

- Montoya, M. Harbour, J. M. Schapiro, and R. W. Shafer. 2002. Evolution of primary protease inhibitor resistance mutations during protease inhibitor salvage therapy. *Antimicrob. Agents Chemother.* 46:1086–1092.
23. Kaplan, A. H., S. F. Michael, R. S. Wehbie, M. F. Knigge, D. A. Paul, L. Everitt, D. J. Kempf, D. W. Norbeck, J. W. Erickson, and R. Swanstrom. 1994. Selection of multiple human immunodeficiency virus type 1 variants that encode viral proteases with decreased sensitivity to an inhibitor of the viral protease. *Proc. Natl. Acad. Sci. USA* 91:5597–5601.
  24. Kemper, C. A., M. D. Witt, P. H. Keiser, M. P. Dube, D. N. Forthal, M. Leibowitz, D. S. Smith, A. Rigby, N. S. Hellmann, Y. S. Lie, J. Leedom, D. Richman, J. A. McCutchan, and R. Haubrich. 2001. Sequencing of protease inhibitor therapy: insights from an analysis of HIV phenotypic resistance in patients failing protease inhibitors. *AIDS* 15:609–615.
  25. Koh, Y., S. Matsumi, D. Das, M. Amano, D. A. Davis, J. Li, S. Leschenko, A. Baldrige, T. Shioda, R. Yarchoan, A. K. Ghosh, and H. Mitsuya. 2007. Potent inhibition of HIV-1 replication by novel non-peptidyl small molecule inhibitors of protease dimerization. *J. Biol. Chem.* 282:28709–28720.
  26. Koh, Y., H. Nakata, K. Maeda, H. Ogata, G. Bilcer, T. Devasamudram, J. F. Kincaid, P. Boross, Y. F. Wang, Y. Tie, P. Volarath, L. Gaddis, R. W. Harrison, I. T. Weber, A. K. Ghosh, and H. Mitsuya. 2003. Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) with potent activity against multi-PI-resistant human immunodeficiency virus in vitro. *Antimicrob. Agents Chemother.* 47:3123–3129.
  27. Li, F., R. Goila-Gaur, K. Salzwedel, N. R. Kilgore, M. Reddick, C. Matalana, A. Castillo, D. Zoumplis, D. E. Martin, J. M. Orenstein, G. P. Allaway, E. O. Freed, and C. T. Wild. 2003. PA-457: a potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing. *Proc. Natl. Acad. Sci. USA* 100:13555–13560.
  28. Little, S. J., S. Holte, J. P. Routy, E. S. Daar, M. Markowitz, A. C. Collier, R. A. Koup, J. W. Mellors, E. Connick, B. Conway, M. Kilby, L. Wang, J. M. Whitcomb, N. S. Hellmann, and D. D. Richman. 2002. Antiretroviral-drug resistance among patients recently infected with HIV. *N. Engl. J. Med.* 347:385–394.
  29. Maeda, K., H. Nakata, Y. Koh, T. Miyakawa, H. Ogata, Y. Takaoka, S. Shibayama, K. Sagawa, D. Fukushima, J. Moravek, Y. Koyanagi, and H. Mitsuya. 2004. Spirodiketopiperazine-based CCR5 inhibitor which preserves CC-chemokine/CCR5 interactions and exerts potent activity against R5 human immunodeficiency virus type 1 in vitro. *J. Virol.* 78:8654–8662.
  30. Maeda, K., K. Yoshimura, S. Shibayama, H. Habashita, H. Tada, K. Sagawa, T. Miyakawa, M. Aoki, D. Fukushima, and H. Mitsuya. 2001. Novel low molecular weight spirodiketopiperazine derivatives potently inhibit R5 HIV-1 infection through their antagonistic effects on CCR5. *J. Biol. Chem.* 276:35194–35200.
  31. Maguire, M., D. Shortino, A. Klein, W. Harris, V. Manohitharajah, M. Tisdale, R. Elston, J. Yeo, S. Randall, F. Xu, H. Parker, J. May, and W. Snowden. 2002. Emergence of resistance to protease inhibitor amprenavir in human immunodeficiency virus type 1-infected patients: selection of four alternative viral protease genotypes and influence of viral susceptibility to coadministered reverse transcriptase nucleoside inhibitors. *Antimicrob. Agents Chemother.* 46:731–738.
  32. Mammano, F., V. Trouplin, V. Zennou, and F. Clavel. 2000. Retracing the evolutionary pathways of human immunodeficiency virus type 1 resistance to protease inhibitors: virus fitness in the absence and in the presence of drug. *J. Virol.* 74:8524–8531.
  33. McCallister, S., V. Kohlbrenner, K. Squires, A. Lazzarin, P. Kumar, E. DeJesus, J. Nadler, J. Gallant, S. Walmsley, P. Yeni, J. Leith, C. Dohnanyi, D. Hall, J. Sabo, T. MacGregor, W. Verbiest, P. McKenna, and D. Mayers. 2003. Characterization of the impact of genotype, phenotype, and inhibitory quotient on antiviral activity of tipranavir in highly treatment-experienced patients. *Antivir. Ther.* 8:S15.
  34. Melamed, D., M. Mark-Danieli, M. Kenan-Eichler, O. Kraus, A. Castiel, N. Laham, T. Pupko, F. Glaser, N. Ben-Tal, and E. Bacharach. 2004. The conserved carboxy terminus of the capsid domain of human immunodeficiency virus type 1 Gag protein is important for virion assembly and release. *J. Virol.* 78:9675–9688.
  35. Mitsuya, H., and J. Erickson. 1999. Discovery and development of antiretroviral therapeutics for HIV infection, p. 751–780. *In* T. C. Merigan, J. G. Bartlett, and D. Bolognesi (ed.), *Textbook of AIDS medicine*. The Williams & Wilkins Co., Baltimore, MD.
  36. Mitsuya, H., K. Maeda, D. Das, and A. K. Ghosh. 2008. Development of protease inhibitors and the fight with drug-resistant HIV-1 variants. *Adv. Pharmacol.* 56:169–197.
  37. Molla, A., M. Korneyeva, Q. Gao, S. Vasavanonda, P. J. Schipper, H. M. Mo, M. Markowitz, T. Chernyavskiy, P. Niu, N. Lyons, A. Hsu, G. R. Granneman, D. D. Ho, C. A. Boucher, J. M. Leonard, D. W. Norbeck, and D. J. Kempf. 1996. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nat. Med.* 2:760–766.
  38. Murphy, E. L., A. C. Collier, L. A. Kalish, S. F. Assmann, M. F. Para, T. P. Flanigan, P. N. Kumar, L. Mintz, F. R. Wallach, and G. J. Nemo. 2001. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Ann. Intern. Med.* 135:17–26.
  39. Murphy, R. L. 2000. New antiretroviral drugs in development. *AIDS* 14(Suppl. 3):S227–S234.
  40. Partaledis, J. A., K. Yamaguchi, M. Tisdale, E. E. Blair, C. Falcione, B. Maschera, R. E. Myers, S. Pazhanisamy, O. Futer, A. B. Cullinan, C. M. Stuver, R. A. Byrn, and D. J. Livingston. 1995. In vitro selection and characterization of human immunodeficiency virus type 1 (HIV-1) isolates with reduced sensitivity to hydroxyethylamino sulfonamide inhibitors of HIV-1 aspartyl protease. *J. Virol.* 69:5228–5235.
  41. Patick, A. K., M. Duran, Y. Cao, D. Shugarts, M. R. Keller, E. Mazabel, M. Knowles, S. Chapman, D. R. Kuritzkes, and M. Markowitz. 1998. Genotypic and phenotypic characterization of human immunodeficiency virus type 1 variants isolated from patients treated with the protease inhibitor nelfinavir. *Antimicrob. Agents Chemother.* 42:2637–2644.
  42. Prado, J. G., T. Wrinn, J. Beauchaine, L. Ruiz, C. J. Petropoulos, S. D. Frost, B. Clotet, R. T. D'Aquila, and J. Martinez-Picado. 2002. Amprenavir-resistant HIV-1 exhibits lopinavir cross-resistance and reduced replication capacity. *AIDS* 16:1009–1017.
  43. Rodriguez-Barrios, F., and F. Gago. 2004. HIV protease inhibition: limited recent progress and advances in understanding current pitfalls. *Curr. Top. Med. Chem.* 4:991–1007.
  44. Salzwedel, K., R. Goila-Gaur, C. Adamson, F. Li, A. Castillo, N. Kilgore, M. Reddick, C. Matalana, D. Zoumplis, D. Martin, G. Allaway, E. Freed, and C. Wild. 2004. Selection for and characterization of HIV-1 isolates resistant to the maturation inhibitor PA-457. *Antivir. Ther.* 9:S8.
  45. Shirasaka, T., M. F. Kavlick, T. Ueno, W. Y. Gao, E. Kojima, M. L. Alcaide, S. Chokekijchai, B. M. Roy, E. Arnold, R. Yarchoan, et al. 1995. Emergence of human immunodeficiency virus type 1 variants with resistance to multiple dideoxynucleosides in patients receiving therapy with dideoxynucleosides. *Proc. Natl. Acad. Sci. USA* 92:2398–23402.
  46. Walensky, R. P., A. D. Paltiel, E. Losina, L. M. Mercincavage, B. R. Schackman, P. E. Sax, M. C. Weinstein, and K. A. Freedberg. 2006. The survival benefits of AIDS treatment in the United States. *J. Infect. Dis.* 194:11–19.
  47. Yoshimura, K., R. Kato, M. F. Kavlick, A. Nguyen, V. Maroun, K. Maeda, K. A. Hussain, A. K. Ghosh, S. V. Gulnik, J. W. Erickson, and H. Mitsuya. 2002. A potent human immunodeficiency virus type 1 protease inhibitor, UIC-94003 (TMC-126), and selection of a novel (A28S) mutation in the protease active site. *J. Virol.* 76:1349–1358.
  48. Yoshimura, K., R. Kato, K. Yusa, M. F. Kavlick, V. Maroun, A. Nguyen, T. Mimoto, T. Ueno, M. Shintani, J. Falloon, H. Masur, H. Hayashi, J. Erickson, and H. Mitsuya. 1999. JE-2147: a dipeptide protease inhibitor (PI) that potently inhibits multi-PI-resistant HIV-1. *Proc. Natl. Acad. Sci. USA* 96:8675–8680.
  49. Zhou, J., X. Yuan, D. Dismuke, B. M. Forshey, C. Lundquist, K. H. Lee, C. Aiken, and C. H. Chen. 2004. Small-molecule inhibition of human immunodeficiency virus type 1 replication by specific targeting of the final step of virion maturation. *J. Virol.* 78:922–929.

平成 21 年度 厚生労働科学研究費補助金エイズ対策研究事業

「HIV 感染症の医療体制の整備に関する研究」班  
総括・分担研究報告書

---

発行日 2010 年 3 月 31 日

発行者 研究代表者 濱口 元洋

発行所 研究班事務局  
国立病院機構名古屋医療センター  
エイズ治療開発センター  
〒 460-0001 名古屋市中区三の丸 4-1-1

---

