallel to the phenotypic changes cited above):

a) Increase in the IFN-γ containing CD3+CD4+ cells post stimulation using p24 in vitro.
b) Decrease in the IL4 containing CD3+CD4+ cells post stimulation
c) Significant increase in the IFN-γ containing CD3+CD8+ cells over time.

Discussion:

Based on the above mentioned changes, it is possible that those patients who exhibit such changes over time are indeed receiving the active compound (ie. They are the active arm of the study). If so, then it would seem plausible that ITV induces a shift in the cytokine profiles in response to the virus. This 'shift' would be to a more beneficial TH1 mediated response and in so doing, indirectly enhancing the activity of the virus-specific CD8 cells and their cytotoxicity. IN parallel, there would be viral control and recovery of the immunological elements (memory cells, etc).

EXPLANATION OF THE COMPLEX BINDING OF IPF – gp41

The spontaneous physical binding of IPF with gp41 HIV- 1 envelope glycol protein is the most important quality of this peptide. Separately, on the electrophoresis gel both proteins move in opposite directions. When these proteins are mixed together before electrophoresis, the gp4l changes its direction and moves in the direction of the IPF as a common molecule. This result is very important for understanding the clinical activity of IPF.

The biological activity of IPF "in vivo" has been studied in healthy animals (mice, rats, and rabbits). The animals were injected with IPF equivalent to human IPF dose on an mg-per-kg-body weight. The morphological and histological investigation of the regional lymph nodes and thymus glands of these animals shows active germinal centers into the cortical follicles and medullar plasmocytosis. The immunological investigation of the sera from those treated animals does not show antibody formation against IPF.

Irreversibly- Inactivated Pepsin Fraction

Explanation of BIACORE Assay

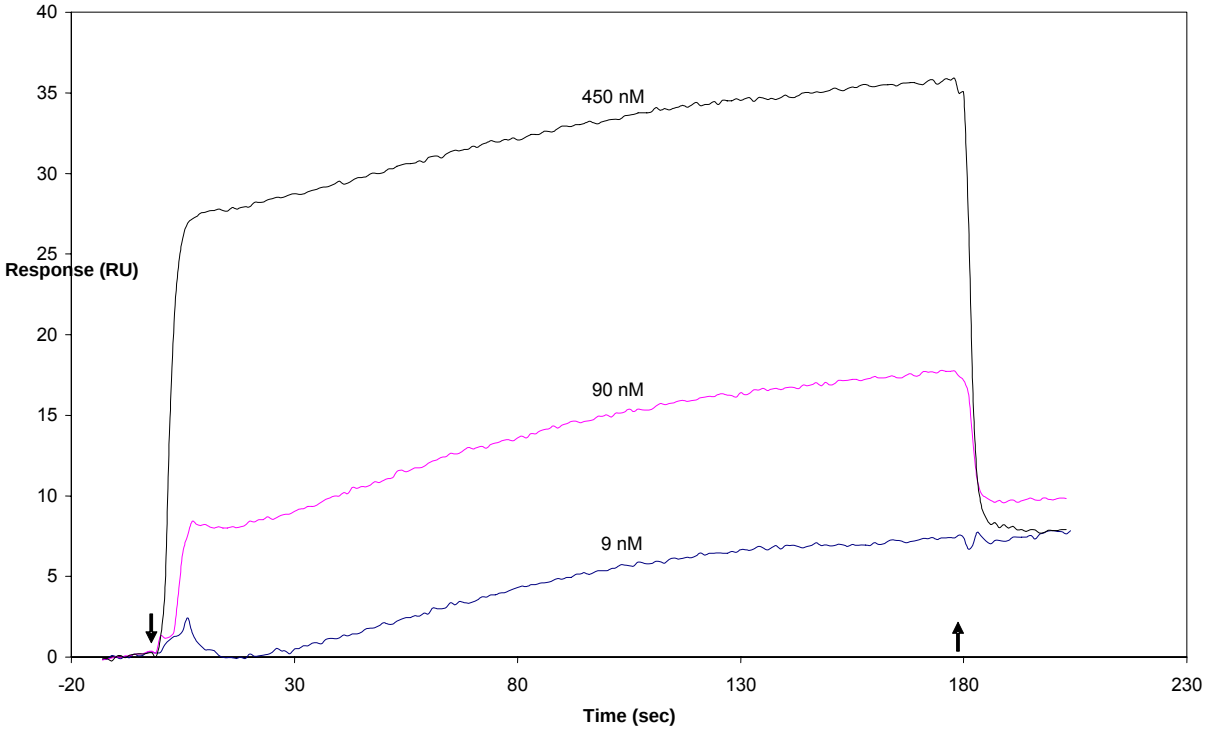
The assay was done using a BIACORE system, a technology based on three major steps as:

- Surface plasma response (SPR), which detects the mass concentration at the surface.
- Sensor chips, which provide surface conditions for SPR for attaching molecules of interest.
- Micro fluidic flow system that delivers sample to the surface.

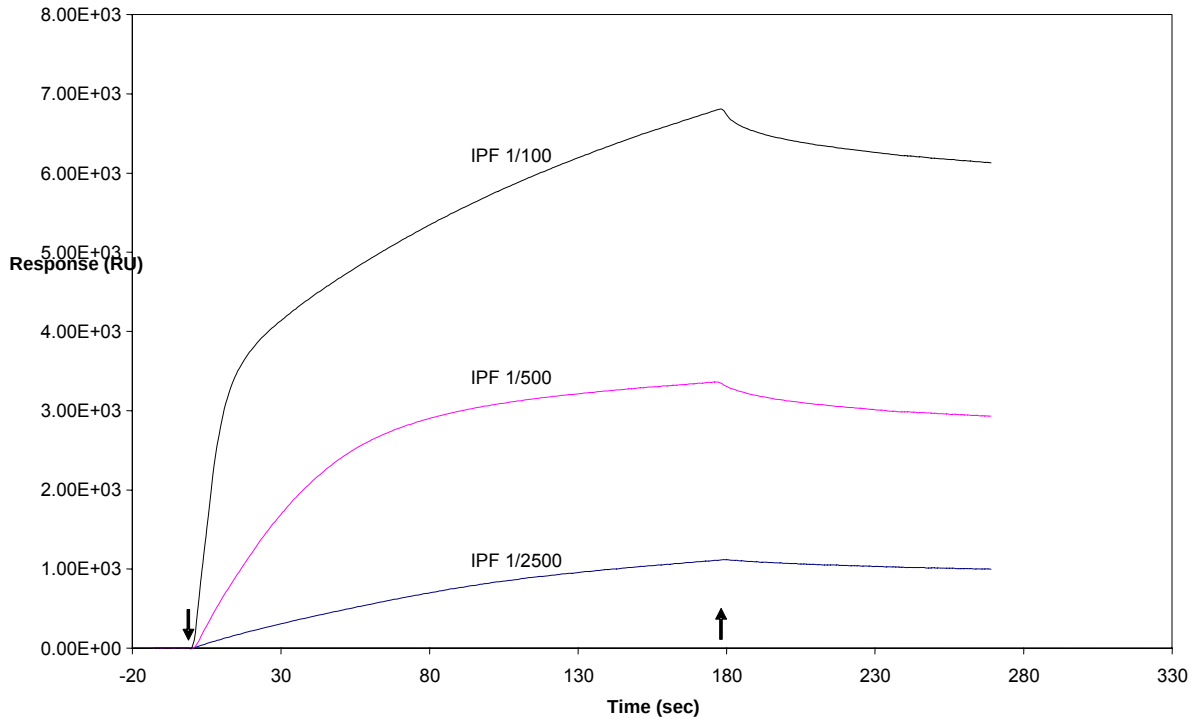
SPR – based biosensors monitor interactions by measuring the mass concentration of bio-molecules close to the surface. An SPR response is measured by local concentration changes. That response is directly proportional to the mass of the molecules, which bind to the surface. The SPR response can be expressed by resonance units (RU). One RU represents change of 0.0001 In the angle of the intensity minimum, it is equivalent to change concentration of 1 pg/ mm. The exact conversion factor between RU and surface concentration depends on properties of the sensor surface and the nature of the molecule responsible for the concentration change. The assay tracking the binding of IPF and CD4, gp41, gp120, human sera is very important because this way we detect the formation of the super antigen responsible for the specific immune response.

		Immobilized Target			
IPF	**CD4**	**gp41 (short)**	**gp120**	**gp41 (long)**	**H-Serum (M)**
	Yes. Fig.2, Fig.5	Yes Fig.3, Fig.5	Yes Fig.4, Fig.5	No	Yes. Fig.7
Yes?? Fig.1					
No					
No					
No					
Yes. Fig.6					

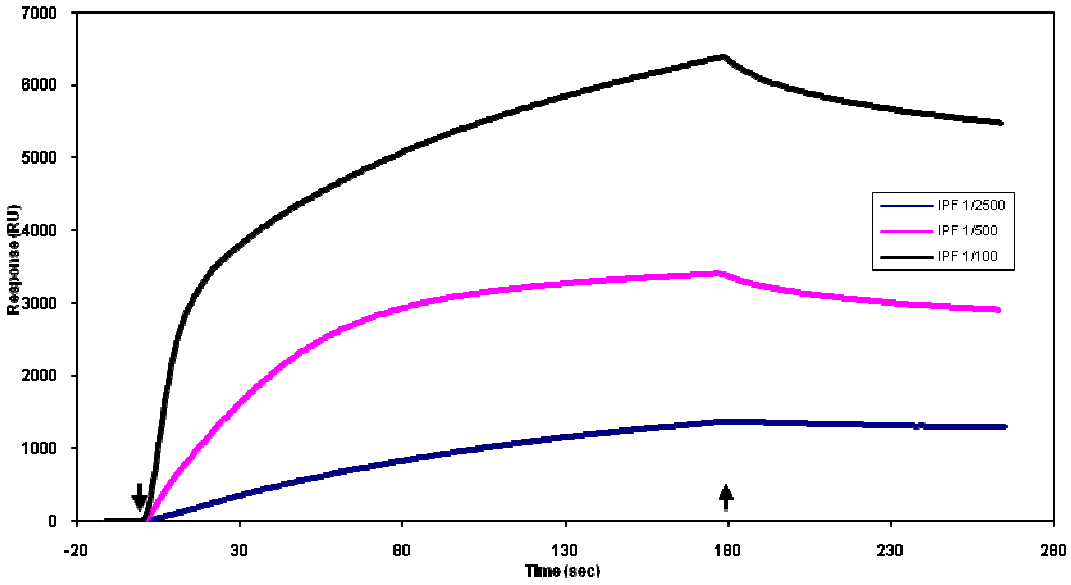
Binding of CD4 to immobilized IPF



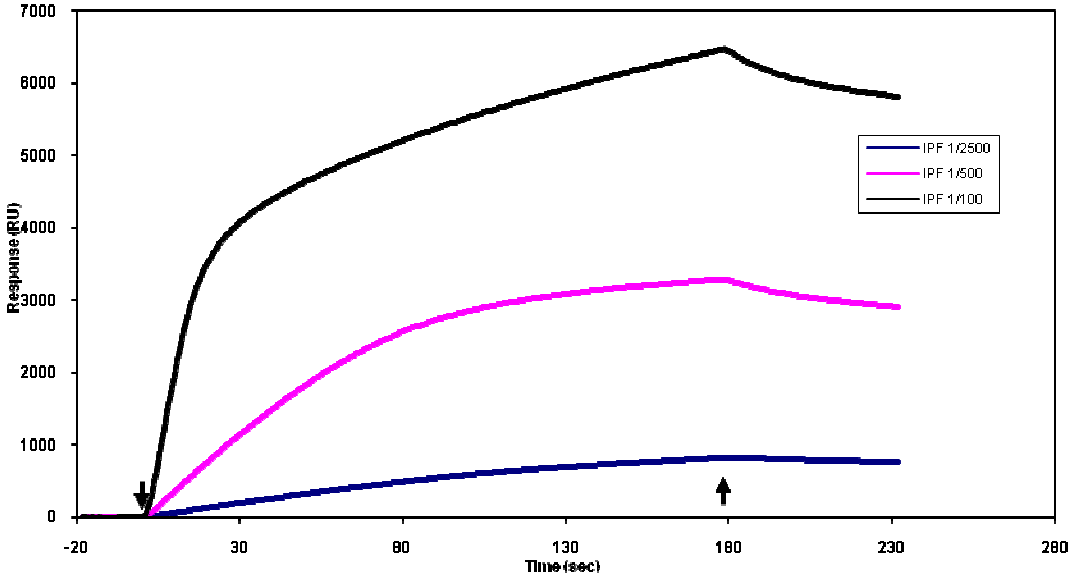
IPF binding to immobilized CD4



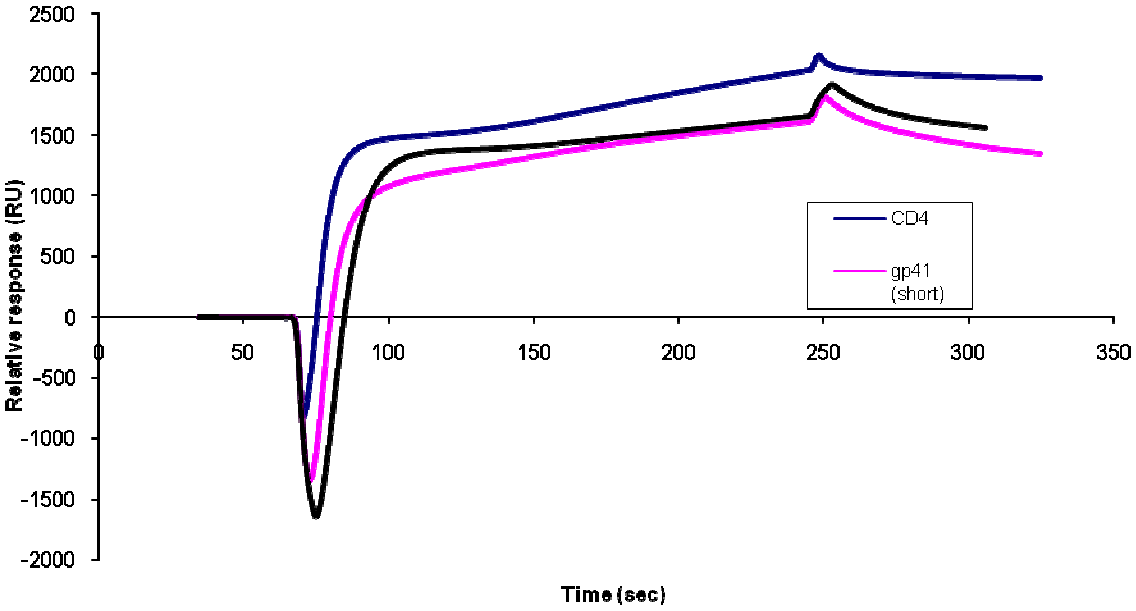
IPF binding to gp41 (short)



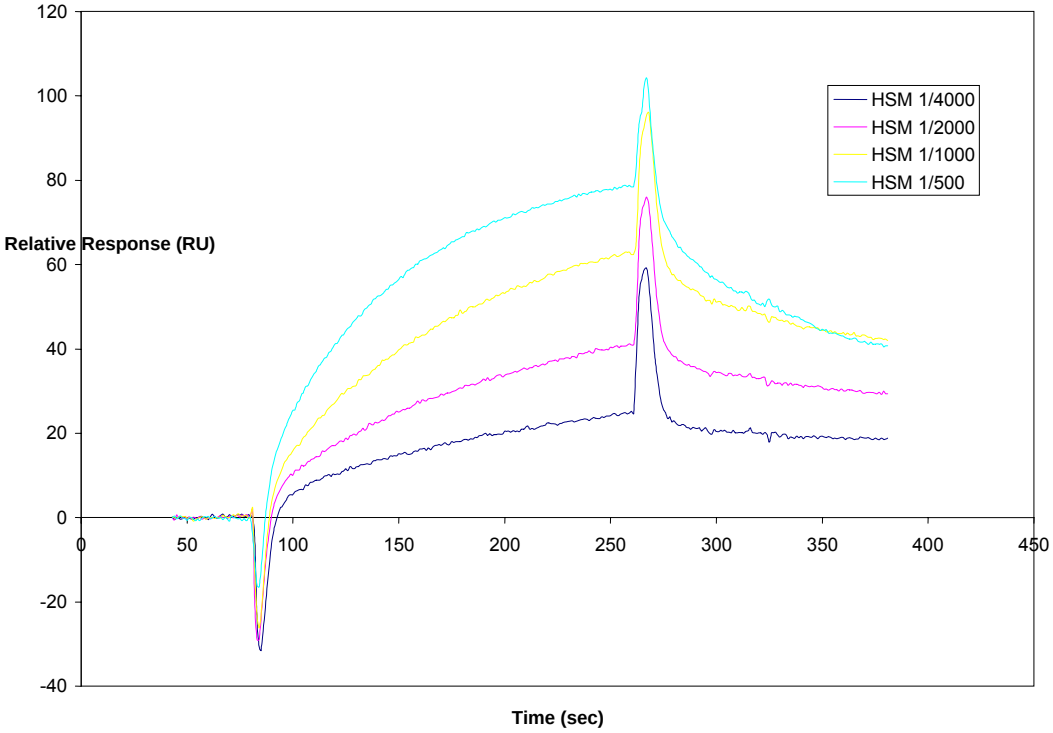
IPF binding to gp120

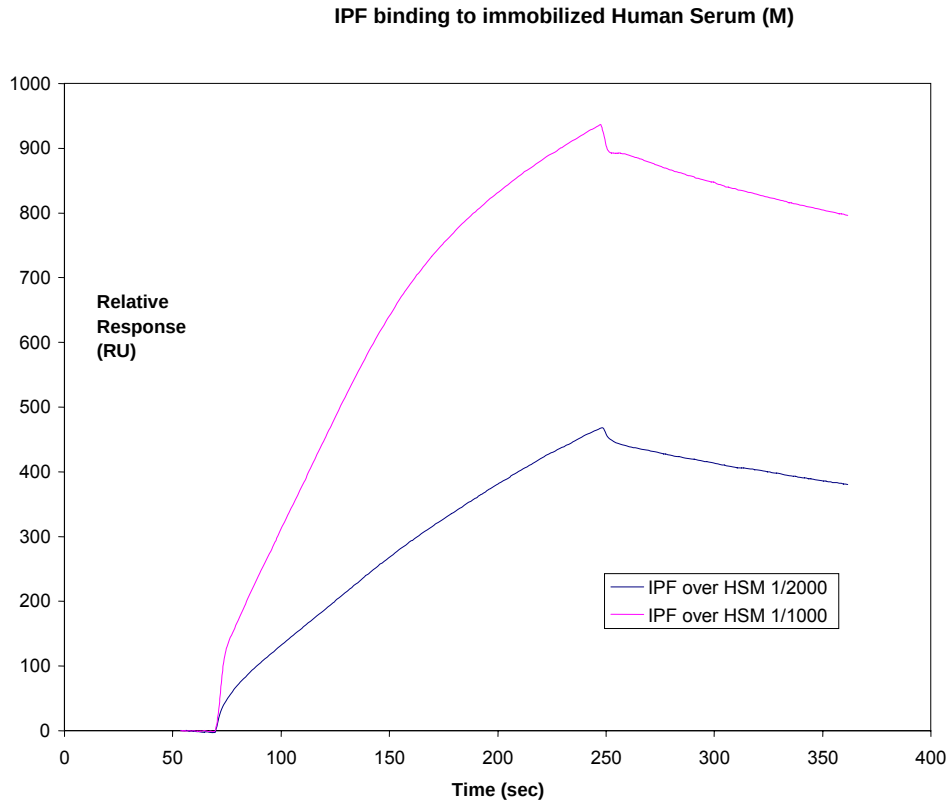


Relative response in IPF binding (1/100)



Human Serum(M) binding to immobilized IPF

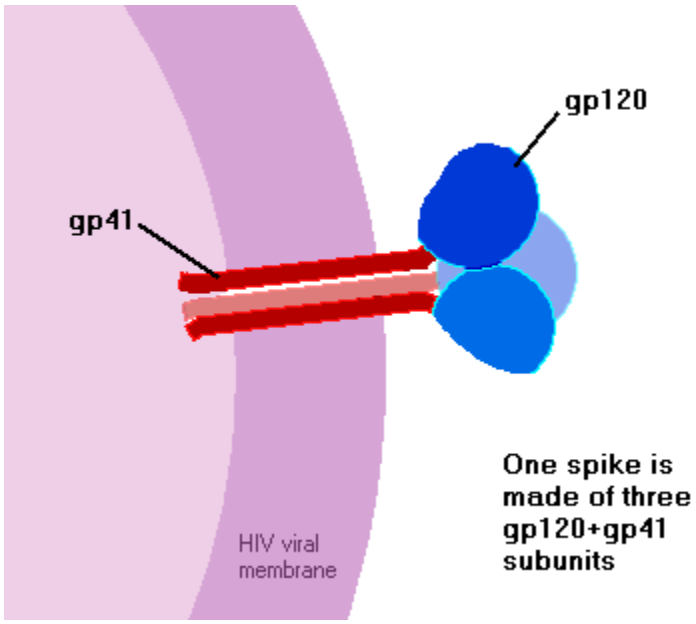




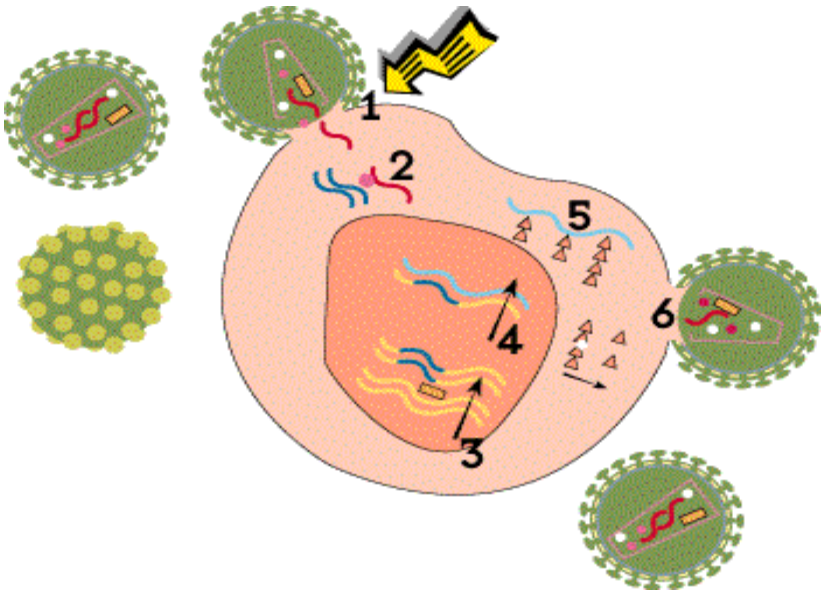
gp 120 gp 41 gp160 complex

The "env" gene in HIV encodes a single protein, gp160. (When gp160 is synthesised in the cell, cellular enzymes add complex carbohydrates and turn it from a protein into a glycoprotein - hence the name "gp160" rather than "p160".)

gp160 travels to the cell surface, where cellular enzymes again attack it, this time chopping into two pieces - **gp120**, and **gp41**. If and when new virus particles bud off from the host cell, these two pieces lie on opposite sides of the virus membrane. **gp120** sits on the outside of the virus particle, forming the virus's spikes, while **gp41** sits just on the inside of the membrane - each **gp41** being anchored to a **gp120** through the membrane.



How many spikes does a HIV particle have? It's a tricky question, but the answer seems likely to be **about 9 or 10**. This is a lot fewer spikes than you'll see on most diagrams of HIV! There's a bit of confusion since some studies have decided that HIV particles normally have 72 spikes, while some other studies have decided that they have normally no more than ten. It's hard to say for certain who's right....



A virus consists of an outer envelope of protein, fat and sugar wrapped around a set of genes (in the case of HIV, genetic information is carried as RNA instead of DNA) and special enzymes.

HIV has proteins on its envelope that are strongly attracted to the CD4+ surface receptor on the outside of the T4-cell. When HIV binds to a CD4+ surface receptor, it activates other proteins on the cell's surface, allowing the HIV envelope to fuse to the outside of the cell. Entry can be blocked by entry inhibitors.

EXPLANATION OF TWO MECHANISM OF ACTION OF IPF

When we are talking for the cancer diseases we have to say that one possibility for cancer treatment is to induce specific cytotoxic T-cells (CTL) responses against tumor cells. There are many mechanisms by which tumor cells can nonspecifically interfere with the expression of immunity in the host. Maybe IPF binds to at least one jet unidentified receptor restricted to antigen – presenting cells (APCs). IPF maybe is able to mediate maturation of dendrites cells as determined by up-regulation of MHC class-ll, CD86 and CD83 molecules, section of pro-inflammatory cytokines IL-12 and INFα, and enhanced T-cells stimulatory capacity. IPF increase synthesis of Th-1 cells. The helper T_1 cells elaborate cytokines INFγ, IL-2 that selectively promote cell-mediated immune response.

Secreted lymphokines activate T cytotoxic-cells macrophages, NK cells and B-cells.

Cytotoxic lymphocytes play a prominent role in host defense against infection by viruses, because proteins encoded by these pathogens enter the endogenous pathway for antigen presentation and therefore are expressed on the surface of the infected cell as a complex with class I MHC- proteins. The ability of Tc lymphocytes to lyses cancer cells that express tumor specific antigens as well as providing an effective mechanism of supplement specific ant-tumor response. And finally IPF shows fundamentally different mechanism of action compared to already known thymus hormonal products. That difference makes IPF winner in the fight against viral diseases.

Four major reasons which are the foundation for giving the green channel for IPF:

Complete absence of any toxicity compared to other antiviral products in recent years toward damage of liver and kidney functions. Good tolerance in application of IPF, Improvement in patients' condition measured by clinical and laboratory results. Possibilities for out-patient application and relatively short period of application-8 weeks.

The fusion inhibitors (FIs) T-20 and T-1249 are currently in Phase III and Phase I/II clinical trials, respectively. The mechanism of action of these FIs targets a structural transition in the viral envelope glycoprotein gp41 required for membrane fusion and virus entry. Genetic analysis of resistant virus isolates supports this mechanism. A recent report suggested that virus tropism and coreceptor preference modulate virus sensitivity to T-20 (J. Virol.74: 8358). To further test this possibility, a large number of primary isolates were characterized for FI sensitivity and coreceptor usage. Methods: Virus infectivity assays included infectious center assays in cMAGI cells, p24 levels in activated PBMCs, and a luciferase reporter gene assay for envelope-

pseudotyped virus. Virus isolates were obtained from an ongoing T-20 clinical trial, T20-205 (111 isolates), an acute seroconvertor study (33 isolates), and from the NIAID Reagent Repository. Virus stocks were prepared in activated PBMCs. Isolates were typed for coreceptor phenotype using either (a) relative infectious titer in MAGI (expresses CXCR4 (X4)) versus cMAGI cells (expresses X4 and CCR5 (R5)), (b)SI/NSI phenotype in MT-2 cells, or (c)U87 cells expressing CD4 in conjunction with either CXCR4 or CCR5. In addition, cloned pseudotyped viruses containing genetically linked envelopes (from serial patient isolates) representing X4, R5, and dual-tropic viruses were evaluated. Results: The geometric mean IC50 concentrations for T-20 from the T20-205 clinical isolates were 14 ng/ml and 12 ng/ml for X4-tropic and R5-tropic isolates, respectively. Similar potencies were noted for viruses from the other cohorts, including paired NSI-SI isolates from patients whose viruses switched coreceptor phenotype. The T-1249 IC50 on average was about 4-fold lower than that of T- 20 but also displayed no differences between the X4 and R5 isolates. Three pseudotyped viruses containing full-length envelope clones from the same patient were equally sensitive to the FIs despite each clone exhibiting X4, R5 and dual X4/R5 phenotypes. Conclusion: Virus coreceptor usage does not modulate sensitivity.

FUSION INHIBITORS: T-20 and T-1249 CHUGGING AHEAD

For inhibitors of fusion such as T-20 and T-1249, no such general safety concerns have been forwarded. These compounds are protein molecules (T20 has 36 amino acids) that basically bind to gp41 and prevent it from coiling up to reel the cell and virus together-preventing fusion. With T-20 nearing completion of its phase III development and T-1249 showing no red flags in phase II, the availability of these drugs to patients sometime soon seems likely. And although both agents have shown significant activity with little evidence of systemic toxicity in clinical trials to date, they are seriously limited by the fact that they are large peptides that cannot be absorbed from the gut. They must therefore be injected (twice daily) and can result in sometimes troubling injection site reactions.

In a 48 week update of T20-206 (Abstract 418-W)-a study comparing abacavir, ritonavir-boosted amprenavir and efavirenz to the same regimen + 3 separate doses of T-20 in a total of 71 patients failing PIs at baseline-Roche-Trimeris presented data confirming previous impressions. Over 48 weeks, approximately 70% of subjects across T-20 arms experienced injection site reactions. Of the subjects with reactions, about half in each T-20 arm reported that these were mild; half reported at least some that were moderate in severity or worse (only 3 of 54 T-20 treated patients discontinued the drug as a result). So while the tolerability of long term T-20 for widespread clinical use is an open question, there were still no notable differences in systemic toxicity between the T-20 and no-T20 groups over the full 48 weeks of T-20-206, and activity of the combinations with or without T-20 reported last year at 16 weeks-slightly favoring the T-20 arms-appeared sustained over 48 weeks.

(**editorial note:** patients receiving the non T20 regimen in that study had 37% <400 copies/ml and 37% <50 at week 48; patients in the 3 T-20 dose arms had 55% <400 and 47% <50. The T20 group appeared to sustain benefits better than the non T20 group. In the T20 group, 69% had <400 and 35% <50 at week 12 compared to 55% and 47% respectively at week 48. In the non T20 group 58% had <400 and 32% had <50 at week 12, compared to 37% <400 and 36%

<50 at week 48. In the 3 T20 dose arms the viral load reduction was -2.24 log at week 12 and it was -2.24 at week 48, showing a sustained result. But in the non T20 group the viral load reduction was -2.13 at week 12 and -1.87 at week 48. The CD4 increase was 132 in the T20 group vs 90 in the non T20 group. This data was not powered for comparison so the differences may not be significant. As well, the poster containing this data did not specify what type of analysis was performed, if results were on-treatment or intent-to-treat).

According Chris E. Baldwin in his article HIV-1 drug – resistance and drug- dependence " In our report on the in vivo emergence of T-20 dependent virus we described for the first time an HR2 amino acid change that was involved in T-20 resistance . Sequence analysis revealed the acquisition of the known

T-20 resistance mutation after 32 weeks of terapy was not only highly resistant to T-20 , but also critically dependent on the T-20 peptide for its replication . Briefly resistance to T-20 is caused by the GIA mutation in HR1 which weakens the interaction with both T20 resistance and HR2 (gp 41 6- helix bundle formation). "

ATTACHMENT INHIBITORS

Focus at this year's conference shifted to the progress in clinical development of two candidate attachment inhibitors that block the attachment of HIV gp120 to CCR5 or CXCR4. These were first introduced to a general audience at last year's conference: Schering-Plough's SCH-C and AMD-3100 from AnorMed.

CCR5: SCH-C TOXICITY

Unlike most other attachment and entry inhibitors, SCH-C is a small molecule that has excellent absorption from the gut (60-90% bioavailability), low protein binding and a prolonged effect after ingestion (~25 hours) in addition to potent antiviral properties. SCH-C had previously shown potent activity in its first phase I trial but had also been noted to cause significant QT prolongation (an electrocardiographic abnormality that, when extreme, can herald life-threatening cardiac arrhythmias). In an oral session on Monday (Abstract 1), M. Laughlin from the Aaron Diamond AIDS Research Center presented detailed results of another phase I experiment in using a range of lower doses of the drug that was somewhat if not entirely reassuring. The doses tested delivered 25 to 200 mg every 12 hours (as compared to the 400mg/day that was toxic in the first trial) to 12 ART-naive patients with NSI-or CCR-5 using-virus. Treatment was monotherapy. Laughlin reported data on the initial low dose group (25 mg). Activity was potent over 10 days with 10/12 patients achieving a 0.5 log (3-fold) drop in viral load and 4/12 dropping more than 1.0 log, or 10-fold. Two patients had no response at all, for reasons that were not clear. Tolerability was better than at higher doses, however 3 patients had headache and 2 complained of bad taste. Most significantly, there was consistent and progressive QT prolongation, to a mean of 11 msec at 10 days of therapy. While this degree of prolongation did not cause the trial to be prematurely terminated for safety, it is clinically meaningful and might represent a serious problem for this particular drug to go forward. These results were taken to indicate that CCR5 is a "valid target" for inhibition; however the potential

safety concerns remain very troubling and are very likely to limit progress of this particular compound. (editorial note: the company developing this drug, Schering Plough, says they are proceeding ahead to the next study and so far do not see a safety problem indicating stopping development of SCH-C. Schering has another drug, SCH-D, a backup drug for the C drug).

Another CCR5 blocker named PRO 140 is an antibody molecule that specifically targets CCR5, and showed impressive activity in a mouse model; some Merck compounds are also undergoing preclinical development and the results of these studies will be the subject of future meetings.

CXCR-4: AMD-3100 STUMBLES

Among the CXCR-4 inhibitors, the granddaddy of compounds is AnorMed's AMD3100, a bicyclam compound that had appeared highly potent in pre-clinical studies but like IPF, has to be given by either subcutaneous or intravenous injection. In a poster presentation (Abstract 391-T), Hendrix and colleagues presented data from a trial in which 40 subjects with stable or no ART were treated in a dose-ranging study to a maximum dose of 160 mcg/day. Antiviral effect was minimal, with no patients reaching the 1.0 log drop definition of successful activity and only 5 having a greater than 0.5 log drop. Despite this, side effects were significant with a majority of patients in all cohorts developing numbness or tingling, atrial and ventricular arrhythmias; 2 developed low platelet counts. The trial was stopped early and the drug is not likely to move forward in its current formulation.

A number of surprising studies showed that predictions as to how viruses might adapt to attachment inhibitors may be wrong. For instance, Xu and colleagues (Abstract 398-T) presented evidence that laboratory viruses that evolve high-level resistance to SCH-C in cell cultures are not associated with a switch to CXCR4, but rather simply attach more firmly to CCR5. The possible results of this kind of adaptation on disease course are completely unknown. In another poster, Van Rij and colleagues from the Netherlands (Abstract 394-T) showed that CXCR-4-using "SI" variants that occurred naturally in a patient with AIDS were actually less sensitive than earlier viruses from the same patient that could use both CXCR-4 and CCR5. This may suggest that even CXCR-4 inhibitors could lead to an "X4 switch"-a somewhat scary possibility if these were to be used in patients with early infection. All in all, the 1st generation of attachment inhibitors have not fared very well in their early trials, and the future of both CCR-5 and CXCR-4 inhibition remain clouded by doubt.

OTHER CANDIDATE ENTRY INHIBITORS

The "holy grail" of entry inhibition is the search for small molecule entry inhibitors that may be given orally. [Abstract 309 gave an update on this search at NIH]. For now, clinicians are trying to figure out ways that injectable fusion and entry inhibitors may be used-for instance as part of "deep salvage" therapy for treatment-experienced patients, "induction" therapy for treatment naive patients, or in eradication protocols. If "cellular resistance" proves to be important as some people think (with cells actively pumping drug out of the interior), then drugs working on

the outside of the cell may ultimately be critical tools in our armamentarium. Interest in attachment and fusion inhibitors appears to be here to stay. o the FIs T20 and T1249.

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