12-1-2000

Technology evaluation: PRO-542, Progenics Pharmaceuticals inc.

Muhammad Mukhtar
Dorrance H Hamilton Laboratories, Department of Medicine, Jefferson Medical College, Philadelphia, PA 19107, United States, Muhammad.Mukhtar@mail.tju.edu

Zahida Parveen
Dorrance H Hamilton Laboratories, Department of Medicine, Jefferson Medical College, Philadelphia, PA 19107, United States, Zahida.Parveen@jefferson.edu

Roger J Pomerantz
Dorrance H Hamilton Laboratories, Department of Medicine, Jefferson Medical College, Philadelphia, PA 19107, United States, Roger.J.Pomerantz@mail.tju.edu

Technology evaluation: PRO-542, Progenics Pharmaceuticals Inc

Muhammad Mukhtar, Zahida Parveen & Roger J Pomerantz

Address
The Dorrance H Hamilton Laboratories
Department of Medicine
Jefferson Medical College
Thomas Jefferson University
Philadelphia
PA 19107
USA
Email: Muhammad.Mukhtar@mail.tju.edu

Current Opinion in Molecular Therapeutics (2000) **2**(6):697-702
 ISSN 1464-8431

Progenics's rCD4-IgG2 (PRO-542) is a recombinant fusion protein, which has been developed using the company's Universal Antiviral Binding (UnAB) technology, and is in phase I/II clinical trials for the treatment of human immunodeficiency virus type I (HIV-1) infection [273391].

At the beginning of 1997, Progenics received a Phase II Small Business Innovation Research Program (SBIR) grant from the National Institute of Allergy and Infectious diseases (NIAID) to fund the development of PRO-542 [236048]. A further grant of $2.7 million was awarded in August 1998 for the clinical evaluation of PRO-542 and other anti-HIV therapies [294200].

Progenics is collaborating with the Aaron Diamond AIDS Research Center (ADARC) in New York and the Center for Disease Control and Prevention in Atlanta [178410]. In February 2000, Progenics and Genzyme Transgenics Corp signed an agreement to continue the development of a transgenic source of PRO-542. Genzyme will develop transgenic goats that produce PRO-542 in their milk in exchange for undisclosed fees and milestone payments. Genzyme will supply PRO-542 to Progenics for clinical trials with a possibility for eventual commercial supply [357291]. Following on from this, in October 2000, Progenics received an SBIR grant to fund a two-year project with Genzyme Transgenics into the development of cost-effective methods for the manufacture of PRO-542, by optimization of the production of the drug in the milk of transgenic dairy animals [385982].

In August 2000, Punk, Ziegel & Company predicted that Progenics Pharmaceuticals will become sustainably profitable in 2003 following the launch of PRO-542 and GMK (Progenics Pharmaceuticals) in 2002 [390063].

Originator Progenics Pharmaceuticals Inc

Licensees Aaron Diamond AIDS Research Center; Genzyme Transgenics Corp

Status Phase II Clinical

Action HIV-binding agent

Indication Acquired immune deficiency syndrome, HIV infection

Biotechnology Protein (Fusion)

Synonyms Antibodies (HIV), Progenics, rCD4-IgG2

Introduction

PRO-542 is a universal antiviral-binding (UnAB)-based therapy. UnAB units are genetically engineered antiviral molecules that mimic permissive cell surface attachment regions. PRO-542 is a hybrid protein, incorporating the HIV-binding region of CD4, which is required by HIV to attach to host cells (T-cells) and initiate infection [383657]. PRO-542 acts as an attachment inhibitor, by binding to a viral surface glycoprotein, gp120, thus preventing HIV from attaching to the CD4 molecules on T-cells.

Since the discovery of HIV-1 interaction with CD4, several therapeutic strategies have been employed for the prevention and treatment of HIV-1 utilizing CD4-based therapeutics [383655], [383666]. A soluble form of CD4, termed sCD4, was developed as a 'molecular decoy' that binds to HIV-1 gp120 and inhibits viral attachment, as well as subsequent infection [383669]. In phase I clinical trials, sCD4 demonstrated a good safety profile; however, its antiviral effect was not well pronounced, probably due to a short half-life (45 min in humans following iv administration) [383679]. A dimeric CD4-human IgG1 heavy chain fusion protein has also been described [383634], which has a longer half-life, as well as *in vitro* antiviral activity [383636]. Development of this molecule was halted, however, due to potential drawbacks of Fc receptor-dependent complement activation [383634], [383637] and transfer of recombinant human CD4-IgG across the placenta [383677]. CD4-IgG2 conjugate (PRO-542) was developed to overcome the potential problems associated with half-life and Fc receptor-mediated complement activation. It has a longer half-life and does not interact with the high-affinity Fc receptors on human monocytic U937 cells [383593].

PRO-542 has been developed for use in two clinical settings: (i) post-exposure prophylaxis and (ii) immunotherapy. In post-exposure prophylaxis therapy, PRO-542 would protect exposed individuals from contracting HIV infection by reducing the concentration of infectious virus in the bloodstream. As an immunotherapy, PRO-542 could be used to treat HIV infection, especially during the early or asymptomatic phase of infection [178410], [278442].

Synthesis and SAR

PRO-542 is a fusion protein comprising human IgG2 in which the Fv portions of both heavy and light chains have been replaced with four copies of the D1 and D2 domains of human CD4 [341870], [383593], [383659]. PRO-542 has been expressed in Chinese hamster ovary (CHO) cells, where it is secreted as a fully assembled heterotetramer, and purified using size-exclusion chromatography. Its tertiary structure was determined based on its high binding affinity for recombinant soluble gp120 from both laboratory-adapted and primary isolates of HIV-1 [383593].

PRO-542 was designed to bind multiple copies of gp120, and appears to be able to neutralize HIV by crosslinking up to four gp120s on the surface of one or more virus particles.

Electron microscopy has been used to visualize PRO-542 alone and complexed with gp120 viral envelope glycoprotein that protrudes from the virus. These studies confirmed the structural flexibility of PRO-542 and its complexation with four molecules of gp120 [366535]. PRO-542 acts by two mechanisms: (i) by high-affinity binding to gp120; and (ii) by detaching gp120 from the HIV particle, thereby inactivating the virus [178410].

In order to produce sufficient quantities of the antibody-like molecule in a cost effective manner, Progenics Pharmaceuticals initiated a program in 1998 with Genzyme Transgenics Corp to develop a means of expressing PRO-542 in the milk of transgenic animals [278442], [279692].

Pharmacology

PRO-542 has been developed as an immunoprophylactic agent for reducing the probability of infection after HIV-1 exposure [383593], [383650]. Binding of PRO-542 to glycoprotein gp120 is the basis of HIV-1 neutralization. It has been observed that PRO-542 binds at nanomolar concentrations to purified gp120 isolated from both primary and laboratory-adapted HIV-1 isolates [383593]. In rabbits, PRO-542 has a terminal half-life of 26.4 h, compared to mean terminal serum half-lives in humans of 4.2 ± 0.9 and 3.3 ± 0.7 days for 5 and 10 mg/kg doses, respectively [383593], [383659].

On the basis of flow cytometric analysis, PRO-542 does not appear to bind to Fc receptors, a property that is desirable since an agent with FcR-binding capability will be lethal for uninfected cells bearing this surface receptor. PRO-542 inhibits syncytia formation in HIV-1-infected cells, suggesting that it would successfully prevent cell-to-cell HIV-1 transmission [383593]. Furthermore, it was effective against diverse laboratory-adapted and primary HIV-1 isolates, including strains with different tropisms and isolated at different stages of disease [383650], [383652]. In a hu-PBL-SCID mouse model, passive administration of PRO-542 10 mg/kg, protected animals against subsequent infectious doses of laboratory-adapted T-cell-tropic isolate HIV-1 (LAI), while a 50 mg/kg dose protected four out of five mice against the primary isolates HIV-1 (JR-CSF) and HIV-1 (AD6) [383652].

The synergistic inhibition of HIV-1 using combinations of PRO-542 and other antiviral agents has also been investigated [374349], [378084], [380352], [381776], [382628]. A combination of PRO-542 and T-20 (pentafuside; Duke University/Trimeris Inc) was especially potent in blocking HIV entry into cells. T-20 is derived from gp41. The activity of each agent, both of which are termed 'entry inhibitors', was greatly enhanced by the presence of the other, resulting in synergistic or supra-additive antiviral effects. In *in vitro* studies, PRO-542 and T-20 synergistically blocked both virus-to-cell and cell-to-cell spread of HIV; the levels of each agent required to achieve biologically relevant inhibition were reduced by approximately 10-fold [374349], [381776].

PRO-542 was also tested in combination with T-20 and PRO-140 (Progenics Pharmaceuticals), each of which inhibits a different step in the sequence of events leading to the entry of HIV into target cells. PRO-140 is a monoclonal antibody to CCR5, which potently blocks HIV-1 entry but not CC-chemokine signaling through CCR5. Potent synergies were observed for certain combinations of these HIV-1 inhibitors. In such instances, the drug levels required to achieve clinically relevant levels of inhibition were reduced 5- to 15-fold and no agent antagonized the activity of another [378084], [380352], [382628].

Metabolism

In a phase I clinical trial in which PRO-542 0.2 to 10 mg/kg was administered iv to HIV-infected adults, the area under the concentration-time curve and peak serum concentrations increased linearly with dose, and the terminal serum half-life was 3 to 4 days [383659].

Toxicity

One of the potential concerns for recombinant fusion protein therapeutics is unintentional product reactivity. Phase I trial data in HIV-infected adults supported the non-immunogenic nature of PRO-542 [341870]. In this study, the drug was well tolerated and no dose-limiting toxicities were identified [341870], [383659].

Clinical Development

Phase I/II

A single-dose phase I/II study was conducted at the Mount Sinai Medical Center, NY, USA, evaluating the safety, pharmacology and antiviral activity of PRO-542 in HIV-1 infected adults (with criteria of viral load ≥ 3000 copies/ml of viral RNA, CD4 counts > 50 cells/mm^3 and stable or not receiving anti-HIV therapy) [341870], [375598], [383659]. In this study, individuals were treated with one of four doses of PRO-542 (0.2, 1.0, 5.0 or 10.0 mg/kg body weight). Patients in the high-dose group reached a serum concentration of > 500 μg/ml and experienced a statistically significant reduction in plasma HIV RNA; the reductions in infectious HIV plasma levels were sustained [341870], [341337], [375598], [383659].

A second multicenter phase I/II study was carried out in pediatric patients at Baylor College of Medicine in Houston, TX, the University of California at San Francisco, CA and the University of Pennsylvania, PA, by the AIDS Clinical Trials Group (ACTG) [284326], [354249]. In one of these multi-dose trials, 18 HIV-1-infected children were treated with a single infusion or 4 weekly doses of PRO-542. The six children treated weekly with PRO-542 all demonstrated a decrease in HIV RNA of up to 1.5 $\log_{10}$. Three of the children showed sustained reductions in viral loads that persisted for as long as 14 days post-treatment [354249], [374349]. No serious drug-related adverse events were observed.

PRO-542 has now completed these two phase I/II clinical trials [383541].

Side Effects and Contraindications

Single-dose iv administration of 0.2 to 10 mg/kg of PRO-542 was well tolerated and no significant drug-related adverse events were reported [341870]. No patients developed antibodies to PRO-542 [383659]. PRO-542 was also well tolerated in pediatric clinical trials [374349].

Current Opinion

AIDS and HIV infection represent one of the most serious health threats facing mankind. Currently, highly active antiretroviral therapy (HAART) is considered the most promising therapeutic option, although a number of studies document residual virus in HAART patients [383681]. UnAB technology, and specifically PRO-542 with its novel mode of action [383657], represents an interesting approach to the treatment of HIV and AIDS. Monotherapy with PRO-542 in phase I/II clinical trials in HIV-infected adults and children, demonstrated good safety, tolerability, pharmacokinetics and reduction of HIV RNA levels [284326], [341870], [374349], [375598], [383659]. With the recent completion of phase I/II clinical trials, and the fact that Progenic Pharmaceuticals are collaborating with Genzyme Transgenics for the development of a transgenic source of PRO-542 (goats milk), with a possibility for eventual commercial supply [357291], indicates that the company are continuing the clinical development of this therapy.

A serious challenge to PRO-542, however, is CD4-independent infection, which suggests that gp120 interaction with CD4 surface molecules is not necessary for infection in certain cell types [383671]. In addition, it is also important to consider previous studies that show that the virus envelope proteins are not required for virus attachment [383675].

In vitro studies of combination therapies, ie, PRO-542 + T-20 and PRO-542 + T-20 + PRO-140, show that these double- and triple-drug cocktails act synergistically and potently [374349], [378084], [380352], [381776], [382628]. The key to these combination therapies is that each individual drug acts at a different step in the sequence of events leading to HIV entry/infection of host cells [382628]. It will be interesting to see how the PRO-542-combination therapies compare with traditional HAART programs currently under investigation and in use.

Licensing

Aaron Diamond AIDS Research Center

Progenics Pharmaceuticals Inc and Aaron Diamond AIDS Research Center are collaborating on the development of PRO-542 [178410].

American Cyanamid Co

American Cyanamid and Progenics agreed to collaborate on the study of several agents combining the use of Progenics HIV Universal Neutralizing Antibody technology (UnAB) with drug conjugates [167582].

Genzyme Transgenics Corp

Progenics and Genzyme Transgenics have signed an agreement to continue the development of a transgenic source of supply for PRO-542. Genzyme will develop transgenic goats that produce PRO-542 in their milk in exchange for undisclosed fees and milestone payments [357291].

Development History

Developer	Country	Status	Indication	Date	Reference
Aaron Diamond AIDS Research Center	US	C2	AIDS	06-JAN-98	273391
Progenics Pharmaceuticals	US	C2	AIDS	06-JAN-98	273391

Literature classifications

Key references relating to the technology are classified according to a set of standard headings to provide a quick guide to the bibliography. These headings are as follows:

Biology: References which discuss synthesis and structure-activity relationships.

Clinical: Reports of clinical phase studies in volunteers providing, where available, data on the following: whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Neutralization of primary HIV-1 isolates.	hu-PBL-SCID mice.	PRO-542 10 mg/kg protects all animals against challenge with laboratory-adapted T-cell-tropic isolate HIV-1 (LAI), while 50 mg/kg protected 4/5 mice against the primary isolates HIV-1 (JR-CSF) and HIV-1 (AD6).	383652
In vitro	gp120 Binding affinity.	Laboratory-adapted strain and a primary isolate of HIV-1.	PRO-542 has nanomolar binding affinity.	383593

Biology (continued)

Study Type	Effect Studied	Experimental Model	Result	Reference
In vitro	Inhibition of syncitium formation.	Virus-free HIV-1 envelope glycoprotein.	Tetrameric CD4-IgG2 (PRO-542) inhibited syncitium formation more effectively than monomeric sCD4 or dimeric CD4-γ 2 fusion protein.	383593
In vivo	Pharmacokinetics.	Rabbit.	Plasma terminal $t_{½}$ = 26.4 h.	383593
In vitro	Synergistic inhibition by PRO-542 + T-20.	Preclinical models of HIV-1 infection.	Good synergy over a range of concentrations, reducing the drug levels required. Drug levels required for clinically relevant inhibition reduced by ~ 10-fold.	374349 381776
In vitro	Synergistic inhibition by PRO-542 + T-20 + PRO-140.	Preclinical models of HIV-1 infection.	Good synergy observed for certain combinations. Drug levels required for clinically relevant inhibition reduced by 5- to 15-fold.	378084 380352 382628

Clinical

Study Type	Effect Studied	Result	Reference
Phase I/II.	Single-dose safety, pharmacology and antiviral activity in HIV-1-infected adults.	PRO-542 0.2 to 10 mg/kg iv was well tolerated, no dose-limiting toxicity observed, terminal $t_{1/2}$ = 3 to 4 days. Evidence of antiviral activity observed as reductions in plasma HIV RNA and plasma viremia.	341337 341870 383659
Phase I/II.	18 HIV-1-infected children, treated with a single infusion or 4 weekly doses of PRO-542.	All six children receiving weekly doses showed decreased plasma HIV-1 RNA (up to 1.5 $\log_{10}$). Three of the children showed sustained reductions in viral load that persisted for as long as 14 days post-treatment. No serious drug-related adverse events were reported.	354249 374349

Associated Patent

Title Compounds capable of inhibiting HIV-1 infection.

Assignee Progenics Pharmaceuticals Inc

Publication WO-09726009 24-JUL-97

Priority US-1996-587458 17-JAN-1997

Inventors Maddon PJ, Allaway GP, Liwin V

References

- of special interest

167582. Progenics Pharmaceuticals Inc: **American Cyanamid and Progenics Pharmeceuticals sign research agreement.** *Press release* 10 May (1994).

178410. Progenics Pharmaceuticals Inc: **Progenics report on HIV antiviral molecule published in AIDS Research and Human Retroviruses.** *Press release* 31 May (1995).

236048. Progenics Pharmaceuticals Inc: **Progenics pharmaceuticals awarded $1.1 million in NIH grant funding to develop novel HIV therapeutics.** *Press release* 30 January (1997).

273391. Progenics Pharmaceuticals Inc: **Progenics Pharmaceuticals and ADARC identify HIV-binding site on CCR5 co-receptor; Results published in the Journal of Virology.** *Press release* 5 January (1998).
• *Announcement of the publication of a paper in Journal of Virology (1998)* ***72****(1), reporting the identification of a binding site for HIV on the CCR5 co-receptor. The finding was the result of a collaboration between scientists from the Aaron Diamond AIDS Research Center (ADARC) and Progenics.*

278442. Genzyme Transgenics Corp: **Progenics and Genzyme Transgenics announce initiation of program to produce novel HIV therapeutics.** *Press release* 18 February (1998).
• *Announcement of an agreement between Genzyme Transgenics Corp and Progenics Pharmaceuticals of a program to produce PRO-542 in the milk of transgenic animals. Following successful completion of the initial development phase, the companies expect to enter into a commercialization agreement for production of PRO-542 in the milk of transgenic goats.*

279692. **Genzyme/Progenics collaborate on PRO-542 for HIV.** *Scrip* (1998) 2312:10.

284326. Progenics Pharmaceuticals Inc: **Progenics Pharmaceuticals lead HIV product protects mice from HIV infection.** *Press release* 16 April (1998).

294200. Progenics Pharmaceuticals Inc: **Progenics awarded $2.7 million grant from NIH to develop novel HIV therapeutic.** *Press release* 11 August (1998).

341337. Progenics Pharmaceuticals Inc: **Progenics reports positive clinical results for HIV therapy - evidence of antiretroviral activity seen with single dose of drug.** *Press release* 27 September (1999).
• *Initial results of a phase I/II trial in 15 HIV-infected patients who received a single injection of PRO-542.*

341870. Jacobson J, Trkola A, Ketas T, O'Neil T, Tran D, Olson W, Isreal R: **Results of a phase I trial of single-dose PRO-542, a novel inhibitor of HIV entry.** *ICAAC* **39**:Abs 323.

354249. Progenics Pharmaceuticals Inc: **PRO-542 reduces HIV viral load in children-encouraging data on new CCR5 antibody and vaccine approach also presented.** *Press release* 2 February (2000).
• *Initial results from a pediatric phase I/II clinical trial of PRO-542.*

357291. Progenics Pharmaceuticals Inc: **Progenics and Genzyme Transgenics enter into development and supply agreement for HIV drug.** *Press release* 25 February (2000).

366535. Progenics Pharmaceuticals Inc: **Progenics reports the structure of HIV entry inhibitor PRO-542.** *Press release* 15 May (2000).
• *Electron microscopy studies demonstrate that PRO-542 possesses exceptional structural flexibility and may be able to neutralize HIV by crosslinking as many as four gp120s on the surface of one or more virus particles.*

374349. Progenics Pharmaceuticals Inc: **Progenics reports PRO-542 and T-20 combination synergistic against HIV.** *Press release* 12 July (2000).
• *Report of the synergistic effect of combinations of PRO-542 and T-20.*

375598. Progenics Pharmaceuticals Inc: **Progenics announces publication of encouraging clinical results with HIV drug.** *Press release* 20 July (2000).

378084. Este J: **Breaking the Silence: 13th International AIDS Congress (Part II), Durban, South Africa.** *IDdb Meeting Report* 9-14 July (2000).

380352. Olson W, Nagashima K, Rosenfield S, Maddon P: **Comparative and combinatorial analysis of the HIV-1 entry inhibitors PRO-542, T-20 and PRO 140.** *Int Conf AIDS* (2000) **2**:WeOrA533.
• *Report of the synergistic effect of combinations of PRO-542 and T-20 from the International Conference on AIDS (2000).*

381776. Olson WC, Nagashima KP, Rosenfield S, Maddon PJ: **Potent, synergistic inhibition of HIV-1 by combinations of the viral entry inhibitors PRO-542 and T-20.** *ICAAC* (2000) **40**:Abs 549.
• *Report of the synergistic effect of combinations of PRO-542 and T-20 from ICAAC meeting (2000).*

382628. Progenics Pharmaceuticals Inc: **Progenics reports new triple drug cocktail potently blocks HIV.** *Press release* 18 September (2000).
• *Report of the synergistic effect of combinations of PRO-542 + T-20 + PRO-140.*

383541. Progenics Pharmaceuticals Inc: **Progenics agent reduces damage and death from stroke in animal model.** *Press release* 26 September (2000).
• *Report that phase I/II clinical trials of PRO-542 have been completed.*

383593. Allaway GP, Davis-Bruno KL, Beaudry GA, Garcia EB, Wong EL, Ryder AM, Hasel KW, Gauduin MC, Koup RA, McDougal JS, Maddon PJ: **Expression and characterization of CD4-IgG2, a novel heterotetramer that neutralizes primary HIV type 1 isolates.** *AIDS Res Hum Retroviruses* (1995) **11**(5):533-539.

383634. Byrn RA, Mordenti J, Lucas C, Smith D, Marsters SA, Johnson JS, Cossum P, Chamow SM, Wurm FM, Gregory T, *et al*: **Biological properties of a CD4 immunoadhesin.** *Nature* (1990) **344**(6267):667-670.

383636. Capon DJ, Chamow SM, Mordenti J, Marsters SA, Gregory T, Mitsuya H, Byrn RA, Lucas C, Wurm FM, Groopman JE, *et al*: **Designing CD4 immunoadhesins for AIDS therapy.** *Nature* (1989) **337**(6207):525-531.

383637. Chamow SM, Zhang DZ, Tan XY, Mhatre SM, Marsters SA, Peers DH, Byrn RA, Ashkenazi A, Junghans RP: **A humanized, bispecific immunoadhesin-antibody that retargets CD3+ effectors to kill HIV-1-infected cells.** *J Immunol* (1994) **153**(9):4268-4280.

383650. Gauduin MC, Allaway GP, Maddon PJ, Barbas CF, Burton DR, Koup RA: **Effective *ex vivo* neutralization of human immundeficiency virus type 1 in plasma by recombinant immunoglobulin molecules.** *J Virol* (1996) **70**(4):2586-2592.

383652. Gauduin MC, Allaway GP, Olson WC, Weir R, Maddon PJ, Koup RA: **CD4-immunoglobulin G2 protects Hu-PBL-SCID mice against challenge by primary human immunodeficiency virus type 1 isolates.** *J Virol* (1998) **72**(4):3475-3478.

383655. Hurez V, Kaveri SV, Mouhoub A, Dietrich G, Mani JC, Klatzmann D, Kazatchkine MD: **Anti-CD4 activity of normal human immunoglobulin G for therapeutic use. (Intravenous immunoglobulin, IVIg).** *Ther Immunol* (1994) **1**(5):269-277.

383657. Israel R, Jurcic J, Sgouros G, Minamoto G, Straus D, Polsky B, Olson W, Allaway G, Maddon P, Larson S: **A phase I trial of ^{131}I-CD4-γ2 (recombinant human CD4-IgG2 fusion protein) in HIV-1 infected patients.** *3rd Conference Retro and Opportun Infect* (1996) **1**:117.

383659. Jacobson JM, Lowy I, Fletcher CV, O'Neill TJ, Tran DN, Ketas TJ, Trkola A, Klotman ME, Maddon PJ, Olson WC, Israel RJ: **Single-dose safety, pharmacology, and antiviral activity of the human immunodeficiency virus (HIV) type 1 entry inhibitor PRO-542 in HIV-infected adults.** *J Infect Dis* (2000) **182**(1):326-329.
• *Publication of the results of phase I/II clinical trials of PRO-542 in HIV-infected patients.*

383666. Lacoux X, Barragan V, Dewynter G, Leydet A, Roque JP, Montero JL: **Synthesis and biological activity of acylated and telomerized peptides as potential HIV-fixation inhibitors.** *Farmaco* (1996) **51**(12):767-773.

383669. Moore JP, McKeating JA, Weiss RA, Sattentau QJ: **Dissociation of gp120 from HIV-1 virions induced by soluble CD4.** *Science* (1990) **250**(4984):1139-1142.

383671. Olinger GG, Saifuddin M, Spear GT: **CD4-negative cells bind human immunodeficiency virus type 1 and efficiently transfer virus to T-cells.** *J Virol* (2000) **74**(18):8550-8557.

383675. Saphire AC, Bobardt MD, Gallay PA: **Host cyclophilin A mediates HIV-1 attachment to target cells via heparans.** *EMBO J* (1999) **18**(23):6771-6785

383677. Shearer WT, Duliege AM, Kline MW, Hammill H, Minoff H, Ammann AJ, Chen S, Izu A, Mordenti J: **Transport of recombinant human CD4-immunoglobulin G across the human placenta: Pharmacokinetics and safety in six mother-infant pairs in AIDS clinical trial group protocol 146.** *Clin Diagn Lab Immunol* (1995) **2**(3):281-285.

383679. Schooley RT, Merigan TC, Gaut P, Hirsch MS, Holodniy M, Flynn T, Liu S, Byington RE, Henochowicz S, Gubish E, *et al*: **Recombinant soluble CD4 therapy in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. A phase I-II escalating dosage trial.** *Ann Intern Med* (1990) **112**(4):247-253.

383681. Zhang H, Dornadula G, Beumont M, Livornese L, Van Uitert B, Henning K, Pomerantz RJ: **Human immunodeficiency virus type 1 in the semen of men receiving highly active anti-retroviral therapy.** *New Engl J Med* (1998) **339**(25):1803-1809.

385982. Progenics Pharmaceuticals Inc: **Progenics awarded $6.0 million for HIV therapy and vaccine programs.** *Press release* 17 October (2000).

390063. **Intra-day Comments: Progenics Pharmaceuticals (PGNX).** Punk, Ziegel & Company *Analyst report* 1 August (2000).