nine protein kinase that mediates sustained activity of FOF_1 ATP synthase, and the latter enzyme complex to which oligomycin A is a known antagonist. Regardless of its cytotoxic potency oligomycin A is inconvenient for clinical use due to general toxicity. In collaboration with Gause Institute of New Antibiotics, Moscow we have synthesized 25 oligomycin A derivatives differentially active against human tumor cell lines. To further screen this series we developed a test system in actinobacterial strain *Streptomyces fradiae* ATCC 19 609 that is exceptionally sensitive to this compound. This bacterial test system is valid for screening of antitumor derivatives since the amino acid sequences of oligomycin A binding sites in the C-subunit of FOF_1 ATP synthase of this strain and *H. sapiens* are close. The β-subunit can be phosphorylated by an upstream kinase, therefore, its inhibition should be therapeutically relevant.

The proposal implies rational design of oligomycin A derivatives and beta subunit antagonists of FOF_1 ATP synthase on Hodgkin's lymphoma cells and patients' samples collected in Moscow. The synthesis and test systems are original. Finally, we will elucidate the mechanisms of lymphoma cell death induced by the leading derivative in combination with C-subunit inhibitor.

Replication of HIV-1 with accessory gene deletions in cell-coculture and cell-free modes of transmission

A.Shunaeva

Moscow, Russia

HIV-1 restriction factors are cellular proteins that inhibit viral replication at post-entry stage of virus life cycle. The dozens of cellular factors with antiviral activities have been described. However, only six main protein families, i.e. APOBEC, TRIM, Tetherin, SAMHD, and MX2, specifically restrict the replication of HIV. The mechanisms of restriction are specific for each factor, and affect different stages of viral replication that overall makes cells highly resistant to virus. Nevertheless, HIV has evolved its own proteins Vif, Vpr, Vpu, Vpx, Nef, which efficiently counteract restriction factors and abolish their protective effects.

The role of restriction factors in HIV-1 replication has been studied extensively upon infection with cell free virus. However, an HIV-1 restriction during cell-to-cell mode of virus transmission, which dominates at the early stages of infection in vivo, is not studied comprehensively.

In this work, we have constructed HIV-1 packaging plasmids with deletions in Vif, Vpu, Vpr or Nef gene, and determined the levels of defective virus replication at the different settings including various types of producer and target cells, and modes of transmission. To quantify the levels of cell-to-cell infection, the improved replication dependent vectors were used (Shunaeva A et al. J Virol. 2015 Oct 15;89 (20):10591–601). The effect of accessory gene deletion on HIV-1 infectivity was dependent on cell type and mode of transmission. Particularly, the differences between wild type and mutated HIV-1 replication levels were significant in lymphoid cells and neglectable in HEK 293T cells. This suggests that lymphoid cells express a wide gamma of HIV-1 restriction factors in the response to infection. When comparing cell-free infection with cell-coclulture infection, the defect in the expression of one of accessory proteins resulted in ten fold and more decrease in infectivity with cell-free virus derived from Jurkat T cells. In contrast, the levels of replication of defective virus in coculture of lymphoid cells were reduced less than 1,5–2 times in comparison to replication of wild type virus, indicating that cell-to-cell transmission overcomes the restriction imposed by deletion of HIV-1 accessory genes. Interestingly, the replication of Vpu-defective HIV-1 was even 3–5 fold more efficient in cell cocultures than infectivity of wild type virus, whilst under cell-free mode of infection the deletion of Vpu decreased the HIV infectivity. Overall, our data suggest that hijacking cell-to-cell mode of transmission can be an additional mechanism that HIV-1 uses to counteract cellular restriction.

Immunotherapy against drug resistance as a therapy compliment increasing the duration of the effective use of art

E.Starodubova, S.Petkov, A.Kilpelaeinen, O.Krotova, A.Latanova, O.Latyshev, O.Eliseeva, M.Abakumov, A.Tukhvatulin, I.Gordeychuk, D.Logunov, M.Bobkova, M.Mikhailov, M.Saguliants

Moscow, Russia; Stockholm, Sweden.

Introduction: Clinical trials demonstrated validity of therapeutic HIV vaccines for reducing viral load and improving patient well-being towards «functional cure» (Noto & Trautmann, 2013; Wahren & Liu, 2014). HIV immunotherapy becomes actual in view of the latest findings of an effective broad T-cell response clearing HIV-1 from the latent reservoirs (Deng et al, 2015; Rawlings SA et al, 2015). Strong immune response against viral antigens responsible for drug resistance can create a bottle-neck to viral evolution forbidding or hindering the development of drug resistance. In HIV-1, such response can complement highly active antiretroviral treatment, and thus prolong the time for its effective application. By controlling the emergence of resistant HIV strains, a combination of ART and immune therapy would delay and may ideally prevent the emergence of HIV/AIDS associated co-morbidities such as cancer or co-infections.

Aims: Develop a complex approach for immunotherapy of HIV/AIDS including generation of synthetic antigens,