in combination with HAART, adequate CT to type and stage of lymphoma, and Rituximab in CD20 B-cell lymphomas improved overall survival rate. Usage of Rituximab reduced the probability of progression of CD20 B-cell lymphoma in HIV infected individuals.

Epstein–Barr virus and HIV-associated lymphomas

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Three main factors of the development of lymphomas in immunosuppressed patients are recognized: immune dysfunctions, oncogenic viruses (Epstein-Barr virus and type 8 herpesvirus), and molecular and cytogenetic anomalies associated with HIV infection (Besson et al., 2003; Martinez, 2011). EBV is oncogenic: it is able to transform B-cells *in vitro* into immortal lymphoblastoid cell lines. EBV genome is found in 30–70% of HIV-associated non-Hodgkin lymphomas, depending on their histological types, and in virtually all Hodgkin lymphomas. HIV influences the development of lymphomas indirectly, since it does not infect tumor cells (Besson et al., 2003; Pivnik et al., 2014). Nevertheless, HIV compromises viral setpoint by suppressing the cellular immunity (Rickinson et al., 1997; Harty et al., 2000) and thus promoting EBV reactivation. In the course of advancing of HIV infection, the initial drastic increase in VEB replication is followed by a slow increase in EBV load in the course of chronic HIV infection (Piriou et al.,2004). The loss of control over EBV results in the expansion of the population of infected lymphocytes and in the development of a lymphoproliferative state (Moses et al., 1998). In patients having HIV-associated lymphomas, EBV loads are higher (>2500 copies per 1 mL) than in controls (Fan et al., 2005), and this is associated with the presence of a lymphoma. High EBV loads found several months before a lymphoma has developed are associated with that the risk of the development of HIV-associated lymphomas, including systemic B-lymphomas, increases (Leruez-Ville et al., 2012). Also, a negative correlation is found between EBV load and CD4 cell counts (Bonnet et al., 2006; Amiel et al., 2009). In their turn, the titers of VCA and EBNA-1 IgG antibodies increase. These serological parameters and EBV load may serve as indirect prognostic markers, albeit week, for managing HIV patients.

Some aspects of the HIV replication inhibitors design: depot forms and new acyclic nucleotide analogues

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There are about 30 currently used drugs against HIV. Since the approval of the first-in-class anti-HIV drug 3'-azido-3'-deoxythymidine (AZT), nucleoside and nucleotide analogues have gained much attention, even now, with new classes of antivirals found. This conservative therapy is the most affordable; currently used drugs offer such pharmaceutical benefits as good water solubility, inexpensive synthesis, thoroughly studied mechanisms of action and resistance. Nevertheless, 30 years on, the topic remains: to make nucleosides and nucleotides less toxic in the long-term treatment. Therefore, prodrug and depot-form approaches have been developed.

We have synthesized two types of prodrugs based on phosphonate and carbamate derivatives that allowed us to lower the toxicity of AZT and L-2',3'-dideoxy-3'-thiacytidine (3TC) and tested them in cell cultures and animal models. We consider that 5'-O-AZT morpholinocarbamate, 5'-O,O'-bis-AZT fluoromethylphosphonate and 5'-O-3TC H-phosphonate are most potent prodrugs of these series.

More of ten than not, several viruses occur in a HIV-infected patient simultaneously, e.g., over 80% of patients suffer from herpes and other virus-induced infections. Search for substances with combined activity against different types of viruses is inevitable. Herein, we report synthesis of new acyclic nucleoside phosphonate analogues bearing unsaturated fragments in the chain. Phosphonate moiety is a useful bypass of the limiting first phosphorylation step, besides, it does not undergo enzymatic hydrolysis as natural phosphates do. The problem of a selective phosphonate attachment may be solved by the «click»-reaction with carbonyl group forming the oximes. Oximes are rarely used in drug design and yet their conformational rigidness and their stability in hydrolytic tests may be useful for nucleoside side chain drug design. One of the synthesized series is oxime-containing nucleoside phosphonates with activity against several types of viruses: 9-{2-[(phosphonomethyl)oximino]ethyl}adenine, -guanine and 9-{2-[(phosphonomethyl)oximino]propyl}adenine.

FOF1 ATP synthase, a Therapeutic Target for AIDS Associated Lymphoma: Design of New Inhibitors

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AIDS is associated with a plethora of diseases among which an aggressive lymphoma is a major cause of lethality. In particular, the frequency of Hodgkin's lymphoma increases sixfold in AIDS patients compared to general cohort. About 1% of total newly diagnosed cancer cases, or one per 25 000 individuals, has been reported to be due to Hodgkin's lymphoma. Treatment of this form is complicated by immunodeficiency.

We propose to develop a drug candidate that inhibits energy metabolism in malignant cells, thereby causing their death. Two targets will be blocked, that is, the serine-threo-

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

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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

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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,