72. Hindmarsh P, Leis J. Retroviral DNA integration. Microbiol Mol Biol Rev 1999;63:836-43

73. Ellison V, Brown PO. A stable complex between integrase and viral DNA ends mediates human immunodeficiency virus integration in vitro. Proc Natl Acad Sci USA 1994;91:7316-20

74. Vink C, Lutzke RAP, Plasterk RHA. Formation of a stable complex between the human immunodeficiency virus integrase protein and viral DNA. Nucleic Acids Res 1994;22:4103-10

75. Wolfe AL, Felock PJ, Hastings JC, et al. The role of manganese in promoting multimerization and assembly of human immunodeficiency virus type 1 integrase as a catalytically active complex on immobilized long terminal repeat substrates. J Virol 1996;70:1424-32

76. Grobler JA, Stillmock K, Hu B, et al. Diketo acid inhibitor mechanism and HIV-1 integrase: Implications for metal binding in the active site of phosphotransferase enzymes. Proc Natl Acad Sci USA 2002;99:6661-6

77. Hazuda DJ, Young SD, Guare JP, et al. Integrase inhibitors and cellular immunity suppress retroviral replication in rhesus macaques. Science 2004;305:528-32

78. Little S, Drusano G, Schooley R, et al. Abstract 161, 12th Conference of Retroviruses and Opportunistic Infections; Boston, MA; 2005

79. Reddy YS, Min SS, Borland J, et al. Safety and pharmacokinetics of GSK364735, a human immunodeficiency virus type 1 integrase inhibitor, following single and repeated administration in healthy adult subjects. Antimicrob Agents Chemother 2007;51:4284-9

80. Jones GS, Yu F, Zeynalzadegan A, et al. Preclinical evaluation of GS-9160, a novel inhibitor of human immunodeficiency virus type 1 integrase. Antimicrob Agents Chemother 2009;53:1194-203

81. Ferrara M, Crescenzi B, Donghi M, et al. Synthesis of a hexahydropyrimido[1,2-a]azepine-2-carboxamide derivative useful as an HIV integrase inhibitor. Tetrahedron Lett 2007;48:8379-82

82. Sato M, Motomura T, Aramaki H, et al. Novel HIV-1 integrase inhibitors derived from quinolone antibiotics. J Med Chem 2006;49:1506-8

• **The development of an integrase inhibitor Elvitegravir.**

83. DeJesus E, Berger D, Markowitz M, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naive and treatment-experienced patients. J Acquir Immune Defic Syndr 2006;43:1-5

84. Mathias AA, German P, Murray BP, et al. Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity. Clin Pharmacol Ther 2010;87:322-9

85. Marinello J, Marchand C, Mott BT, et al. Comparison of Raltegravir and Elvitegravir on HIV-1 integrase catalytic reactions and on a series of drug-resistant integrase mutants. Biochemistry 2008;47:9345-54

86. Bar-Magen T, Sloan RD, Donahue DA, et al. Identification of novel mutations responsible for resistance to MK-2048, a second-generation HIV-1 integrase inhibitor. J Virol 2010;84:9210-16

• **The development of an integrase inhibitor MK-2048.**

87. Johns BA, Svolto AC. Advances in two-metal chelation inhibitors of HIV integrase. Expert Opin Ther Patents 2008;18:1225-37

88. Min S, Song I, Borland J, et al. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. ?Antimicrob Agents Chemother 2010;54:254-8

• **The development of an integrase inhibitor Dolutegravir.**

89. Kobayashi M, Yoshinaga T, Seki T, et al. In vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother 2011;55:813-21

90. Ovenden SP, Yu J, Wan SS, et al. Globoidnan A: a lignan from Eucalyptus globoidea inhibits HIV integrase. Phytochemistry 2004;65:3255-9

91. Valkov E, Gupta SS, Hare S, et al. Functional and structural characterization of the integrase from the prototype foamy virus. Nucleic Acids Res 2009;37:243-55

92. Hare S, Gupta SS, Valkov E, et al. Retroviral intasome assembly and inhibition of DNA strand transfer. Nature 2010;464:232-6

93. De Luca L, De Grazia S, Ferro S, et al. HIV-1 integrase strand-transfer inhibitors: design, synthesis and molecular modeling investigation. Eur J Med Chem 2011;46:756-64

94. Suzuki S, Urano E, Hashimoto C, et al. Peptide HIV-1 integrase inhibitors from HIV-1 gene products. J Med Chem 2010;53:5356-60

95. Suzuki S, Maddali K, Hashimoto C, et al. Peptidic HIV integrase inhibitors derived from HIV gene products: structure–activity relationship studies. Bioorg Med Chem 2010;18:6771-5

96. Zhao Q, Ma L, Jiang S, et al. Identification of N-phenyl-N'-(2,2,6,6-tetramethyl-piperidin-4-yl)-oxalamides as a new class of HIV-1 entry inhibitors that prevent gp120 binding to CD4. Virology 2005;339:213-25

97. Schon A, Madani N, Klein JC, et al. Thermodynamics of binding of a low-molecular-weight CD4 mimetic to HIV-1 gp120. Biochemistry 2006;45:10973-80

98. Yamada Y, Ochiai C, Yoshimura K, et al. CD4 mimics targeting the mechanism of HIV entry. Bioorg Med Chem Lett 2010;20:354-8

99. Narumi T, Ochiai C, Yoshimura K, et al. CD4 mimics targeting the HIV entry mechanism and their hybrid molecules with a CXCR4 antagonist. Bioorg Med Chem Lett 2010;20:5853-8

100. Yoshimura K, Harada S, Shibata J, et al. Enhanced exposure of human immunodeficiency virus type 1 primary isolate neutralization epitopes through binding of CD4 mimetic compounds. J Virol 2010;84:7558-68

101. Lalonde JM, Elban MA, Courter JR, et al. Design, synthesis and biological evaluation of small molecule inhibitors of CD4-gp120 binding based on virtual screening. Bioorg Med Chem 2011;19:91-101

102. Lu RJ, Tucker JA, Zinevitch T, et al. Design and synthesis of human immunodeficiency virus entry

inhibitors: sulfonamide as an isostere for the alpha-ketoamide group. J Med Chem 2007;50:6535-44

103. Zou Y-R, Kottmann AH, Kuroda M, et al. Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. Nature 1998;393:595-9

104. Nakata H, Steinberg SM, Koh Y, et al. Potent synergistic anti-human immunodeficiency virus (HIV) effects using combinations of the CCR5 inhibitor aplaviroc with other anti-HIV drugs. Antimicrob Agents Chemother 2008;52:2111-19

105. Abraham M, Biyder K, Begin M, et al. Enhanced unique pattern of hematopoietic cell mobilization induced by the CXCR4 antagonist 4F-benzoyl-TN14003. Stem Cells 2007;25:2158-66

106. Broxmeyer HE, Orschell CM, Clapp DW, et al. Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist. J Exp Med 2005;201:1307-18

107. Liles WC, Broxmeyer HE, Rodger E, et al. Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist. Blood 2003;102:2728-30

108. Koh Y, Nakata H, Maeda K, et al. 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 2003;47:3123-9

109. Ghosh AK, Sridhar PR, Leshchenko S, et al. Structure-based design of novel HIV-1 protease inhibitors to combat drug resistance. J Med Chem 2006;49:5252-61

110. Thayer AM. This is the news from Chemical & Engineering News, American Chemical Society. p29, 2008

Affiliation

Chie Hashimoto, Tomohiro Tanaka, Tetsuo Narumi, Wataru Nomura* & Hirokazu Tamamura†
*,†Author for correspondence
Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Chiyoda-ku, Tokyo 101-0062, Japan
Tel: +81 3 5280 8036; Fax: +81 3 5280 8039;
E-mail: tamamura.mr@tmd.ac.jp;
E-mail: nomura.mr@tmd.ac.jp