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European Consortium on Antiviral Drug Development: SILVER

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The project aims to identify Small molecule Inhibitor Leads Versus Emerging and neglected RNA viruses (SILVER). It will focus its activities on selected medically important RNA viruses for which the development of drugs is considered essential (Dengue-, entero- and paramyxoviruses), whereas other relatively neglected and/or emerging RNA viruses will be explored to identify the most promising viral protein targets and antiviral compounds. A pipeline strategy will be employed to progress this work plan, whilst multidisciplinary workgroups (WAVEs) will ensure the proper flow of information, data, exploitation and dissemination. This organization allows any virus and viral target to enter the pipeline at its current state of knowledge and art. Targets for potential drugs include infectious virus, structurally characterised viral enzymes and other proteins. Leads for currently available antiviral drugs have been identified by screening compound libraries in virus-infected cell culture systems and *in vitro* assays using purified viral enzymes. Selective inhibitors of viral replication have also been (and are being) derived using detailed structural knowledge of viral proteins and structure-based drug design. Hits will be assayed using individual viral protein targets and replicative proteins in complex with viral RNA. The potential protective activity of the most potent inhibitors, that have a favourable (*in vitro*) ADME-tox profile, will be assessed in relevant infection models in animals. The consortium will also be prepared to re-align its specific research objectives immediately in the case of emergence of new RNA viruses threatening human health during the lifetime of the project. To this end, one workpackage will develop an "outbreak pipeline" in which SILVER partners will collaborate with worldwide network. The combined virus group-specific expertise of these specialists will ensure a broad coverage of human RNA viruses, which in the case of a novel emerging agent should maximize its processing speed and incorporation into the drug development pipeline. Licenses on promising compounds or compound classes will be presented to the interested pharmaceutical industry and will provide a multidisciplinary framework for rapid knowledge-based response to emerging infections.

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***In-vitro* Screening for Compounds Active Against Polyomavirus BK: A Seven Year Experience**

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Background: Polyomavirus BK causes nephropathy in solid organ transplant patients and hemorrhagic cystitis after bone marrow and stem cell transplantation. Antiviral drugs with proven efficacy are not available.

Methods: 1061 compounds were selected for screening based on known biology of the virus and published literature on other small DNA viruses. This effort was supplemented by a homology modeling based virtual screening of 5.1 million compounds directed at the viral capsid protein VP-1 and the large T antigen (LTA). Crystal structures of SV40 VP-1-ganglioside and LTA-ATP ligand complexes were used as templates for construction of the homology models. Anti-BKV activity of compounds was confirmed by direct measurement of BKV Gardner strain replication in WI-38 cells using real time PCR. Toxicity to host cells was evaluated by the neutral red assay and by quantifying the housekeeping gene aspartoacylase as an index of host cell replication.

Results: Based on EC50, selectivity index, or FDA approval for other indications, compounds worthy of further pursuit found in the following categories: (i) Nucleotide analogs: HDP-cidofovir, ODE-cidofovir, HDP-cidofovir-(S)-HPMPA, ODE-(S)-HPMPA, PMEA derivatives. (ii) Malonitrilamide inhibitors of dihydro-orotate dehydrogenase: leflunomide, FK778. (iii) Topoisomerase inhibitors: camptothecin, ciprofloxacin, NSC 270718. (iv) Receptor analogs: BTB11968. (v) Anti-microbial peptides: hecate, tachyplesin. (vi) Anti-VP-1 monoclonal antibodies with >90% virus neutralizing ability. (vii) Commerically available immunoglobulin preparations. (viii) Compounds interfering with intra-cellular transport: chloroquine, nystatin. (ix) Kinase inhibitors: Tyrphostin RG13022, STO-18584, STO-18812, STO-18816, Erlotininb, Sorafenib.

Conclusions: Several compounds with in-vitro anti-BKV activity have been identified. Further testing is desirable in additional cell lines, multiple viral strains, and in animal models. Drugs already approved by FDA for other indications can proceed directly to human trials. Computerized homology modeling has shown the conceptual feasibility of discovering additional drugs that may disrupt viral capsid assembly and LTA mediated ATP-dependent unwinding of BKV DNA prior to its replication.

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Studies on Anti-HSV Activity and Cytotoxicity of *Morinda citrifolia* L. Noni Leaf

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Backround: The development of antiviral drugs has provided crucial new means to mitigate or relieve the debilitating effects of many viral pathogens. A rich source for the discovery of new HSV infection inhibitors has been and continues to be, the 'mining' of the large diversity of compounds already available in nature and specifically those from botanical extracts. *Morinda citrifolia* is used in the Indian system of medicine for the treatment of variety of diseases and enriched with flavinoids, anthroquinone and glycoside, but antiviral activity against Herpes Simplex Virus (HSV) not yet been studied, based on this fact present work is to study HSV inhibitory activity of different extracts of *Morinda citrifolia*

Method: The chloroform (CMC) and ethanol (ETMC) leaf extracts of *M. citrifolia* have been evaluated for antiviral activity against HSV in HFF cells by plaque reduction assay. The both extracts of the leaf of *M. citrifolia* were also investigated for cytotoxicity in KB (oral cancer) cells.

Results: Chloroform and ethanolic extracts of *M. citrifolia* exhibited inhibitory activity against of HSV activity at the concentration of 5 and 20 μg/ml, respectively. Chloroform and ethanolic extracts of *M. citrifolia* also exhibited cytotoxic activity against of KB cells at the concentration of 45 and 100 μg/ml respectively.

Conclusion: Anthroquine, flavinoid and alkaloids are the principle active constituents of *M. citrifolia*, which may responsible for HSV inhibitory activity. This is the first report showing the anti-HSV activity of *M. citrifolia*.