2.- Receptores solubles y sus derivados.

Una gran esperanza para la prevención de la infección por VIH-1 fue la utilización de la forma soluble del receptor primario CD4 (sCD4) y sus derivados (182, 184-191). La idea de esta terapia se basaba en que, ya que el lugar de unión para el receptor primario sobre gp120 esta conservado, sCD4 sería un inhibidor eficiente para la mayoría de cepas virales y el tratamiento no resultaría en la aparición de cepas resistentes. Los ensayos clínicos fueron decepcionantes, no consiguiéndose ni una disminución en la carga viral ni un aumento en el número de células CD4 (192, 193).

El compuesto más reciente, basado en esta estrategia, es PRO 542 una proteína de fusión de un sCD4 multimérico y una IgG2 que incorpora la región de unión de VIH del CD4 humano (194). Ensayos clínicos en fase 1 y en fase 2 se están llevando a cabo actualmente en niños y adultos infectados con VIH, en los cuales se observa una disminución en la carga viral (195, 196).

3.- Péptidos que imitan componentes de la maquinaria de entrada del VIH-1.

La idea de que péptidos de los componentes de la maquinaria de entrada de VIH-1 pueden imitar alguna de las estructuras implicadas en el mecanismo de entrada y competir con ellos, resultó en el desarrollo de una variedad de péptidos que inhiben la infeccion de VIH-1 con una eficiencia variable. Los péptidos más prometedores son los que imitan partes del bucle V3(197, 198).

4.- Moléculas cargadas negativamente: polianiónes.

Varias moléculas orgánicas han sido descritas por tener un efecto inhibidor de la entrada viral. El compuesto más notorio es Dextrán Sulfato (DS) (199). El mecanismo de inhibición de este compuesto está relacionado a su carga negativa: DS se une a gp120 probablemente al bucle V3 cargado positivamente(200). Otros derivados sulfatados como heparán sulfato o curdlan sulfato (CRDS) han mostrado tener un efecto similar. Este tipo de compuestos sulfatados presentan una vida media muy corta en la circulación además de tener efectos tóxicos (201), sin embargo, en ensayos clínicos CRDS fue bien tolerado a dosis elevadas, lo que resultó en una concentración en plasma efectiva para la inhibición de VIH (202).

Taninos, ácido chebulinico y punicalin (203), así como Evans blue, tripan blue y otros compuestos polianiónicos son también capaces de bloquear la unión de gp120 recombinante a CD4 e inhibir la formación de sincitios (204).

Los ácidos nucleicos están cargados negativamente y pueden adoptar una variedad de estructuras que pueden, especificamente, unirse a componentes de la

maquinaria de entrada del VIH. Por tanto, debido a la negatividad de estos ácidos, el bucle V3, cargado positivamente, puede ser una de sus dianas. El ácido poliadenílico-poliuridílico (poli(A).poli(U)) y el oligodeoxicitidina fosforotioato demostraron tener actividad anti-VIH (205) (206). Estos oligonucleótidos fosforotioatos pueden ejercer su efecto inhibitorio por unión al bucle V3 y a la molécula CD4 (207).

1.7.1.2. Los correceptores como diana para la inhibición del VIH.

Varias clases de agentes bloqueantes de los correceptores de VIH han sido descritas (Figura 13).

1.- Quimiocinas y sus derivados.

Los primeros experimentos que demostraron el potencial de los ligandos de los correceptores para inhibir la infección por VIH-1, fueron realmente realizados con RANTES, MIP-1α y MIP-1β, antes del descubrimiento de los receptores de quimiocinas como correceptores del VIH (99). En esos estudios se demostró que esas quimiocinas podían inhibir la infección de VIH-1, cepas M-trópicas, y la fusión célula-célula a concentraciones muy bajas (101-104, 106).

Experimentos similares fueron realizados con SDF-1, el ligando para CXCR4 (96, 97), encontrándose la concentración inhibitoria en el mismo rango. Los ligandos para otros receptores de quimiocinas, los cuales funcionan como correceptores, también son capaces de inhibir su función correceptor (102, 107).

Alteraciones en el amino terminal de ciertas quimiocinas resultan en un profundo cambio de su actividad. Truncaciones del amino terminal o modificaciones de esta región pueden resultar en proteínas que hayan perdido su capacidad de activar su receptor, aunque reteniendo su capacidad de unirse al mismo. De este modo, pueden generarse antagonistas de los correceptores que competirán por la unión del ligando natural. Las CC quimiocinas RANTES, MCP-1 y MCP-3 han sido producidas como proteínas truncadas en sus N-terminales o como quimiocinas modificadas, y esas variantes antagonizan el efecto de sus ligandos parentales *in vitro* (208-213).

MIP-1α y MIP-1β compiten con la unión de gp120 a CCR5 (148) lo cual sugiere un mecanismo de inhibición basado en una competición. Desde el punto de vista del desarrollo de drogas esto es muy importante, ya que hay que tener en cuenta que cualquier candidato a fármaco que interactúe con los correceptores de VIH puede afectar la función normal de éstos. Para CCR5 esto puede no ser crítico, a la luz de los hallazgos que un mutante defectivo existe en la población humana (169). Sin embargo,

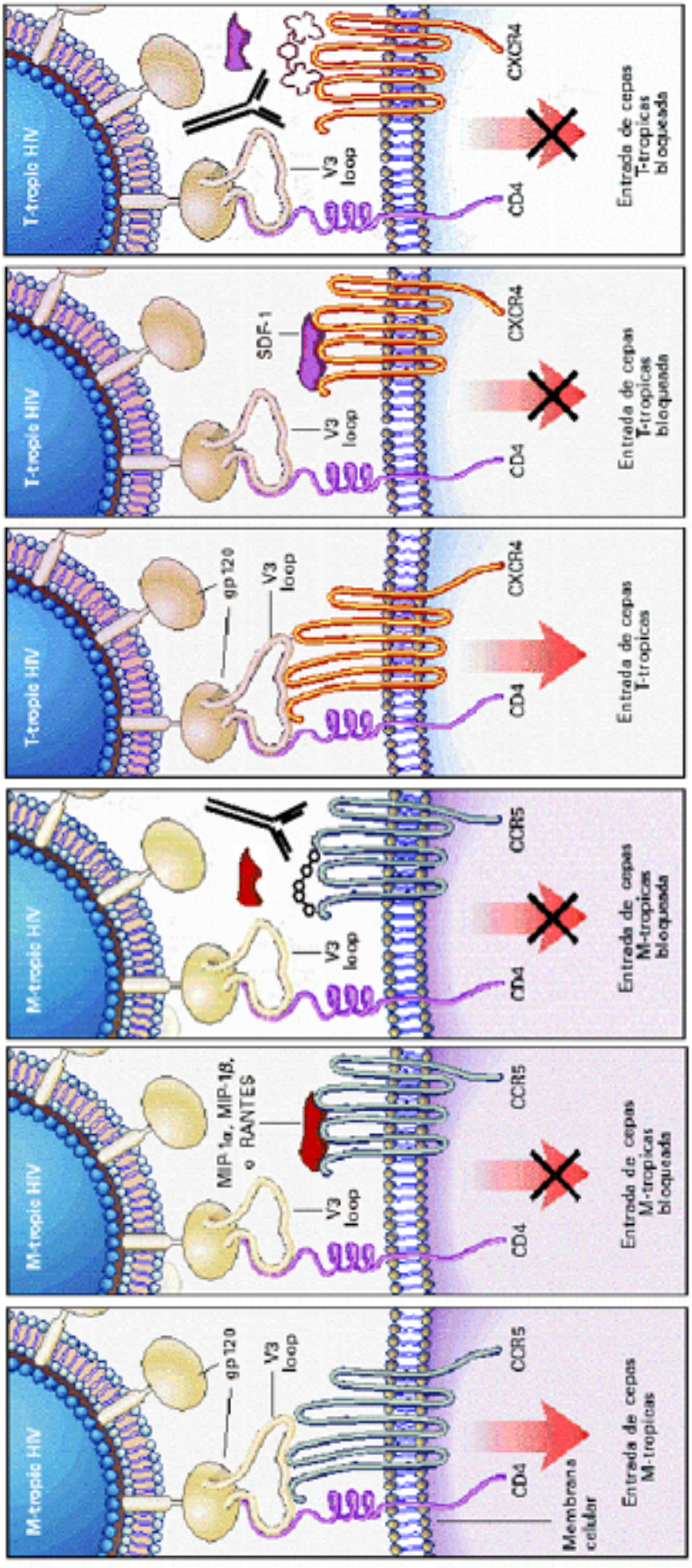

Figura 13. Inhibición de la entrada de VIH mediante el bloqueo de los receptores de quimiocinas. La entrada de la cepas M-trópicas a través de CCR5 puede ser bloqueada mediante los ligandos naturales de CCR5: las quimiocinas RANTES, MIP-1α y MIP-1β. Esta entrada también puede ser inhibida mediante antagonistas como qimiocinas modificadas, anticuerpos anti-receptor o pequeñas moléculas como TAK-779. La entrada de la cepas T-trópicas a través del receptor CXCR4 puede ser bloqueada por SDF-1α, el ligando natural o mediante antagonistas como AMD3100, anticuerpos anti-receptor o la quimiocina SDF-1α modificada.

para CXCR4, el cual está expresado en una gran variedad de tejidos, la inhibición de su función podría ser deletérea, ya que la ausencia de su ligando (SDF-1) en ratones transgenicos “knock-out” crea un fenotipo letal (214). Esto último seraçá ampliado posteriormente en la discusión de este trabajo.

2.- Anticuerpos anti-receptor.

Anticuerpos monoclonales anti-correceptor que inhiben la entrada viral, representan otra clase de agentes bloqueantes. Anticuerpos monoclonales murinos con actividad inhibitoria han sido descritos para CXCR4 (215), CCR5 (145, 216) y CCR3 (116). Tales anticuerpos pueden ser humanizados y probados para su posible papel en la clínica.

El último de estos anticuerpos descrito es PRO 140 (PA14) un anticuerpo monoclonal anti-CCR5 que inhibe potentemente la entrada de VIH-1 a concentraciones que no afectan la actividad de CCR5 como receptor de quimiocinas (217), quizá dimerizando al receptor y así bloqueando la infección por el VIH (218).

3.- Compuestos de bajo peso molecular.

La más prometedora clase de compuestos es aquella formada por compuestos de bajo peso molecular que se unen directamente al correceptor e inhiben su función. Varios compuestos específicos contra el receptor CXCR4 han sido descritos (219-221). La clase más potente de estos compuestos es la formada por los biciclanes, cuyo prototipo AM3100 es de 10 a 50 veces más activo en inhibir la infección por VIH-1 que el ligando natural SDF-1 (220, 222). Los otros antagonistas descritos son un péptido de 18 aminoácidos cíclico (T22) y un péptido de 9 residuos arginina (ALX40-4C). Todos estos compuestos parecen unirse a CXCR4 de una manera similar: las tres clases de compuestos son fuertemente catiónicos, lo cual puede conducir a interacciones electrostáticas con el segundo bucle extracelular de CXCR4. Tal unión puede prevenir interacciones similares con el bucle V3 de los aislados T-trópicos. Terapéuticamente, sólo los componentes de la familia de los biciclanes pueden ser lo suficientemente pequeños como para permitir el desarrollo de un compuesto que sea biodisponible oralmente.

La primera pequeña molécula inhibidora de CCR5 cuya estructura fue descrita es TAK-779, un antagonista que bloquea tanto la entrada viral como la unión de las quimiocinas (223). Schering C es otro pequeño antagonista selectivo de CCR5, biodisponible oralmente, y que inhibe un amplio espectro de aislados de VIH. Los datos preclínicos son esperanzadores en términos de perfil farmacológico y de la ausencia de

aparición de virus resistentes, después de 20 semanas de administración del fármaco (224).

1.7.1.3. Fusión de las membranas viral y celular.

La proteína gp41 media la fusión de las membranas viral y celular y consecuentemente es una diana importante para la generación de compuestos antivirales. Especialmente interesante es un péptido sintético de 36 aminoácidos, T-20 (DP-178) derivado de un epítopo conservado de gp41 (225). Este péptido inhibe potentemente la entrada de VIH mediante su unión a la molécula gp41, lo que conduce a una irreversible pérdida de la actividad fusogénica de gp41. T-20 demostró una potente actividad antiviral *in vitro* (225) y aunque está derivado de una región conservada de gp41, un mutante resistente fue aislado por pases seriados en dosis crecientes del péptido (226). El estudio clínico de T-20 en fase 1 se terminó con mucho éxito, y un estudio clínico en fase 2 muestra una significativa y sostenida caída de la carga viral con un aumento en los niveles de CD4 (227-229). Nuevos péptidos análogos (T-1249 o el péptido 2) parecen ser muy prometedores (230). De estos nuevos compuestos, se puede destacar la pequeña proteína recientemente presentada 5-Helix, la cual muestra una actividad inhibitoria del VIH muy potente (231).

1.7.2.-INHIBICIÓN DE LA TRANSCRIPCIÓN REVERSA: RT.

Los inhibidores de la RT viral fueron los primeros agentes desarrollados para el tratamiento de la infección del VIH y permanecen como componentes importantes en el armamento terapéutico anti-VIH. La mayoría de los inhibidores de RT son análogos de los nucleósidos. Estos agentes actúan como terminadores de la cadena de DNA. Los inhibidores de RT no nucleosídicos son también ampliamente usados en clínica. Los inhibidores de RT como grupo, presentan varias desventajas, incluyendo su asociación con múltiples efectos adversos hematológicos y neurológicos, la rapidez con la que se seleccionan cepas virales resistentes cuando son usados solos, y su falta de efecto sobre células que están ya infectadas con VIH, las cuales ya no necesitan de la actividad de la RT para completar su ciclo viral (232).

1.7.3.- PROCESO DE INTEGRACIÓN: INTEGRASA.

La determinación de la estructura cristalográfica de la integrasa (233) estimuló la búsqueda de inhibidores de este enzima, y a pesar del detallado conocimiento de la actividad catalítica de la integrasa viral, ningún compuesto que inhiba este enzima ha llegado al mercado.Sin embargo, algunas moléculas interesantes han sido recientemente

identificadas (234) habiendo algunos inhibidores de la integrasa que están actualmente en fase de desarrollo preclínico (235).

Tabla 3.- Agentes antivirales que actúan en el proceso de entrada viral (228).

INHIBIDOR	CARACTERÍSTICAS	ESTADO ACTUAL	COMENTARIOS
Agentes que actúan sobre CD4			
sCD4-IgG (ej: PRO 542)	Receptor celular soluble	Estudio clínico	Mayor vida media que los antecesores.
Agentes que actúan sobre CCR5			
AOP-RANTES NNY-RANTES 9-68 RANTES 3-68 RANTES Met-RANTES	Derivados de la quimiocina	Estudio Preclínico	Baja biodisponibiliad, no especificidad para CCR5.
Schering C	Pequeña molécula no peptídica.	Estudio Preclínico	Alta biodisponibilidad
TAK-779	Pequeña molécula no peptídica.	Estudio Preclínico	Específico para CCR5
Agentes que actúan sobre CXCR4			
Variantes de SDF-1	Derivados de la quimiocina	Estudio Preclínico	Baja biodisponibiliad
T-22	Péptido de 18 aminoácidos	Estudio Preclínico	Baja biodisponibiliad, posiblemente pobre farmacocinética.
ALX40-4C	Péptido de 9 D-aminoácidos	Estudio Preclínico	Baja biodisponibiliad
AMD3100	Pequeña molécula	Estudio clínico en fase II.	Baja biodisponibiliad
Agentes que actúan sobre gp41			
T-20	Péptido de 36 aminoácidos	Estudio clínico	Significativa caída de la carga viral y aumento del nº de $CD4^+$.
5-Helix	Molécula pequeña		Alta potencia antiviral

1.7.4.- PROCESAMIENTO DE LAS PROTEÍNAS VIRALES: LA PROTEASA VIRAL.

Inhibidores de la proteasa habían sido diseñados en un principio en base a los oligopéptidos substratos del enzima. Mientras que la primera generación de inhibidores fueron peptidomiméticos, con una muy baja disponibilidad oral, los últimos inhibidores de la proteasa disponibles han podido ser optimizados usando técnicas de diseño molecular. Estos compuestos han tenido un gran éxito en regímenes de combinación en suprimir la replicación del VIH en pacientes infectados (232). Sin embargo, su uso a

largo plazo puede estar asociado a efectos adversos como la lipodistrofia, hiperlipidemia y resistencia a la insulina (236).

1.7.5.- GENES REGULADORES Y ACCESORIOS DEL VIH.

Dirigirse a las proteínas accesorias del VIH ha sido difícil, por el problema en delinear las actividades bioquímicas precisas de estas proteínas. Un ensayo clínico del antagonista de Tat, Ro24-7429 falló en demostrar actividad antiviral (237), sin embargo, agentes dirigidos contra Rev y Nef están siendo desarrollados actualmente.

1.8.- BIBLIOGRAFÍA.

1. 1981. Pneumocystis pneumonia--Los Angeles. *MMWR Morb Mortal Wkly Rep 30:250*.
2. 1981. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. *MMWR Morb Mortal Wkly Rep 30:305*.
3. Gottlieb, M. S., R. Schroff, H. M. Schanker, J. D. Weisman, P. T. Fan, R. A. Wolf, and A. Saxon. 1981. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med 305:1425*.
4. Masur, H., M. A. Michelis, J. B. Greene, I. Onorato, R. A. Stouwe, R. S. Holzman, G. Wormser, L. Brettman, M. Lange, H. W. Murray, and S. Cunningham-Rundles. 1981. An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med 305:1431*.
5. Siegal, F. P., C. Lopez, G. S. Hammer, A. E. Brown, S. J. Kornfeld, J. Gold, J. Hassett, S. Z. Hirschman, C. Cunningham-Rundles, B. R. Adelsberg, and et al. 1981. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med 305:1439*.
6. Barre-Sinoussi, F., J. C. Chermann, F. Rey, M. T. Nugeyre, S. Chamaret, J. Gruest, C. Dauguet, C. Axler-Blin, F. Vezinet-Brun, C. Rouzioux, W. Rozenbaum, and L. Montagnier. 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science 220:868*.
7. Gallo, R. C., S. Z. Salahuddin, M. Popovic, G. M. Shearer, M. Kaplan, B. F. Haynes, T. J. Palker, R. Redfield, J. Oleske, B. Safai, and et al. 1984. Frequent

detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science 224:500*.

8. Levy, J. A., A. D. Hoffman, S. M. Kramer, J. A. Landis, J. M. Shimabukuro, and L. S. Oshiro. 1984. Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science 225:840*.
9. Coffin, J., A. Haase, J. A. Levy, L. Montagnier, S. Oroszlan, N. Teich, H. Temin, K. Toyoshima, H. Varmus, P. Vogt, and et al. 1986. Human immunodeficiency viruses. *Science 232:697*.
10. Clavel, F., D. Guetard, F. Brun-Vezinet, S. Chamaret, M. A. Rey, M. O. Santos-Ferreira, A. G. Laurent, C. Dauguet, C. Katlama, C. Rouzioux, and et al. 1986. Isolation of a new human retrovirus from West African patients with AIDS. *Science 233:343*.
11. Guyader, M., M. Emerman, P. Sonigo, F. Clavel, L. Montagnier, and M. Alizon. 1987. Genome organization and transactivation of the human immunodeficiency virus type 2. *Nature 326:662*.
12. Letvin, N. L., M. D. Daniel, P. K. Sehgal, R. C. Desrosiers, R. D. Hunt, L. M. Waldron, J. J. MacKey, D. K. Schmidt, L. V. Chalifoux, and N. W. King. 1985. Induction of AIDS-like disease in macaque monkeys with T-cell tropic retrovirus STLV-III. *Science 230:71*.
13. Levy, J. 1994. *The Retroviridae. The simian retroviruses: SIV and SRV, ed EM. Garder MB, Barry PA, New York: Plenem Press.*
14. Pedersen, N. C., E. W. Ho, M. L. Brown, and J. K. Yamamoto. 1987. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. *Science 235:790*.
15. Gao, F., E. Bailes, D. L. Robertson, Y. Chen, C. M. Rodenburg, S. F. Michael, L. B. Cummins, L. O. Arthur, M. Peeters, G. M. Shaw, P. M. Sharp, and B. H. Hahn. 1999. Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. *Nature 397:436*.
16. Gao, F., L. Yue, A. T. White, P. G. Pappas, J. Barchue, A. P. Hanson, B. M. Greene, P. M. Sharp, G. M. Shaw, and B. H. Hahn. 1992. Human infection by genetically diverse SIVSM-related HIV-2 in west Africa. *Nature 358:495*.
17. Baltimore, D. 1970. RNA-dependent DNA polymerase in virions of RNA tumour viruses. *Nature 226:1209*.

18. Temin, H. M., and S. Mizutani. 1970. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. *Nature 226:1211*.
19. Gelderblom, H. R., M. Ozel, and G. Pauli. 1989. Morphogenesis and morphology of HIV. Structure-function relations. *Arch Virol 106:1*.
20. Frankel, A. D., and J. A. Young. 1998. HIV-1: fifteen proteins and an RNA. *Annu Rev Biochem 67:1*.
21. Muesing, M. A., D. H. Smith, C. D. Cabradilla, C. V. Benton, L. A. Lasky, and D. J. Capon. 1985. Nucleic acid structure and expression of the human AIDS/lymphadenopathy retrovirus. *Nature 313:450*.
22. Gallo, R., F. Wong-Staal, L. Montagnier, W. A. Haseltine, and M. Yoshida. 1988. HIV/HTLV gene nomenclature. *Nature 333:504*.
23. Field, B. K., D. Howlwy, P. 1996. *Virology*. Lippincott-Raven.
24. Gottlinger, H. G., J. G. Sodroski, and W. A. Haseltine. 1989. Role of capsid precursor processing and myristoylation in morphogenesis and infectivity of human immunodeficiency virus type 1. *Proc Natl Acad Sci U S A 86:5781*.
25. Coffin, J. 1996. *Retroviridae:the viruses and their replication. In: Fields BN, Knipe DM, Howley PM, ed. Fundamental virology. Philadelphia: Lippincott-Raven Publishers,*.
26. Mansky, L. M., and H. M. Temin. 1995. Lower in vivo mutation rate of human immunodeficiency virus type 1 than that predicted from the fidelity of purified reverse transcriptase. *J Virol 69:5087*.
27. Goodenow, M., T. Huet, W. Saurin, S. Kwok, J. Sninsky, and S. Wain-Hobson. 1989. HIV-1 isolates are rapidly evolving quasispecies: evidence for viral mixtures and preferred nucleotide substitutions. *J Acquir Immune Defic Syndr 2:344*.
28. Domingo, E., D. Sabo, T. Taniguchi, and C. Weissmann. 1978. Nucleotide sequence heterogeneity of an RNA phage population. *Cell 13:735*.
29. Zennou, V., C. Petit, D. Guetard, U. Nerhbass, L. Montagnier, and P. Charneau. 2000. HIV-1 genome nuclear import is mediated by a central DNA flap. *Cell 101:173*.
30. Bukrinsky, M. I., N. Sharova, M. P. Dempsey, T. L. Stanwick, A. G. Bukrinskaya, S. Haggerty, and M. Stevenson. 1992. Active nuclear import of human immunodeficiency virus type 1 preintegration complexes. *Proc Natl Acad Sci U S A 89:6580*.

31. Bukrinsky, M. I., N. Sharova, T. L. McDonald, T. Pushkarskaya, W. G. Tarpley, and M. Stevenson. 1993. Association of integrase, matrix, and reverse transcriptase antigens of human immunodeficiency virus type 1 with viral nucleic acids following acute infection. *Proc Natl Acad Sci U S A 90:6125*.

32. Bukrinsky, M. I., S. Haggerty, M. P. Dempsey, N. Sharova, A. Adzhubel, L. Spitz, P. Lewis, D. Goldfarb, M. Emerman, and M. Stevenson. 1993. A nuclear localization signal within HIV-1 matrix protein that governs infection of non-dividing cells. *Nature 365:666*.

33. Heinzinger, N. K., M. I. Bukinsky, S. A. Haggerty, A. M. Ragland, V. Kewalramani, M. A. Lee, H. E. Gendelman, L. Ratner, M. Stevenson, and M. Emerman. 1994. The Vpr protein of human immunodeficiency virus type 1 influences nuclear localization of viral nucleic acids in nondividing host cells. *Proc Natl Acad Sci U S A 91:7311*.

34. von Schwedler, U., R. S. Kornbluth, and D. Trono. 1994. The nuclear localization signal of the matrix protein of human immunodeficiency virus type 1 allows the establishment of infection in macrophages and quiescent T lymphocytes. *Proc Natl Acad Sci U S A 91:6992*.

35. Gallay, P., S. Swingler, C. Aiken, and D. Trono. 1995. HIV-1 infection of nondividing cells: C-terminal tyrosine phosphorylation of the viral matrix protein is a key regulator. *Cell 80:379*.

36. Neumann, M., J. Harrison, M. Saltarelli, E. Hadziyannis, V. Erfle, B. K. Felber, and G. N. Pavlakis. 1994. Splicing variability in HIV type 1 revealed by quantitative RNA polymerase chain reaction. *AIDS Res Hum Retroviruses 10:1531*.

37. Crawford, S., and S. P. Goff. 1985. A deletion mutation in the 5' part of the pol gene of Moloney murine leukemia virus blocks proteolytic processing of the gag and pol polyproteins. *J Virol 53:899*.

38. Katoh, I., Y. Yoshinaka, A. Rein, M. Shibuya, T. Odaka, and S. Oroszlan. 1985. Murine leukemia virus maturation: protease region required for conversion from "immature" to "mature" core form and for virus infectivity. *Virology 145:280*.

39. Kohl, N. E., E. A. Emini, W. A. Schleif, L. J. Davis, J. C. Heimbach, R. A. Dixon, E. M. Scolnick, and I. S. Sigal. 1988. Active human immunodeficiency virus protease is required for viral infectivity. *Proc Natl Acad Sci U S A 85:4686*.

40. Lifson, J. D., M. B. Feinberg, G. R. Reyes, L. Rabin, B. Banapour, S. Chakrabarti, B. Moss, F. Wong-Staal, K. S. Steimer, and E. G. Engleman. 1986. Induction of CD4-dependent cell fusion by the HTLV-III/LAV envelope glycoprotein. *Nature 323:725*.

41. Nara, P. L., R. R. Garrity, and J. Goudsmit. 1991. Neutralization of HIV-1: a paradox of humoral proportions. *Faseb J 5:2437*.

42. Capon, D. J., and R. H. Ward. 1991. The CD4-gp120 interaction and AIDS pathogenesis. *Annu Rev Immunol 9:649*.

43. Veronese, F. D., A. L. DeVico, T. D. Copeland, S. Oroszlan, R. C. Gallo, and M. G. Sarngadharan. 1985. Characterization of gp41 as the transmembrane protein coded by the HTLV-III/LAV envelope gene. *Science 229:1402*.

44. Earl, P. L., R. W. Doms, and B. Moss. 1990. Oligomeric structure of the human immunodeficiency virus type 1 envelope glycoprotein. *Proc Natl Acad Sci U S A 87:648*.

45. Yang, X., M. Farzan, R. Wyatt, and J. Sodroski. 2000. Characterization of stable, soluble trimers containing complete ectodomains of human immunodeficiency virus type 1 envelope glycoproteins. *J Virol 74:5716*.

46. Yang, X., L. Florin, M. Farzan, P. Kolchinsky, P. D. Kwong, J. Sodroski, and R. Wyatt. 2000. Modifications that stabilize human immunodeficiency virus envelope glycoprotein trimers in solution. *J Virol 74:4746*.

47. Bernstein, H. B., S. P. Tucker, S. R. Kar, S. A. McPherson, D. T. McPherson, J. W. Dubay, J. Lebowitz, R. W. Compans, and E. Hunter. 1995. Oligomerization of the hydrophobic heptad repeat of gp41. *J Virol 69:2745*.

48. Dimitrov, D. B., C. 1997. *HIV and Membrane Receptors*. Chapman & Hall.

49. Hoxie, J. A. 1991. Hypothetical assignment of intrachain disulfide bonds for HIV-2 and SIV envelope glycoproteins. *AIDS Res Hum Retroviruses 7:495*.

50. Leonard, C. K., M. W. Spellman, L. Riddle, R. J. Harris, J. N. Thomas, and T. J. Gregory. 1990. Assignment of intrachain disulfide bonds and characterization of potential glycosylation sites of the type 1 recombinant human immunodeficiency virus envelope glycoprotein (gp120) expressed in Chinese hamster ovary cells. *J Biol Chem 265:10373*.

51. Kowalski, M., J. Potz, L. Basiripour, T. Dorfman, W. C. Goh, E. Terwilliger, A. Dayton, C. Rosen, W. Haseltine, and J. Sodroski. 1987. Functional regions of

the envelope glycoprotein of human immunodeficiency virus type 1. *Science 237:1351*.

52. Lasky, L. A., G. Nakamura, D. H. Smith, C. Fennie, C. Shimasaki, E. Patzer, P. Berman, T. Gregory, and D. J. Capon. 1987. Delineation of a region of the human immunodeficiency virus type 1 gp120 glycoprotein critical for interaction with the CD4 receptor. *Cell 50:975*.
53. Starcich, B. R., B. H. Hahn, G. M. Shaw, P. D. McNeely, S. Modrow, H. Wolf, E. S. Parks, W. P. Parks, S. F. Josephs, R. C. Gallo, and et al. 1986. Identification and characterization of conserved and variable regions in the envelope gene of HTLV-III/LAV, the retrovirus of AIDS. *Cell 45:637*.
54. Wong-Staal, F., G. M. Shaw, B. H. Hahn, S. Z. Salahuddin, M. Popovic, P. Markham, R. Redfield, and R. C. Gallo. 1985. Genomic diversity of human T-lymphotropic virus type III (HTLV-III). *Science 229:759*.
55. Modrow, S., B. H. Hahn, G. M. Shaw, R. C. Gallo, F. Wong-Staal, and H. Wolf. 1987. Computer-assisted analysis of envelope protein sequences of seven human immunodeficiency virus isolates: prediction of antigenic epitopes in conserved and variable regions. *J Virol 61:570*.
56. Meyerhans, A., R. Cheynier, J. Albert, M. Seth, S. Kwok, J. Sninsky, L. Morfeldt-Manson, B. Asjo, and S. Wain-Hobson. 1989. Temporal fluctuations in HIV quasispecies in vivo are not reflected by sequential HIV isolations. *Cell 58:901*.
57. Moore, J. P., and P. L. Nara. 1991. The role of the V3 loop of gp120 in HIV infection. *Aids 5:S21*.
58. Milich, L., B. Margolin, and R. Swanstrom. 1993. V3 loop of the human immunodeficiency virus type 1 Env protein: interpreting sequence variability. *J Virol 67:5623*.
59. Takeuchi, Y., M. Akutsu, K. Murayama, N. Shimizu, and H. Hoshino. 1991. Host range mutant of human immunodeficiency virus type 1: modification of cell tropism by a single point mutation at the neutralization epitope in the env gene. *J Virol 65:1710*.
60. Ivanoff, L. A., D. J. Looney, C. McDanal, J. F. Morris, F. Wong-Staal, A. J. Langlois, S. R. Petteway, Jr., and T. J. Matthews. 1991. Alteration of HIV-1 infectivity and neutralization by a single amino acid replacement in the V3 loop domain. *AIDS Res Hum Retroviruses 7:595*.

61. Myers, G., . Korber, B. Wain-Hobson, S. Jeang, KT. Henderson, LE. Pavlakis, GN. 1994. *Human retroviruses and AIDS. A compilation and analisis of nucleid acid and amino acid sequences. Los Alamos, NM: Los Alamos National Laboratory*.

62. Ivanoff, L. A., J. W. Dubay, J. F. Morris, S. J. Roberts, L. Gutshall, E. J. Sternberg, E. Hunter, T. J. Matthews, and S. R. Petteway, Jr. 1992. V3 loop region of the HIV-1 gp120 envelope protein is essential for virus infectivity. *Virology 187:423*.

63. Freed, E. O., D. J. Myers, and R. Risser. 1991. Identification of the principal neutralizing determinant of human immunodeficiency virus type 1 as a fusion domain. *J Virol 65:190*.

64. Willey, R. L., T. S. Theodore, and M. A. Martin. 1994. Amino acid substitutions in the human immunodeficiency virus type 1 gp120 V3 loop that change viral tropism also alter physical and functional properties of the virion envelope. *J Virol 68:4409*.

65. Pedroza-Martins, L., K. B. Gurney, B. E. Torbett, and C. H. Uittenbogaart. 1998. Differential tropism and replication kinetics of human immunodeficiency virus type 1 isolates in thymocytes: coreceptor expression allows viral entry, but productive infection of distinct subsets is determined at the postentry level. *J Virol 72:9441*.

66. Schmidtmayerova, H., M. Alfano, G. Nuovo, and M. Bukrinsky. 1998. Human immunodeficiency virus type 1 T-lymphotropic strains enter macrophages via a CD4- and CXCR4-mediated pathway: replication is restricted at a postentry level. *J Virol 72:4633*.

67. Asjo, B., L. Morfeldt-Manson, J. Albert, G. Biberfeld, A. Karlsson, K. Lidman, and E. M. Fenyo. 1986. Replicative capacity of human immunodeficiency virus from patients with varying severity of HIV infection. *Lancet 2:660*.

68. Tersmette, M., R. E. de Goede, B. J. Al, I. N. Winkel, R. A. Gruters, H. T. Cuypers, H. G. Huisman, and F. Miedema. 1988. Differential syncytium-inducing capacity of human immunodeficiency virus isolates: frequent detection of syncytium-inducing isolates in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. *J Virol 62:2026*.

69. Connor, R. I., and D. D. Ho. 1994. Human immunodeficiency virus type 1 variants with increased replicative capacity develop during the asymptomatic stage before disease progression. *J Virol 68:4400*.

70. Chesebro, B., K. Wehrly, J. Nishio, and S. Perryman. 1992. Macrophage-tropic human immunodeficiency virus isolates from different patients exhibit unusual V3 envelope sequence homogeneity in comparison with T-cell-tropic isolates: definition of critical amino acids involved in cell tropism. *J Virol 66:6547*.

71. De Jong, J. J., A. De Ronde, W. Keulen, M. Tersmette, and J. Goudsmit. 1992. Minimal requirements for the human immunodeficiency virus type 1 V3 domain to support the syncytium-inducing phenotype: analysis by single amino acid substitution. *J Virol 66:6777*.

72. Fouchier, R. A., M. Groenink, N. A. Kootstra, M. Tersmette, H. G. Huisman, F. Miedema, and H. Schuitemaker. 1992. Phenotype-associated sequence variation in the third variable domain of the human immunodeficiency virus type 1 gp120 molecule. *J Virol 66:3183*.

73. Dalgleish, A. G., P. C. Beverley, P. R. Clapham, D. H. Crawford, M. F. Greaves, and R. A. Weiss. 1984. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature 312:763*.

74. Klatzmann, D., E. Champagne, S. Chamaret, J. Gruest, D. Guetard, T. Hercend, J. C. Gluckman, and L. Montagnier. 1984. T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature 312:767*.

75. Harouse, J. M., S. Bhat, S. L. Spitalnik, M. Laughlin, K. Stefano, D. H. Silberberg, and F. Gonzalez-Scarano. 1991. Inhibition of entry of HIV-1 in neural cell lines by antibodies against galactosyl ceramide. *Science 253:320*.

76. Yahi, N., S. Baghdiguian, H. Moreau, and J. Fantini. 1992. Galactosyl ceramide (or a closely related molecule) is the receptor for human immunodeficiency virus type 1 on human colon epithelial HT29 cells. *J Virol 66:4848*.

77. Maddon, P. J., D. R. Littman, M. Godfrey, D. E. Maddon, L. Chess, and R. Axel. 1985. The isolation and nucleotide sequence of a cDNA encoding the T cell surface protein T4: a new member of the immunoglobulin gene family. *Cell 42:93*.

78. Reinherz, E. L., P. C. Kung, G. Goldstein, and S. F. Schlossman. 1979. Separation of functional subsets of human T cells by a monoclonal antibody. *Proc Natl Acad Sci U S A 76:4061*.

79. Hussain, L. A., and T. Lehner. 1995. Comparative investigation of Langerhans' cells and potential receptors for HIV in oral, genitourinary and rectal epithelia. *Immunology 85:475*.

80. Weiss, R. 1994. *Human receptors for retroviruses. In: Wimmer E, ed. Cellular receptor for animal viruses. Plainview: Cold Spring Harbor Laboratory Press*.

81. James, W. W., RA. Simon JHM. 1996. *The receptor for VIH:Dissection of CD4 and studies on putative accessory factors. In:Littman DR, ed. The CD4 molecule. Roles in T lymphocytes and in VIH disease. Berlin: Springer-Verlag*.

82. Harouse, J. M., and F. Gonzalez-Scarano. 1996. Infection of SK-N-MC cells, a CD4-negative neuroblastoma cell line, with primary human immunodeficiency virus type 1 isolates. *J Virol 70:7290*.

83. Albright, A. V., J. Strizki, J. M. Harouse, E. Lavi, M. O'Connor, and F. Gonzalez-Scarano. 1996. HIV-1 infection of cultured human adult oligodendrocytes. *Virology 217:211*.

84. Strizki, J. M., A. V. Albright, H. Sheng, M. O'Connor, L. Perrin, and F. Gonzalez-Scarano. 1996. Infection of primary human microglia and monocyte-derived macrophages with human immunodeficiency virus type 1 isolates: evidence of differential tropism. *J Virol 70:7654*.

85. Brogi, A., R. Presentini, P. Piomboni, G. Collodel, M. Strazza, D. Solazzo, and E. Costantino-Ceccarini. 1995. Human sperm and spermatogonia express a galactoglycerolipid which interacts with gp120. *J Submicrosc Cytol Pathol 27:565*.

86. Brogi, A., R. Presentini, D. Solazzo, P. Piomboni, and E. Costantino-Ceccarini. 1996. Interaction of human immunodeficiency virus type 1 envelope glycoprotein gp120 with a galactoglycerolipid associated with human sperm. *AIDS Res Hum Retroviruses 12:483*.

87. Endres, M. J., P. R. Clapham, M. Marsh, M. Ahuja, J. D. Turner, A. McKnight, J. F. Thomas, B. Stoebenau-Haggarty, S. Choe, P. J. Vance, T. N. Wells, C. A. Power, S. S. Sutterwala, R. W. Doms, N. R. Landau, and J. A. Hoxie. 1996. CD4-independent infection by HIV-2 is mediated by fusin/CXCR4. *Cell 87:745*.

88. Willett, B. J., M. J. Hosie, J. C. Neil, J. D. Turner, and J. A. Hoxie. 1997. Common mechanism of infection by lentiviruses. *Nature 385:587*.

89. Zhang, J., A. Gupta, R. Dave, M. Yimen, B. Zerhouni, and K. Saha. 2001. Isolation of primary HIV-1 that target CD8+ T Lymphocytes using CD8 as a receptor. *Nat Med 7:65*.

90. Berger, E. A. 1997. HIV entry and tropism: the chemokine receptor connection. *Aids 11:S3*.

91. Maddon, P. J., A. G. Dalgleish, J. S. McDougal, P. R. Clapham, R. A. Weiss, and R. Axel. 1986. The T4 gene encodes the AIDS virus receptor and is expressed in the immune system and the brain. *Cell 47:333*.

92. Chesebro, B., R. Buller, J. Portis, and K. Wehrly. 1990. Failure of human immunodeficiency virus entry and infection in CD4-positive human brain and skin cells. *J Virol 64:215*.

93. Clapham, P. R., D. Blanc, and R. A. Weiss. 1991. Specific cell surface requirements for the infection of CD4-positive cells by human immunodeficiency virus types 1 and 2 and by Simian immunodeficiency virus. *Virology 181:703*.

94. Ashorn, P. A., E. A. Berger, and B. Moss. 1990. Human immunodeficiency virus envelope glycoprotein/CD4-mediated fusion of nonprimate cells with human cells. *J Virol 64:2149*.

95. Feng, Y., C. C. Broder, P. E. Kennedy, and E. A. Berger. 1996. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science 272:872*.

96. Oberlin, E., A. Amara, F. Bachelerie, C. Bessia, J. L. Virelizier, F. Arenzana-Seisdedos, O. Schwartz, J. M. Heard, I. Clark-Lewis, D. F. Legler, M. Loetscher, M. Baggiolini, and B. Moser. 1996. The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1 [published erratum appears in Nature 1996 Nov 21;384(6606):288]. *Nature 382:833*.

97. Bleul, C. C., M. Farzan, H. Choe, C. Parolin, I. Clark-Lewis, J. Sodroski, and T. A. Springer. 1996. The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature 382:829*.

98. Murphy, P. M. 1994. The molecular biology of leukocyte chemoattractant receptors. *Annu Rev Immunol 12:593*.

99. Cocchi, F., A. L. DeVico, A. Garzino-Demo, S. K. Arya, R. C. Gallo, and P. Lusso. 1995. Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8+ T cells. *Science 270:1811*.

100. Walker, C. M., D. J. Moody, D. P. Stites, and J. A. Levy. 1986. CD8+ lymphocytes can control HIV infection in vitro by suppressing virus replication. *Science 234:1563*.

101. Alkhatib, G., C. Combadiere, C. C. Broder, Y. Feng, P. E. Kennedy, P. M. Murphy, and E. A. Berger. 1996. CC CKR5: a RANTES, MIP-1alpha, MIP-1beta receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science 272:1955*.

102. Choe, H., M. Farzan, Y. Sun, N. Sullivan, B. Rollins, P. D. Ponath, L. Wu, C. R. Mackay, G. LaRosa, W. Newman, N. Gerard, C. Gerard, and J. Sodroski. 1996. The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell 85:1135*.

103. Deng, H., R. Liu, W. Ellmeier, S. Choe, D. Unutmaz, M. Burkhart, P. Di Marzio, S. Marmon, R. E. Sutton, C. M. Hill, C. B. Davis, S. C. Peiper, T. J. Schall, D. R. Littman, and N. R. Landau. 1996. Identification of a major co-receptor for primary isolates of HIV-1. *Nature 381:661*.

104. Doranz, B. J., J. Rucker, Y. Yi, R. J. Smyth, M. Samson, S. C. Peiper, M. Parmentier, R. G. Collman, and R. W. Doms. 1996. A dual-tropic primary HIV-1 isolate that uses fusin and the beta-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell 85:1149*.

105. Zhang, L., Y. Huang, T. He, Y. Cao, and D. D. Ho. 1996. HIV-1 subtype and second-receptor use. *Nature 383:768*.

106. Dragic, T., V. Litwin, G. P. Allaway, S. R. Martin, Y. Huang, K. A. Nagashima, C. Cayanan, P. J. Maddon, R. A. Koup, J. P. Moore, and W. A. Paxton. 1996. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature 381:667*.

107. Horuk, R., J. Hesselgesser, Y. Zhou, D. Faulds, M. Halks-Miller, S. Harvey, D. Taub, M. Samson, M. Parmentier, J. Rucker, B. J. Doranz, and R. W. Doms. 1998. The CC chemokine I-309 inhibits CCR8-dependent infection by diverse HIV-1 strains. *J Biol Chem 273:386*.

108. Tiffany, H. L., L. L. Lautens, J. L. Gao, J. Pease, M. Locati, C. Combadiere, W. Modi, T. I. Bonner, and P. M. Murphy. 1997. Identification of CCR8: a human monocyte and thymus receptor for the CC chemokine I-309. *J Exp Med 186:165*.

109. Lee, S., H. L. Tiffany, L. King, P. M. Murphy, H. Golding, and M. B. Zaitseva. 2000. CCR8 on human thymocytes functions as a human immunodeficiency virus type 1 coreceptor. *J Virol 74:6946*.

110. Zabel, B. A., W. W. Agace, J. J. Campbell, H. M. Heath, D. Parent, A. I. Roberts, E. C. Ebert, N. Kassam, S. Qin, M. Zovko, G. J. LaRosa, L. L. Yang, D. Soler, E. C. Butcher, P. D. Ponath, C. M. Parker, and D. P. Andrew. 1999. Human G protein-coupled receptor GPR-9-6/CC chemokine receptor 9 is selectively expressed on intestinal homing T lymphocytes, mucosal lymphocytes, and thymocytes and is required for thymus-expressed chemokine-mediated chemotaxis. *J Exp Med 190:1241*.

111. Papadakis, K. A., J. Prehn, V. Nelson, L. Cheng, S. W. Binder, P. D. Ponath, D. P. Andrew, and S. R. Targan. 2000. The role of thymus-expressed chemokine and its receptor CCR9 on lymphocytes in the regional specialization of the mucosal immune system. *J Immunol 165:5069*.

112. Imai, T., K. Hieshima, C. Haskell, M. Baba, M. Nagira, M. Nishimura, M. Kakizaki, S. Takagi, H. Nomiyama, T. J. Schall, and O. Yoshie. 1997. Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell 91:521*.

113. Raport, C. J., V. L. Schweickart, R. L. Eddy, T. B. Shows, and P. W. Gray. 1995. The orphan G-protein-coupled receptor-encoding gene V28 is closely related to genes for chemokine receptors and is expressed in lymphoid and neural tissues. *Gene 163:295*.

114. Rucker, J., A. L. Edinger, M. Sharron, M. Samson, B. Lee, J. F. Berson, Y. Yi, B. Margulies, R. G. Collman, B. J. Doranz, M. Parmentier, and R. W. Doms. 1997. Utilization of chemokine receptors, orphan receptors, and herpesvirus-encoded receptors by diverse human and simian immunodeficiency viruses. *J Virol 71:8999*.

115. Combadiere, C., K. Salzwedel, E. D. Smith, H. L. Tiffany, E. A. Berger, and P. M. Murphy. 1998. Identification of CX3CR1. A chemotactic receptor for the human CX3C chemokine fractalkine and a fusion coreceptor for HIV-1. *J Biol Chem 273:23799*.

116. He, J., Y. Chen, M. Farzan, H. Choe, A. Ohagen, S. Gartner, J. Busciglio, X. Yang, W. Hofmann, W. Newman, C. R. Mackay, J. Sodroski, and D. Gabuzda.

1997. CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. *Nature 385:645*.

117. Albright, A. V., J. T. Shieh, T. Itoh, B. Lee, D. Pleasure, M. J. O'Connor, R. W. Doms, and F. Gonzalez-Scarano. 1999. Microglia express CCR5, CXCR4, and CCR3, but of these, CCR5 is the principal coreceptor for human immunodeficiency virus type 1 dementia isolates. *J Virol 73:205*.
118. Zhang, Y. J., and J. P. Moore. 1999. Will multiple coreceptors need to be targeted by inhibitors of human immunodeficiency virus type 1 entry? *J Virol 73:3443*.
119. Zhang, Y. J., T. Dragic, Y. Cao, L. Kostrikis, D. S. Kwon, D. R. Littman, V. N. KewalRamani, and J. P. Moore. 1998. Use of coreceptors other than CCR5 by non-syncytium-inducing adult and pediatric isolates of human immunodeficiency virus type 1 is rare in vitro. *J Virol 72:9337*.
120. Unutmaz, D., W. Xiang, M. J. Sunshine, J. Campbell, E. Butcher, and D. R. Littman. 2000. The primate lentiviral receptor Bonzo/STRL33 is coordinately regulated with CCR5 and its expression pattern is conserved between human and mouse. *J Immunol 165:3284*.
121. Mognetti, B., M. Moussa, J. Croitoru, E. Menu, D. Dormont, P. Roques, and G. Chaouat. 2000. HIV-1 co-receptor expression on trophoblastic cells from early placentas and permissivity to infection by several HIV-1 primary isolates. *Clin Exp Immunol 119:486*.
122. Deng, H. K., D. Unutmaz, V. N. KewalRamani, and D. R. Littman. 1997. Expression cloning of new receptors used by simian and human immunodeficiency viruses. *Nature 388:296*.
123. Farzan, M., H. Choe, K. Martin, L. Marcon, W. Hofmann, G. Karlsson, Y. Sun, P. Barrett, N. Marchand, N. Sullivan, N. Gerard, C. Gerard, and J. Sodroski. 1997. Two orphan seven-transmembrane segment receptors which are expressed in CD4-positive cells support simian immunodeficiency virus infection. *J Exp Med 186:405*.
124. Tokizawa, S., N. Shimizu, L. Hui-Yu, F. Deyu, Y. Haraguchi, T. Oite, and H. Hoshino. 2000. Infection of mesangial cells with HIV and SIV: identification of GPR1 as a coreceptor. *Kidney Int 58:607*.
125. Edinger, A. L., T. L. Hoffman, M. Sharron, B. Lee, B. O'Dowd, and R. W. Doms. 1998. Use of GPR1, GPR15, and STRL33 as coreceptors by diverse

human immunodeficiency virus type 1 and simian immunodeficiency virus envelope proteins. *Virology 249:367*.

126. Park, I. W., J. F. Wang, and J. E. Groopman. 1999. Expression and utilization of co-receptors in HIV and simian immunodeficiency virus infection of megakaryocytes. *Aids 13:2023*.
127. Liao, F., G. Alkhatib, K. W. Peden, G. Sharma, E. A. Berger, and J. M. Farber. 1997. STRL33, A novel chemokine receptor-like protein, functions as a fusion cofactor for both macrophage-tropic and T cell line-tropic HIV-1. *J Exp Med 185:2015*.
128. Loetscher, M., A. Amara, E. Oberlin, N. Brass, D. Legler, P. Loetscher, M. D'Apuzzo, E. Meese, D. Rousset, J. L. Virelizier, M. Baggiolini, F. Arenzana-Seisdedos, and B. Moser. 1997. TYMSTR, a putative chemokine receptor selectively expressed in activated T cells, exhibits HIV-1 coreceptor function. *Curr Biol 7:652*.
129. Alkhatib, G., F. Liao, E. A. Berger, J. M. Farber, and K. W. Peden. 1997. A new SIV co-receptor, STRL33. *Nature 388:238*.
130. Unutmaz, D., V. N. KewalRamani, and D. R. Littman. 1998. G protein-coupled receptors in HIV and SIV entry: new perspectives on lentivirus-host interactions and on the utility of animal models. *Semin Immunol 10:225*.
131. Pleskoff, O., C. Treboute, A. Brelot, N. Heveker, M. Seman, and M. Alizon. 1997. Identification of a chemokine receptor encoded by human cytomegalovirus as a cofactor for HIV-1 entry. *Science 276:1874*.
132. Owman, C., A. Garzino-Demo, F. Cocchi, M. Popovic, A. Sabirsh, and R. C. Gallo. 1998. The leukotriene B4 receptor functions as a novel type of coreceptor mediating entry of primary HIV-1 isolates into CD4-positive cells. *Proc Natl Acad Sci U S A 95:9530*.
133. Samson, M., A. L. Edinger, P. Stordeur, J. Rucker, V. Verhasselt, M. Sharron, C. Govaerts, C. Mollereau, G. Vassart, R. W. Doms, and M. Parmentier. 1998. ChemR23, a putative chemoattractant receptor, is expressed in monocyte-derived dendritic cells and macrophages and is a coreceptor for SIV and some primary HIV-1 strains. *Eur J Immunol 28:1689*.
134. Choe, H., M. Farzan, M. Konkel, K. Martin, Y. Sun, L. Marcon, M. Cayabyab, M. Berman, M. E. Dorf, N. Gerard, C. Gerard, and J. Sodroski. 1998. The orphan seven-transmembrane receptor apj supports the entry of primary T-cell-

line-tropic and dualtropic human immunodeficiency virus type 1. *J Virol 72:6113*.

135. Edinger, A. L., T. L. Hoffman, M. Sharron, B. Lee, Y. Yi, W. Choe, D. L. Kolson, B. Mitrovic, Y. Zhou, D. Faulds, R. G. Collman, J. Hesselgesser, R. Horuk, and R. W. Doms. 1998. An orphan seven-transmembrane domain receptor expressed widely in the brain functions as a coreceptor for human immunodeficiency virus type 1 and simian immunodeficiency virus. *J Virol 72:7934*.
136. Hinuma, S., Y. Habata, R. Fujii, Y. Kawamata, M. Hosoya, S. Fukusumi, C. Kitada, Y. Masuo, T. Asano, H. Matsumoto, M. Sekiguchi, T. Kurokawa, O. Nishimura, H. Onda, and M. Fujino. 1998. A prolactin-releasing peptide in the brain. *Nature 393:272*.
137. Tatemoto, K., M. Hosoya, Y. Habata, R. Fujii, T. Kakegawa, M. X. Zou, Y. Kawamata, S. Fukusumi, S. Hinuma, C. Kitada, T. Kurokawa, H. Onda, and M. Fujino. 1998. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem Biophys Res Commun 251:471*.
138. Cayabyab, M., S. Hinuma, M. Farzan, H. Choe, S. Fukusumi, C. Kitada, N. Nishizawa, M. Hosoya, O. Nishimura, T. Messele, G. Pollakis, J. Goudsmit, M. Fujino, and J. Sodroski. 2000. Apelin, the natural ligand of the orphan seven-transmembrane receptor APJ, inhibits human immunodeficiency virus type 1 entry. *J Virol 74:11972*.
139. Pal, R., A. Garzino-Demo, P. D. Markham, J. Burns, M. Brown, R. C. Gallo, and A. L. DeVico. 1997. Inhibition of HIV-1 infection by the beta-chemokine MDC. *Science 278:695*.
140. Imai, T., D. Chantry, C. J. Raport, C. L. Wood, M. Nishimura, R. Godiska, O. Yoshie, and P. W. Gray. 1998. Macrophage-derived chemokine is a functional ligand for the CC chemokine receptor 4. *J Biol Chem 273:1764*.
141. Struyf, S., P. Proost, S. Sozzani, A. Mantovani, A. Wuyts, E. De Clercq, D. Schols, and J. Van Damme. 1998. Enhanced anti-HIV-1 activity and altered chemotactic potency of NH2-terminally processed macrophage-derived chemokine (MDC) imply an additional MDC receptor. *J Immunol 161:2672*.
142. Berson, J. F., and R. W. Doms. 1998. Structure-function studies of the HIV-1 coreceptors. *Semin Immunol 10:237*.

143. Lu, Z., J. F. Berson, Y. Chen, J. D. Turner, T. Zhang, M. Sharron, M. H. Jenks, Z. Wang, J. Kim, J. Rucker, J. A. Hoxie, S. C. Peiper, and R. W. Doms. 1997. Evolution of HIV-1 coreceptor usage through interactions with distinct CCR5 and CXCR4 domains. *Proc Natl Acad Sci U S A 94:6426*.

144. Dragic, T., A. Trkola, S. W. Lin, K. A. Nagashima, F. Kajumo, L. Zhao, W. C. Olson, L. Wu, C. R. Mackay, G. P. Allaway, T. P. Sakmar, J. P. Moore, and P. J. Maddon. 1998. Amino-terminal substitutions in the CCR5 coreceptor impair gp120 binding and human immunodeficiency virus type 1 entry. *J Virol 72:279*.

145. Wu, L., G. LaRosa, N. Kassam, C. J. Gordon, H. Heath, N. Ruffing, H. Chen, J. Humblias, M. Samson, M. Parmentier, J. P. Moore, and C. R. Mackay. 1997. Interaction of chemokine receptor CCR5 with its ligands: multiple domains for HIV-1 gp120 binding and a single domain for chemokine binding. *J Exp Med 186:1373*.

146. Picard, L., D. A. Wilkinson, A. McKnight, P. W. Gray, J. A. Hoxie, P. R. Clapham, and R. A. Weiss. 1997. Role of the amino-terminal extracellular domain of CXCR-4 in human immunodeficiency virus type 1 entry. *Virology 231:105*.

147. Trkola, A., T. Dragic, J. Arthos, J. M. Binley, W. C. Olson, G. P. Allaway, C. Cheng-Mayer, J. Robinson, P. J. Maddon, and J. P. Moore. 1996. CD4-dependent, antibody-sensitive interactions between HIV-1 and its co-receptor CCR-5. *Nature 384:184*.

148. Wu, L., N. P. Gerard, R. Wyatt, H. Choe, C. Parolin, N. Ruffing, A. Borsetti, A. A. Cardoso, E. Desjardin, W. Newman, C. Gerard, and J. Sodroski. 1996. CD4-induced interaction of primary HIV-1 gp120 glycoproteins with the chemokine receptor CCR-5. *Nature 384:179*.

149. Berger, E. A., R. W. Doms, E. M. Fenyo, B. T. Korber, D. R. Littman, J. P. Moore, Q. J. Sattentau, H. Schuitemaker, J. Sodroski, and R. A. Weiss. 1998. A new classification for HIV-1. *Nature 391:240*.

150. Schuitemaker, H., M. Koot, N. A. Kootstra, M. W. Dercksen, R. E. de Goede, R. P. van Steenwijk, J. M. Lange, J. K. Schattenkerk, F. Miedema, and M. Tersmette. 1992. Biological phenotype of human immunodeficiency virus type 1 clones at different stages of infection: progression of disease is associated with a shift from monocytotropic to T-cell-tropic virus population. *J Virol 66:1354*.

151. Connor, R. I., and D. D. Ho. 1994. Transmission and pathogenesis of human immunodeficiency virus type 1. *AIDS Res Hum Retroviruses 10:321*.

152. Fear, W. R., A. M. Kesson, H. Naif, G. W. Lynch, and A. L. Cunningham. 1998. Differential tropism and chemokine receptor expression of human immunodeficiency virus type 1 in neonatal monocytes, monocyte-derived macrophages, and placental macrophages. *J Virol 72:1334*.

153. Zaitseva, M., A. Blauvelt, S. Lee, C. K. Lapham, V. Klaus-Kovtun, H. Mostowski, J. Manischewitz, and H. Golding. 1997. Expression and function of CCR5 and CXCR4 on human Langerhans cells and macrophages: implications for HIV primary infection. *Nat Med 3:1369*.

154. Tedla, N., P. Palladinetti, M. Kelly, R. K. Kumar, N. DiGirolamo, U. Chattophadhay, B. Cooke, P. Truskett, J. Dwyer, D. Wakefield, and A. Lloyd. 1996. Chemokines and T lymphocyte recruitment to lymph nodes in HIV infection. *Am J Pathol 148:1367*.

155. Trumpfheller, C., K. Tenner-Racz, P. Racz, B. Fleischer, and S. Frosch. 1998. Expression of macrophage inflammatory protein (MIP)-1alpha, MIP-1beta, and RANTES genes in lymph nodes from HIV+ individuals: correlation with a Th1-type cytokine response. *Clin Exp Immunol 112:92*.

156. Margolis, L. B., S. Glushakova, J. C. Grivel, and P. M. Murphy. 1998. Blockade of CC chemokine receptor 5 (CCR5)-tropic human immunodeficiency virus-1 replication in human lymphoid tissue by CC chemokines. *J Clin Invest 101:1876*.

157. Connor, R. I., H. Mohri, Y. Cao, and D. D. Ho. 1993. Increased viral burden and cytopathicity correlate temporally with CD4+ T-lymphocyte decline and clinical progression in human immunodeficiency virus type 1-infected individuals. *J Virol 67:1772*.

158. D'Souza, M. P., and V. A. Harden. 1996. Chemokines and HIV-1 second receptors. Confluence of two fields generates optimism in AIDS research. *Nat Med 2:1293*.

159. Fauci, A. S. 1996. Host factors and the pathogenesis of HIV-induced disease. *Nature 384:529*.

160. Tersmette, M., J. M. Lange, R. E. de Goede, F. de Wolf, J. K. Eeftink-Schattenkerk, P. T. Schellekens, R. A. Coutinho, J. G. Huisman, J. Goudsmit, and F. Miedema. 1989. Association between biological properties of human

immunodeficiency virus variants and risk for AIDS and AIDS mortality. *Lancet 1:983*.

161. van 't Wout, A. B., H. Blaak, L. J. Ran, M. Brouwer, C. Kuiken, and H. Schuitemaker. 1998. Evolution of syncytium-inducing and non-syncytium-inducing biological virus clones in relation to replication kinetics during the course of human immunodeficiency virus type 1 infection. *J Virol 72:5099*.
162. Herbein, G., U. Mahlknecht, F. Batliwalla, P. Gregersen, T. Pappas, J. Butler, W. A. O'Brien, and E. Verdin. 1998. Apoptosis of CD8+ T cells is mediated by macrophages through interaction of HIV gp120 with chemokine receptor CXCR4. *Nature 395:189*.
163. Blanco, J., E. Jacotot, C. Cabrera, A. Cardona, B. Clotet, E. De Clercq, and J. A. Este. 1999. The implication of the chemokine receptor CXCR4 in HIV-1 envelope protein-induced apoptosis is independent of the G protein-mediated signalling. *Aids 13:909*.
164. Esser, M. T., J. W. Bess, Jr., K. Suryanarayana, E. Chertova, D. Marti, M. Carrington, L. O. Arthur, and J. D. Lifson. 2001. Partial Activation and Induction of Apoptosis in CD4(+) and CD8(+) T Lymphocytes by Conformationally Authentic Noninfectious Human Immunodeficiency Virus Type 1. *J Virol 75:1152*.
165. Berkowitz, R. D., S. Alexander, C. Bare, V. Linquist-Stepps, M. Bogan, M. E. Moreno, L. Gibson, E. D. Wieder, J. Kosek, C. A. Stoddart, and J. M. McCune. 1998. CCR5- and CXCR4-utilizing strains of human immunodeficiency virus type 1 exhibit differential tropism and pathogenesis in vivo. *J Virol 72:10108*.
166. Liu, R., W. A. Paxton, S. Choe, D. Ceradini, S. R. Martin, R. Horuk, M. E. MacDonald, H. Stuhlmann, R. A. Koup, and N. R. Landau. 1996. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell 86:367*.
167. Huang, Y., W. A. Paxton, S. M. Wolinsky, A. U. Neumann, L. Zhang, T. He, S. Kang, D. Ceradini, Z. Jin, K. Yazdanbakhsh, K. Kunstman, D. Erickson, E. Dragon, N. R. Landau, J. Phair, D. D. Ho, and R. A. Koup. 1996. The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. *Nat Med 2:1240*.
168. Samson, M., F. Libert, B. J. Doranz, J. Rucker, C. Liesnard, C. M. Farber, S. Saragosti, C. Lapoumeroulie, J. Cognaux, C. Forceille, G. Muyldermans, C.

Verhofstede, G. Burtonboy, M. Georges, T. Imai, S. Rana, Y. Yi, R. J. Smyth, R. G. Collman, R. W. Doms, G. Vassart, and M. Parmentier. 1996. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature 382:722*.

169. Dean, M., M. Carrington, C. Winkler, G. A. Huttley, M. W. Smith, R. Allikmets, J. J. Goedert, S. P. Buchbinder, E. Vittinghoff, E. Gomperts, S. Donfield, D. Vlahov, R. Kaslow, A. Saah, C. Rinaldo, R. Detels, and S. J. O'Brien. 1996. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science 273:1856*.
170. Theodorou, I., L. Meyer, M. Magierowska, C. Katlama, and C. Rouzioux. 1997. HIV-1 infection in an individual homozygous for CCR5 delta 32. Seroco Study Group. *Lancet 349:1219*.
171. Biti, R., R. Ffrench, J. Young, B. Bennetts, G. Stewart, and T. Liang. 1997. HIV-1 infection in an individual homozygous for the CCR5 deletion allele. *Nat Med 3:252*.
172. van Rij, R. P., P. Portegies, T. Hallaby, J. M. Lange, J. Visser, A. M. Husman, A. B. van 't Wout, and H. Schuitemaker. 1999. Reduced prevalence of the CCR5 delta32 heterozygous genotype in human immunodeficiency virus-infected individuals with AIDS dementia complex. *J Infect Dis 180:854*.
173. McDermott, D. H., P. A. Zimmerman, F. Guignard, C. A. Kleeberger, S. F. Leitman, and P. M. Murphy. 1998. CCR5 promoter polymorphism and HIV-1 disease progression. Multicenter AIDS Cohort Study (MACS). *Lancet 352:866*.
174. Quillent, C., E. Oberlin, J. Braun, D. Rousset, G. Gonzalez-Canali, P. Metais, L. Montagnier, J. L. Virelizier, F. Arenzana-Seisdedos, and A. Beretta. 1998. HIV-1-resistance phenotype conferred by combination of two separate inherited mutations of CCR5 gene. *Lancet 351:14*.
175. Kostrikis, L. G., Y. Huang, J. P. Moore, S. M. Wolinsky, L. Zhang, Y. Guo, L. Deutsch, J. Phair, A. U. Neumann, and D. D. Ho. 1998. A chemokine receptor CCR2 allele delays HIV-1 disease progression and is associated with a CCR5 promoter mutation. *Nat Med 4:350*.
176. Lee, B., B. J. Doranz, S. Rana, Y. Yi, M. Mellado, J. M. Frade, A. C. Martinez, S. J. O'Brien, M. Dean, R. G. Collman, and R. W. Doms. 1998. Influence of the

CCR2-V64I polymorphism on human immunodeficiency virus type 1 coreceptor activity and on chemokine receptor function of CCR2b, CCR3, CCR5, and CXCR4. *J Virol 72:7450*.

177. Winkler, C., W. Modi, M. W. Smith, G. W. Nelson, X. Wu, M. Carrington, M. Dean, T. Honjo, K. Tashiro, D. Yabe, S. Buchbinder, E. Vittinghoff, J. J. Goedert, T. R. O'Brien, L. P. Jacobson, R. Detels, S. Donfield, A. Willoughby, E. Gomperts, D. Vlahov, J. Phair, and S. J. O'Brien. 1998. Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. ALIVE Study, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC). *Science 279:389*.
178. Mummidi, S., S. S. Ahuja, E. Gonzalez, S. A. Anderson, E. N. Santiago, K. T. Stephan, F. E. Craig, P. O'Connell, V. Tryon, R. A. Clark, M. J. Dolan, and S. K. Ahuja. 1998. Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression. *Nat Med 4:786*.
179. Dimmock, N. 1993. *Neutralization of animal viruses. Berlin:Springer-Verlag*.
180. Sattentau, Q. J. 1996. Neutralization of HIV-1 by antibody. *Curr Opin Immunol 8:540*.
181. Zolla-Pazner, S., and M. K. Gorny. 1992. Passive immunization for the prevention and treatment of HIV infection [editorial]. *Aids 6:1235*.
182. Trkola, A., A. B. Pomales, H. Yuan, B. Korber, P. J. Maddon, G. P. Allaway, H. Katinger, C. F. Barbas, 3rd, D. R. Burton, D. D. Ho, and et al. 1995. Cross-clade neutralization of primary isolates of human immunodeficiency virus type 1 by human monoclonal antibodies and tetrameric CD4-IgG. *J Virol 69:6609*.
183. Jonker, M., P. Neuhaus, C. Zurcher, A. Fucello, and G. Goldstein. 1985. OKT4 and OKT4A antibody treatment as immunosuppression for kidney transplantation in rhesus monkeys. *Transplantation 39:247*.
184. Smith, D. H., R. A. Byrn, S. A. Marsters, T. Gregory, J. E. Groopman, and D. J. Capon. 1987. Blocking of HIV-1 infectivity by a soluble, secreted form of the CD4 antigen. *Science 238:1704*.
185. Fisher, R. A., J. M. Bertonis, W. Meier, V. A. Johnson, D. S. Costopoulos, T. Liu, R. Tizard, B. D. Walker, M. S. Hirsch, R. T. Schooley, and et al. 1988. HIV infection is blocked in vitro by recombinant soluble CD4. *Nature 331:76*.

186. Hussey, R. E., N. E. Richardson, M. Kowalski, N. R. Brown, H. C. Chang, R. F. Siliciano, T. Dorfman, B. Walker, J. Sodroski, and E. L. Reinherz. 1988. A soluble CD4 protein selectively inhibits HIV replication and syncytium formation. *Nature 331:78*.

187. Deen, K. C., J. S. McDougal, R. Inacker, G. Folena-Wasserman, J. Arthos, J. Rosenberg, P. J. Maddon, R. Axel, and R. W. Sweet. 1988. A soluble form of CD4 (T4) protein inhibits AIDS virus infection. *Nature 331:82*.

188. Capon, D. J., S. M. Chamow, J. Mordenti, S. A. Marsters, T. Gregory, H. Mitsuya, R. A. Byrn, C. Lucas, F. M. Wurm, J. E. Groopman, and et al. 1989. Designing CD4 immunoadhesins for AIDS therapy. *Nature 337:525*.

189. Clapham, P. R., J. N. Weber, D. Whitby, K. McIntosh, A. G. Dalgleish, P. J. Maddon, K. C. Deen, R. W. Sweet, and R. A. Weiss. 1989. Soluble CD4 blocks the infectivity of diverse strains of HIV and SIV for T cells and monocytes but not for brain and muscle cells. *Nature 337:368*.

190. Byrn, R. A., I. Sekigawa, S. M. Chamow, J. S. Johnson, T. J. Gregory, D. J. Capon, and J. E. Groopman. 1989. Characterization of in vitro inhibition of human immunodeficiency virus by purified recombinant CD4. *J Virol 63:4370*.

191. Byrn, R. A., J. Mordenti, C. Lucas, D. Smith, S. A. Marsters, J. S. Johnson, P. Cossum, S. M. Chamow, F. M. Wurm, T. Gregory, and et al. 1990. Biological properties of a CD4 immunoadhesin. *Nature 344:667*.

192. Kahn, J. O., J. D. Allan, T. L. Hodges, L. D. Kaplan, C. J. Arri, H. F. Fitch, A. E. Izu, J. Mordenti, J. E. Sherwin, J. E. Groopman, and et al. 1990. The safety and pharmacokinetics of recombinant soluble CD4 (rCD4) in subjects with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. A phase 1 study. *Ann Intern Med 112:254*.

193. Schooley, R. T., T. C. Merigan, P. Gaut, M. S. Hirsch, M. Holodniy, T. Flynn, S. Liu, R. E. Byington, S. Henochowicz, E. Gubish, and et al. 1990. 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 112:247*.

194. Allaway, G. P., K. L. Davis-Bruno, G. A. Beaudry, E. B. Garcia, E. L. Wong, A. M. Ryder, K. W. Hasel, M. C. Gauduin, R. A. Koup, J. S. McDougal, and et al. 1995. Expression and characterization of CD4-IgG2, a novel heterotetramer that neutralizes primary HIV type 1 isolates. *AIDS Res Hum Retroviruses 11:533*.

195. Jacobson, J. L., I. Trkola, A. et al. 1999. Results of a phase I trial of single-dose PRO 542, a novel inhibitor of HIV entry. In *39th Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Diego, California.

196. Shearer, W. I., R. et al. 2000. rCD4-IgG2 in HIV infected children phase I/II study. In *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, calif.

197. Seddiki, N., S. Nisole, B. Krust, C. Callebaut, G. Guichard, S. Muller, J. P. Briand, and A. G. Hovanessian. 1999. The V3 loop-mimicking pseudopeptide 5[Kpsi(CH2N)PR]-TASP inhibits HIV infection in primary macrophage cultures. *AIDS Res Hum Retroviruses 15:381*.

198. Callebaut, C., E. Jacotot, B. Krust, G. Guichard, J. Blanco, A. Valenzuela, J. Svab, S. Muller, J. P. Briand, and A. G. Hovanessian. 1997. Pseudopeptide TASP inhibitors of HIV entry bind specifically to a 95-kDa cell surface protein. *J Biol Chem 272:7159*.

199. Mitsuya, H., D. J. Looney, S. Kuno, R. Ueno, F. Wong-Staal, and S. Broder. 1988. Dextran sulfate suppression of viruses in the HIV family: inhibition of virion binding to CD4+ cells. *Science 240:646*.

200. Baba, M., D. Schols, R. Pauwels, H. Nakashima, and E. De Clercq. 1990. Sulfated polysaccharides as potent inhibitors of HIV-induced syncytium formation: a new strategy towards AIDS chemotherapy. *J Acquir Immune Defic Syndr 3:493*.

201. Hartman, N. R., D. G. Johns, and H. Mitsuya. 1990. Pharmacokinetic analysis of dextran sulfate in rats as pertains to its clinical usefulness for therapy of HIV infection. *AIDS Res Hum Retroviruses 6:805*.

202. Gordon, M., M. Guralnik, Y. Kaneko, T. Mimura, J. Goodgame, and W. Lang. 1995. Further clinical studies of curdlan sulfate (CRDS)--an anti-HIV agent. *J Med 26:97*.

203. Weaver, J. L., P. S. Pine, G. Dutschman, Y. C. Cheng, K. H. Lee, and A. Aszalos. 1992. Prevention of binding of rgp120 by anti-HIV active tannins. *Biochem Pharmacol 43:2479*.

204. Pal, R., S. Mumbauer, G. Hoke, R. Larocca, C. Myers, M. G. Sarngadharan, and C. A. Stein. 1991. Effect of Evans blue and trypan blue on syncytia formation and infectivity of human immunodeficiency virus type I and type II in vitro. *AIDS Res Hum Retroviruses 7:537*.

205. Krust, B., C. Callebaut, and A. G. Hovanessian. 1993. Inhibition of entry of HIV into cells by poly(A).poly(U). *AIDS Res Hum Retroviruses 9:1087*.

206. Stein, C. A., L. M. Neckers, B. C. Nair, S. Mumbauer, G. Hoke, and R. Pal. 1991. Phosphorothioate oligodeoxycytidine interferes with binding of HIV-1 gp120 to CD4. *J Acquir Immune Defic Syndr 4:686*.

207. Wyatt, J. R., T. A. Vickers, J. L. Roberson, R. W. Buckheit, Jr., T. Klimkait, E. DeBaets, P. W. Davis, B. Rayner, J. L. Imbach, and D. J. Ecker. 1994. Combinatorially selected guanosine-quartet structure is a potent inhibitor of human immunodeficiency virus envelope-mediated cell fusion. *Proc Natl Acad Sci U S A 91:1356*.

208. Proudfoot, A. E., C. A. Power, A. J. Hoogewerf, M. O. Montjovent, F. Borlat, R. E. Offord, and T. N. Wells. 1996. Extension of recombinant human RANTES by the retention of the initiating methionine produces a potent antagonist. *J Biol Chem 271:2599*.

209. Gong, J. H., M. Uguccioni, B. Dewald, M. Baggiolini, and I. Clark-Lewis. 1996. RANTES and MCP-3 antagonists bind multiple chemokine receptors. *J Biol Chem 271:10521*.

210. Zhang, Y., and B. J. Rollins. 1995. A dominant negative inhibitor indicates that monocyte chemoattractant protein 1 functions as a dimer. *Mol Cell Biol 15:4851*.

211. Simmons, G., P. R. Clapham, L. Picard, R. E. Offord, M. M. Rosenkilde, T. W. Schwartz, R. Buser, T. N. Wells, and A. E. Proudfoot. 1997. Potent inhibition of HIV-1 infectivity in macrophages and lymphocytes by a novel CCR5 antagonist. *Science 276:276*.

212. Mack, M., B. Luckow, P. J. Nelson, J. Cihak, G. Simmons, P. R. Clapham, N. Signoret, M. Marsh, M. Stangassinger, F. Borlat, T. N. Wells, D. Schlondorff, and A. E. Proudfoot. 1998. Aminooxypentane-RANTES induces CCR5 internalization but inhibits recycling: a novel inhibitory mechanism of HIV infectivity. *J Exp Med 187:1215*.

213. Heveker, N., M. Montes, L. Germeroth, A. Amara, A. Trautmann, M. Alizon, and J. Schneider-Mergener. 1998. Dissociation of the signalling and antiviral properties of SDF-1-derived small peptides. *Curr Biol 8:369*.

214. Nagasawa, T., S. Hirota, K. Tachibana, N. Takakura, S. Nishikawa, Y. Kitamura, N. Yoshida, H. Kikutani, and T. Kishimoto. 1996. Defects of B-cell

lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature 382:635*.

215. McKnight, A., D. Wilkinson, G. Simmons, S. Talbot, L. Picard, M. Ahuja, M. Marsh, J. A. Hoxie, and P. R. Clapham. 1997. Inhibition of human immunodeficiency virus fusion by a monoclonal antibody to a coreceptor (CXCR4) is both cell type and virus strain dependent. *J Virol 71:1692*.
216. Wu, L., W. A. Paxton, N. Kassam, N. Ruffing, J. B. Rottman, N. Sullivan, H. Choe, J. Sodroski, W. Newman, R. A. Koup, and C. R. Mackay. 1997. CCR5 levels and expression pattern correlate with infectability by macrophage-tropic HIV-1, in vitro. *J Exp Med 185:1681*.
217. Trkola, A., T. J. Ketas, K. A. Nagashima, L. Zhao, T. Cilliers, L. Morris, J. P. Moore, P. J. Maddon, and W. C. Olson. 2001. Potent, broad-spectrum inhibition of human immunodeficiency virus type 1 by the CCR5 monoclonal antibody PRO 140. *J Virol 75:579*.
218. Vila-Coro, A. J., M. Mellado, A. Martin de Ana, P. Lucas, G. del Real, A. C. Martinez, and J. M. Rodriguez-Frade. 2000. HIV-1 infection through the CCR5 receptor is blocked by receptor dimerization. *Proc Natl Acad Sci U S A 97:3388*.
219. Doranz, B. J., K. Grovit-Ferbas, M. P. Sharron, S. H. Mao, M. B. Goetz, E. S. Daar, R. W. Doms, and W. A. O'Brien. 1997. A small-molecule inhibitor directed against the chemokine receptor CXCR4 prevents its use as an HIV-1 coreceptor. *J Exp Med 186:1395*.
220. Schols, D., S. Struyf, J. Van Damme, J. A. Este, G. Henson, and E. De Clercq. 1997. Inhibition of T-tropic HIV strains by selective antagonization of the chemokine receptor CXCR4. *J Exp Med 186:1383*.
221. Murakami, T., T. Nakajima, Y. Koyanagi, K. Tachibana, N. Fujii, H. Tamamura, N. Yoshida, M. Waki, A. Matsumoto, O. Yoshie, T. Kishimoto, N. Yamamoto, and T. Nagasawa. 1997. A small molecule CXCR4 inhibitor that blocks T cell line-tropic HIV-1 infection. *J Exp Med 186:1389.*
222. Donzella, G. A., D. Schols, S. W. Lin, J. A. Este, K. A. Nagashima, P. J. Maddon, G. P. Allaway, T. P. Sakmar, G. Henson, E. De Clercq, and J. P. Moore. 1998. AMD3100, a small molecule inhibitor of HIV-1 entry via the CXCR4 co-receptor. *Nat Med 4:72*.
223. Baba, M., O. Nishimura, N. Kanzaki, M. Okamoto, H. Sawada, Y. Iizawa, M. Shiraishi, Y. Aramaki, K. Okonogi, Y. Ogawa, K. Meguro, and M. Fujino. 1999.

A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity. *Proc Natl Acad Sci U S A 96:5698.*

224. Baroudy, B. 2000. A small molecule antagonist of CCR5 that effectively inhibits HIV-1 potential as novel antiretroviral agent. In *7th Conference on Retroviruses and Opportunistics Infections*, San Francisco, Calif.
225. Wild, C. T., D. C. Shugars, T. K. Greenwell, C. B. McDanal, and T. J. Matthews. 1994. Peptides corresponding to a predictive alpha-helical domain of human immunodeficiency virus type 1 gp41 are potent inhibitors of virus infection. *Proc Natl Acad Sci U S A 91:9770.*
226. Chen, C. H., T. J. Matthews, C. B. McDanal, D. P. Bolognesi, and M. L. Greenberg. 1995. A molecular clasp in the human immunodeficiency virus (HIV) type 1 TM protein determines the anti-HIV activity of gp41 derivatives: implication for viral fusion. *J Virol 69:3771*.
227. Kilby, J. M., S. Hopkins, T. M. Venetta, B. DiMassimo, G. A. Cloud, J. Y. Lee, L. Alldredge, E. Hunter, D. Lambert, D. Bolognesi, T. Matthews, M. R. Johnson, M. A. Nowak, G. M. Shaw, and M. S. Saag. 1998. Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. *Nat Med 4:1302*.
228. D'Souza, M. P., J. S. Cairns, and S. F. Plaeger. 2000. Current evidence and future directions for targeting HIV entry: therapeutic and prophylactic strategies. *Jama 284:215*.
229. Lalezari, J. E., J. Carlson, M. et al. 1999. Sixteen week analysis of hevily pre-treated patients receiving T-20 as a component of multi-drug salvage therapy. In *39th Interscience Conference on Antimicronial Agents and Chemotherapy*, San Diego, Calif.
230. Eron, J. 2000. The prospector new agents in the management of treatment failure. In *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, Calif.
231. Root, M. J., M. S. Kay, and P. S. Kim. 2001. Protein Design of an HIV-1 Entry Inhibitor. *Science 291:884*.
232. Unger, R. K., J. Rübsamen-Waigmann, H. 2000. *Antivirals against AIDS*. Marcel Dekker, Inc.

233. Dyda, F., A. B. Hickman, T. M. Jenkins, A. Engelman, R. Craigie, and D. R. Davies. 1994. Crystal structure of the catalytic domain of HIV-1 integrase: similarity to other polynucleotidyl transferases. *Science 266:1981*.

234. Hazuda, D. J., P. Felock, M. Witmer, A. Wolfe, K. Stillmock, J. A. Grobler, A. Espeseth, L. Gabryelski, W. Schleif, C. Blau, and M. D. Miller. 2000. Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells. *Science 287:646*.

235. Gogliotti, R. E., EL. Holler, TP. Hupe, D.Foltin, SK. Kennedy, RM. Sanchez, JP. Domagala, JM. 1998. Quinolones as novel HIV integrase inhibitor. In *5th Conference on Retroviruses and Opportunistic Infectious,* Chicago.

236. Carr, A., K. Samaras, D. J. Chisholm, and D. A. Cooper. 1998. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet 351:1881*.

237. Haubrich, R. H., C. Flexner, M. M. Lederman, M. Hirsch, C. P. Pettinelli, R. Ginsberg, P. Lietman, F. M. Hamzeh, S. A. Spector, and D. D. Richman. 1995. A randomized trial of the activity and safety of Ro 24-7429 (Tat antagonist) versus nucleoside for human immunodeficiency virus infection. The AIDS Clinical Trials Group 213 Team. *J Infect Dis 172:1246*.