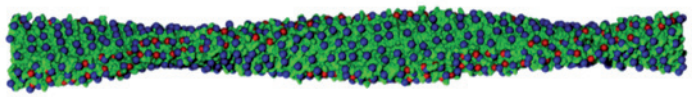
Institute of Molecular Virology

HIV-1 and AIDS

Head: Frank Kirchhoff

One of our major research interests is to clarify why only one of at least four independent zoonotic transmissions of SIVs found in chimpanzees or gorillas to humans is responsible for the AIDS pandemic. Our results showed that only pandemic HIV-1 M strains evolved a fully functional Vpu that counteracts tetherin (a cellular factor that blocks virus release) and degrades CD_4 (the primary receptor of HIV) to promote the release of fully infectious viral particles. Vpus from non-pandemic HIV-1 O and P strains are poor tetherin antagonists, whereas those from the rare group N viruses do not degrade CD_4 (1) although they seem to be in the process of adapting to humans (2). We also found that primate lentiviruses can rapidly reacquire accessory gene functions that are lost after cross-species transmission (3). Our findings may explain why group M viruses are almost entirely responsible for the global HIV/AIDS pandemic.

Our second major focus is the characterization and optimization of novel inhibitors or enhancers of HIV-1 and other viral pathogens. To achieve this, we screen complex peptide-protein libraries from natural sources, such as hemofiltrate, semen, spleen, saliva and breast milk, for natural compounds affecting HIV-1 infection. These studies have led to the discovery of several HIV-1 inhibitors. One of them, VIRIP, blocks HIV-1 entry by direct binding to the gp41 fusion peptide. Mono-therapy with an optimized VIRIP variant reduces the viral loads by about 1.3 orders of magnitude without causing severe side effects (4). We also used this approach to identify endogenous factors involved in sexual transmission of HIV-1 and found that fragments of the abundant semen marker prostatic acidic phosphatase (PAP) form amyloid fibrils, termed Semen-derived Enhancer of Virus Infection (SEVI), that capture HIV virions and enhance their infectious



Refined molecular model of an EF-C fibril (N in blue, O in red, backbone in green)

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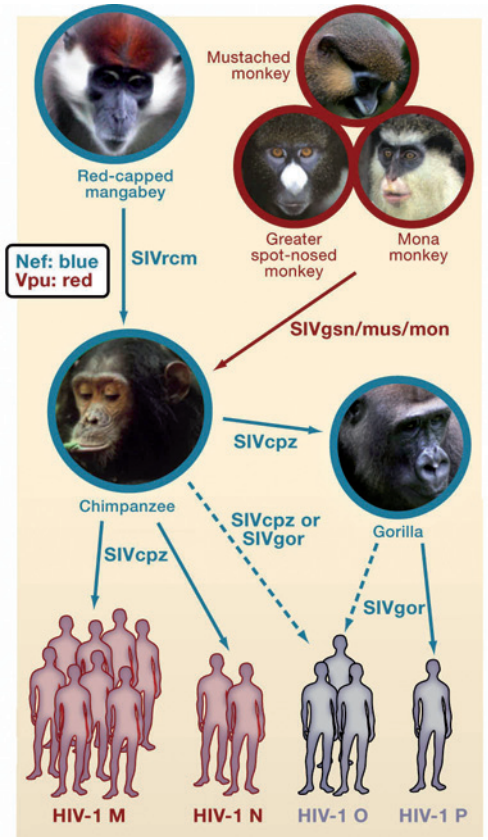
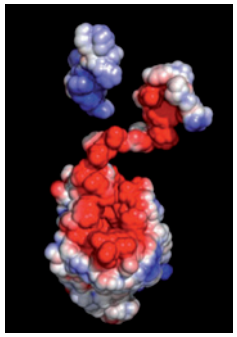


Evolution of HIV-1. SIVcpz represents a recombinant of the precursors of viruses nowadays found in Red-capped mangabeys and *Cercopithecus* monkeys and was subsequently transmitted to humans and gorillas. Nef-mediated tetherin antagonism is indicated by green and Vpu-mediated tetherin antagonism by red lines or contours, respectively. As indicated by the dashed line it is unknown whether HIV-1 group O strains originated from chimpanzees or gorillas. Photos of nonhuman primates are courtesy of M.L. Wilson, Cecile Neel and Martine Peeters.

virus titer by several orders of magnitude. Thus, SEVI may play an important role in sexual transmission of HIV and represents a new target for its prevention. Recently, we developed analogous amyloidogenic peptides for the enhancement of retroviral gene delivery in basic research and clinical approaches (5). In our ongoing studies we identified, among others, novel inhibitors and enhancers of HIV in breast milk, and also an as-yet unknown CXCR4 antagonist that blocks X4-tropic HIV-1 strains (6).



Model of the docking of a naturally occurring peptide to the CXCR4 receptor

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Selected Publications:

- *Yolamanova M, Meier C, Shaytan AK, Vas V, Bertoncini CW, Arnold F, Zirafi O, Usmani SM, Müller JA, Sauter D, Goffinet C, Palesch D, Walther P, Roan NR, Geiger H, Lunov O, Simmet T, Bohne J, Schrezenmeier H, Schwarz K, Ständker L, Forssmann WG, Salvatella X, Khalatur PG, Khokhlov AR, Knowles TP, Weil T, Kirchhoff F, Münch J (2013): Peptide nanofibrils boost retroviral gene transfer and provide a rapid means for concentrating viruses. Nat Nanotechnol. 8(2):130-6*
- *Sauter D, Unterweger D, Vogl M, Usmani SM, Heigele A, Kluge SF, Hermkes E, Moll M, Barker E, Peeters M, Learn GH, Bibollet-Ruche F, Fritz JV, Fackler OT, Hahn BH, Kirchhoff F (2012): Human tetherin exerts strong selection pressure on the HIV-1 group N Vpu protein. PLoS Pathog. 8(12):e1003093.*
- *Götz N, Sauter D, Usmani SM, Fritz JV, Goffinet C, Heigele A, Geyer M, Bibollet-Ruche F, Learn GH, Fackler OT, Hahn BH, Kirchhoff F (2012): Reacquisition of Nef-mediated tetherin antagonism in a single in vivo passage of HIV-1 through its original chimpanzee host. Cell Host Microbe. 12(3):373-80.*
- *Forssmann WG, The YH, Stoll M, Adermann K, Albrecht U, Barlos K, Busmann A, Canales-Mayordomo A, Giménez-Gallego G, Hirsch J, Jiménez-Barbero J, Meyer-Olson D, Münch J, Pérez-Castells J, Ständker L, Kirchhoff F, Schmidt RE (2010): Short-term monotherapy in HIV-infected patients with a virus entry inhibitor against the gp41 fusion peptide. Sci Transl Med. 2(63):63re3*
- *Sauter D, Schindler M, Specht A, Landford WN, Münch J, Kim KA, Votteler J, Schubert U, Bibollet-Ruche F, Keele BF, Takehisa J, Ogando Y, Ochsenbauer C, Kappes JC, Ayouba A, Peeters M, Learn GH, Shaw G, Sharp PM, Bieniasz P, Hahn BH, Hatziioannou T, Kirchhoff F (2009): Tetherin-driven adaptation of Vpu and Nef function and the evolution of pandemic and nonpandemic HIV-1 strains. Cell Host Microbe. 6(5):409-21.*
- *Kim K-A et al.: Discovery and characterization of an endogenous CXCR4 antagonist. (submitted)*