


## PhD Project Description

| School/Department:   | Department of Biochemistry, Erasmus MC   |
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| <b>Supervisor information:</b><br> | <p>Prof. dr. Tokameh Mahmoudi, PhD, <a href="mailto:t.mahmoudi@erasmusmc.nl">t.mahmoudi@erasmusmc.nl</a><br/>           Selected personal grants: ERC StG laureate (2014)<br/>           Selected publications:</p> <ol style="list-style-type: none"> <li>1. <a href="#">Stoszko, M. et al., 2020. Science Advances 6(32):6617-6629</a></li> <li>2. <a href="#">Ne, E et al., 2020 Cell Host Microbe (revision 'Sneak Peak')</a>.</li> <li>3. <a href="#">Marian, C et al., 2018. Cell Chemical Biology 25(12):1443-1455.e14.</a></li> <li>4. <a href="#">Palstra, RJ et al., 2018. Science Advances 4(2):e1701729.</a></li> <li>5. <a href="#">Zhao, M et al., 2019. Pharmacol Res. 2019 Jan;139:524-534.</a></li> <li>6. <a href="#">Bertoldi, A. et al., 2020 Journal of Virological Methods.</a></li> <li>7. <a href="#">Lungu, C et al., 2020 Viruses. 12(9):E973.</a></li> <li>8. <a href="#">Stoszko M et al., 2016. EBioMedicine. 3:108-121.</a></li> </ol>   |
| <b>Project Title:</b>  | <b>HIV Cure: mechanisms, drug discovery, clinical study and valorization</b>   |
| <b>Abstract:</b>   | <p>Combination antiretroviral therapy (cART) effectively halts HIV replication and has significantly reduced AIDS-associated mortality. However, cART is not curative, it has side-effects, and apart from the costs of lifelong therapy, the global roll-out of cART, particularly in resource-limited countries, remains an ongoing challenge (UNAIDS fact sheet 2019). HIV persists because subsequent to stable integration into the CD4+ T cell host genome, the provirus can remain in a nonproductive latent state, defined by the absence of HIV-1 gene expression. Because of this reservoir of latently HIV-1 infected cells, interruption of cART leads to a rapid rebound of unrestricted viral replication, necessitating life-long treatment (Siliciano and Siliciano, 2015). Ongoing progress in understanding the molecular mechanisms that control HIV transcription and latency has led to the development of strategies to target the reservoir, to stimulate the virus to emerge out of latency, coupled to either induction of death in the infected reactivated cell or its clearance by the immune system.</p> <p>Below five ongoing focus areas of our research into HIV-1 cure:</p> <p>[1] An innovative approach to eliminate HIV-1-infected cells emerging out of latency is to pharmacologically reactivate viral expression and concomitantly trigger intracellular pro-apoptotic pathways in order to selectively induce cell death (ICD) of infected cells. We showed that a new class of compounds, DDX3 inhibitors, induce selective cell death in HIV infected patient cells and lead to depletion of the inducible latent reservoir in these patients.</p> <p>[2] Using a medium through-put screen of fungal metabolites combined with HIV latency reversal bioassays and state of the art fractionation coupled to MS and NMR bioassays, we identified GTX, a molecule capable of activating latent HIV, and unravelled its mechanism of action at the molecular level in targeting the elongation phase of HIV transcription.</p> <p>[3] The unbiased identification of factors physically associated with the latent HIV-1 provirus would be highly valuable to unravel the molecular correlates of latency and develop new latency reversal agents. But, due to technical limitations, this has not been possible. We developed dCas9 targeted chromatin and histone enrichment strategy coupled to mass spectrometry (Catchet-MS) to isolate the latent HIV-1 promoter and identified a novel transcriptional repressor, IKZF1. We also found the clinically advanced IKZF1 targeting drug iberdomide, to reverse latency in CD4+T-cells isolated from virally suppressed HIV-1 infected participants.</p> <p>[4] We identified the BAF complex as a central player in repressing HIV transcription, highlighting it as a potential target to reverse HIV latency. In collaboration with the Purdue University and the Broad Institute, we found that small-molecule inhibition of BAF re-activates latent HIV in a spectrum of primary models as well as in cells obtained from HIV-infected patients using drug screens. To develop next-generation BAF inhibitors, we performed a screen of more than 350,000 compounds, uncovering a novel class of molecules that displays potent latency reversal with significantly less associated cytotoxicity (patent filed 2018).</p> <p>[5] Combining genome-wide association, functional genomics data and mechanistic interrogation, we unraveled the underlying biological basis of HIV non-coding disease associated genomic variants near the IL-32 gene in determining susceptibility to HIV-1 infection.</p> |
| <b>Requirements of candidate:</b>  | <ul style="list-style-type: none"> <li>• We are looking for a highly motivated PhD student who has received excellent scientific and practical training in the areas of Molecular Virology or Molecular Biology who also has some basic training or interest in bioinformatics to join our research team.</li> <li>• The student should be fluent in English (<i>English speaking countries &amp; Netherlands</i>: no requirement; <i>Other countries</i>: IELTS 7.0 (<i>min 6.0 for all subs</i>), TOEFL 100 (<i>min 20 for all subs</i>)).</li> <li>• We offer: Supervision, lab facilities and infrastructure, and training. We will cover Laboratory costs. As a candidate PhD student at Erasmus MC, your salary and living expenses will be covered by your University or Scholarship Council.</li> </ul>  |

Application requirements & Deadlines:

<https://www.eur.nl/en/about-eur/erasmus-university-china-centre/csc-scholarship>

Erasmus MC, ranked world

\* No.32 for Clinical Medicine US News 2020:

<https://www.usnews.com/education/best-global-universities/clinical-medicine?page=3>

\* No. 30 Nature Index for Biomedical Sciences 2019:

<https://www.natureindex.com/supplements/nature-index-2019-biomedical-sciences/tables/healthcare>