BIOGRAPHICAL SKETCH

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NAME: Ploss, Alexander

eRA COMMONS USER NAME (credential, e.g., agency login): PLOSSA1

POSITION TITLE: Full Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Tübingen, Baden-Württemberg, Germany	B.S.	04/1999	Biochemistry
University of Washington, Seattle, WA	no degree	09/1999-06/2000	Biochemistry /Immunology
Memorial Sloan-Kettering Cancer Center, New York City, NY	no degree	11/2001	Immunology
University of Tübingen, Baden-Württemberg, Germany	M.S.	11/2001	Immunology/Biochemistry
Weill Graduate School of Medical Sciences of Cornell University/Memorial Sloan-Kettering Cancer Center, New York City, NY	Ph.D.	05/2005	Immunology
The Rockefeller University	postdoc	09/2008	Virology

A. Personal Statement

I am a Full Professor in the Department of Molecular Biology, member of the executive committee of the Center Health and Wellbeing and a fellow in the Program in Global Health and Health Policy at Princeton University. I am also a full member of the Cancer Institute of New Jersey. In addition to my contributions to research and teaching at the university, I am a member of the MolBio graduate, the MD PhD admission committees at Princeton and Princeton/Rutgers, respectively and I am a faculty advisor for Forbes College at Princeton and serve in various departmental and institutional committees. I am committed to serving as training faculty for early career investigators and for pre- or post-doctoral trainees with an interest in clinical and translational sciences in the New Jersey Alliance for Clinical and Translational Science (NJ ACTS) program. As a member of the mentor pool, I can serve as a scientific mentor for scholars in my area of research expertise may meet regularly with a scholar to provide guidance, help with resolving roadblocks, make referrals/introductions to other scholars in the field, monitor the scholar's progress, and meet with the Scholar's other mentors.

My lab is interested in human (hepato-)tropic viral pathogens, such as hepatitis viruses, classical flaviviruses such as Zika, yellow fever, dengue viruses and since the beginning of the pandemic SARS-CoV2. Research in my lab covers three main areas of investigation: Deciphering mechanisms of viral infection/replication, systematically identifying barriers preventing transmission of human (hepatotropic) pathogens to non-primate species, and translating our discoveries into devising experimental systems that will allow us to understand and dissect host responses to these diseases. My group combines a variety of tools used to study molecular virology and pathogenesis, such as biochemical approaches, genetic screens and tissue and genome engineering methods, to achieve these goals. We have successfully employed genetic-host adaptation approaches to create the first humanized mouse models with inheritable susceptibility to hepatitis C (HCV) and delta virus (HDV) infection. In parallel we have pioneered humanized xenotransplantation models that have brought utility for study human (hepato-) tropic pathogens, including but not limited to HBV, HCV, HDV, HEV and parasites causing malaria in humans.

1. Douam, F., Gaska, J., Winer, B.Y., Ding, Q., von Schaewen, M., **Ploss, A.** (2015) Genetic dissection of the host tropism of human tropic pathogens, *Annual Reviews in Genetics*, 2015; 49:21-45. doi: 10.1146/annurev-genet-112414-054823. PMCID: PMC5075990.
2. Douam, F., **Ploss, A.** (2018) Yellow fever virus: Knowledge gaps impeding the fight against an old foe, *Trends in Microbiology*, 26(11):913-928, PMCID: PMC6340642
3. Nimgaonkar, I., Ding, Q., Schwartz, R.E., **Ploss, A.** (2018) Hepatitis E virus: Advances and Challenges, *Nature Reviews Hepatology & Gastroenterology*, 15(2):96-110
4. Mesev, E.*, Ledesma, R.*, **Ploss, A.** (2019) Decoding type I and III interferon signaling during viral infection, *Nature Microbiology*, 4(6):914-924. PMCID: PMC6554024

Ongoing and recently completed projects that I would like to highlight include:
R01 AI107301 NIH NIAID, Alexander Ploss (PI) 07/01/2018-06/30/2023
Genetic Viral and Host Adaptations to Breach Species Barriers of HCV
Major goals: To improve understanding of the barriers of interspecies transmission of hepatitis C virus (HCV). Data will be critical for generating improved animal models to study HCV and other viruses that infect primarily humans. Role: PI

R01 AI138797 NIH NIAID, Alexander Ploss (PI) 09/01/2018-08/30/2023
Modeling immune impairments and pathogenesis in novel humanized mice for HBV-HIV co-infection
Major Goals: This jproject focusses on characterizing co-infections with hepatitis B (HBV) and human immunodeficiency viruses (HIV) in humanized mice. A particular focus will be on in depth immunophenotyping of antigen-specific T cells using single cell RNA seq. Role: PI

R01 AI153236 NIH NIAID, Alexander Ploss (PI) 05/01/2020 – 04/30/2025
Mechanisms of hepatitis B virus cccDNA formation
Major goals: To mechanistically dissect the steps of the HBV life-cycle that are critical for persistence and could yield new targets for novel antiviral therapies. Role: PI

R01 AI146917 NIH NIAID, Harel Dahari (PI) 02/01/2020 – 01/31/2025
Data-Driven Mathematical and Computational Modeling of Hepatitis D Infection and Treatment Response
Major goals: The goal of this project is to develop new mathematical models to elucidate the dynamics of HDV-HBV-host infection and treatment response to determine how to effectively treat HDV. Role: Co-I

R01 AI168048 NIH NIAID, Tom Fuerst & Alexander Ploss (MPI) 05/01/2022 – 04/30/2027
Rational design and efficacy of vaccines against HCV
Major Goals: The goal of this R01 consortium is to generate a vaccine that induces broadly neutralizing antibodies against HCV. The Ploss lab will assess the efficacy of different vaccine candidates produced by other groups of consortium in humanized mouse models. Role: PI

B. Positions, Scientific Appointments, and Honors
Scientific Appointments

2023-present	Member of Molbio Undergraduate Committee
2022-present	Full Professor, Department of Molecular Biology, Princeton University
2022-present	Chair, Institutional Biosafety Committee, Princeton University
2014-present	Vice-Chair, Institutional Animal Care and Use Committee, Princeton University
2018-2022	Associate Professor (with tenure), Department of Molecular Biology, Princeton University
2014-present	Member of the Executive Committee, Center for Health and Wellbeing, Princeton University
2013-present	Member, Cancer Institute of New Jersey
2013-present	Faculty Affiliate, Program in Global Health and Health Policy, Princeton University
2013-2018	Assistant Professor, Department of Molecular Biology, Princeton University
2013	Research Associate Professor, The Rockefeller University
2009-2012	Research Assistant Professor, The Rockefeller University
2008-2009	Research Associate, Laboratory of Virology & Infectious Disease, The Rockefeller University
2005-2008	Postdoctoral Fellow, Laboratory of Virology & Infectious Disease, The Rockefeller University
2001-2004	Ph.D. Student, Weill Cornell Graduate School/MSKCC, New York, NY, USA
2000	Graduate Research Associate, German Cancer Research Center, Heidelberg, Germany,
1999-2000	Visiting Ph.D. Student, HHMI, University of Washington, Seattle, WA, USA

Positions

2022-present	Member of the Scientific Advisory Board, TWINCORE, Center for Experimental and Clinical Infection Research GmbH, Hannover, Germany
2022-present	Member of the Medicine and Biology Panel, University Grants Committee, Hong Kong
2021-present	Consultant for Lycia Therapeutics
2020-present	Consultant for PharmaSeq
2019-present	President & Founder, Acurasset Therapeutics
2019-present	Associate Editor, Journal of Hepatology
2017-present	Associate Editor, Viruses
2017-present	Associate Editor, Journal of Virology
2016-present	Instructor for summer courses, Torhea Education Group/Neoscholar Education group

Adhoc grant reviewer (selected) for IOM&NRG (2011, National Academies report on "Chimpanzees in Biomedical and Behaviorial Research: Assessing the Necessity"), NIAID (2011-present)), NIDDK (*2013-present*), National Research Agency (Agence National de la Recherche, France, 2011-present), German Research Foundation (Deutsche Forschungsgemeinschaft, 2013- present), UK Wellcome Trust (2015-present); Israeli Science Foundation (2016-2018), Science Foundation Ireland (2020), Swiss National Science Foundation (2019-present), American Cancer Society (2016-present)

Ad hoc reviewer (selected) for Cell Host & Microbe, Nature Communications, Nature Protocols, Nature Medicine, Science, Science Translational Medicine, J. Exp. Med., J. Hepatol., J. Virol.,Hepatology, PLoS Path.

Honors

2023	Elected Fellow to the American Academy of Microbiology
2016	Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Disease Award
2015	Viruses Young Investigator Award, Runner-up
2015	Löffler-Frosch Prize of the German Society of Virology
2015	Young Investigator Award, Theobald Smith Society
2015	Merck Irving S. Sigal Memorial Award of the American Society of Microbiology
2015	American Cancer Society Research Scholar Award
2012-2013	American Liver Foundation Gregg Allman Liver Scholar Award
2011-2012	Astellas Young Investigator Award by the Infectious Disease Society of America
2005-2006	Kimberly Lawrence-Netter Cancer Research Discovery Fund Award
2003-2004	Cancer Research Institute pre-doctoral fellowship
2002	Best Diploma Thesis Awarded, Assoc. of Biochemists of Tübingen, Germany
1999-2002	Studienstiftung des deutschen Volkes (German National Merit Foundation)

C. Contributions to Science

1. Molecular virology of hepatitis B and delta viruses: Hepatitis B virus (HBV) remains a major medical problem affecting at least 257 million chronically infected patients who are at risk of developing serious, frequently fatal liver diseases. HBV is a small, partially double-stranded DNA virus that goes through an intricate replication cycle in its native cellular environment: human hepatocytes. Central to HBV replication is the formation of covalently closed circular DNA (cccDNA) from relaxed circular DNA (rcDNA) which is carried into the host cell by the virus during the initial infection. We have previously established biochemical and genetic tools that allowed us to define minimal set of host factors that is necessary are necessary and sufficient for this conversion step. Most recently we delineated precisely how each lesion on the two strands of the viral genome is repaired. Progress towards a better understanding of the complex interplay between HBV and hepatitis delta virus (HDV) – a small satellite virus of HBV - and development of more effective therapies against these pathogens has been hampered by the scarcity of suitable cell culture and animal models. We have previously reported that microscalable self-assembling primary hepatocyte co-culture support persistent HBV infection. In parallel we have constructed different types of humanized mice which support persistent HBV and HDV infection.
   a. Winer, B.Y., Huang, T.S., Pludwinski, E., Wojcik, F. Lipkowitz, G., Parekh, A., Cho, C., Shrirao, A., Muir, T., Novik, E., **Ploss, A.** (2017) Long-term persistent hepatitis B virus infection in a scalable micro-well primary hepatocyte coculture system, *Nature Communications*, 8(1):125, PMCID: PMC5527081
   b. Winer, B.Y., Shirvani-Dastgerdi, E., Bram, Y., Sellau, J., Low, B.E., Johnson, H., Huang, T., Hrebikova, G., Heller, B., Sharon, Y., Giersch, J., Gerges, S., Seneca, K., Pais, M.A., Frankel, A.S., Lipkowitz, G., Chiriboga, L., Cullen, J., Nahass, R.G., Lutgehetmann, M., Toettcher, J.E., Wiles, M.V.,

Schwartz, R.E., **Ploss, A.** (2018) Preclinical assessment of antiviral combination therapy in a genetically humanized mouse model for persistent hepatitis delta virus infection, *Science Translational Medicine*, 10(447). pii: eaap9328. doi: 10.1126/scitranslmed. aap9328. PMCID: PMC6337727

c. Wei, L., **Ploss, A.** (2020) Core components of DNA lagging strand synthesis machinery is essential for hepatitis B virus cccDNA formation *Nature Microbiology*, 5(5):715-726. PMCID: PMC7190442

d. Wei, L., **Ploss, A.** (2021) Hepatitis B virus cccDNA is formed through distinct repair processes of each strand. *Nature Communications*, 12(1):1591. PMCID: PMC7952586

2. Breaking the species barrier of hepatitis C virus: Hepatitis C virus (HCV) is an important and underreported infectious disease, causing chronic infection in ~71 million people worldwide. People infected with HCV are at high risk for multiple severe liver diseases including fibrosis, cirrhosis, and hepatocellular carcinoma. The highly restricted species tropism of HCV, which is limited to chimpanzees and humans, has made in vivo study of this virus notoriously difficult. This has become even more challenging with the NIH moratorium on research in chimpanzees, underscoring the need for a small animal model suitable for studying HCV pathogenesis. Using cDNA complementation screens, we identified the minimal set of human factors, CD81 and occludin (OCLN) required for hepatitis C virus (HCV) uptake into rodent cells. We have shown that expression of the two human genes is sufficient to allow HCV infection of fully immunocompetent inbred mice. When blunting antiviral innate responses in engineered mouse cells and genetically humanized mice expressing CD81 and OCLN the entire viral life-cycle can be established in vivo. Complementary, we have shown attempted viral adaptation of HCV to infection in small non-human primates and mice. More generally, we apply this approach of genetic host and viral adaptation to defining species barriers of other human-tropic pathogens.

a. **Ploss A.***, Evans M.J.*, Gaysinskaya V.A., Panis M., You H., de Jong Y.P., Rice C.M. (2009) Human occludin is a hepatitis C virus entry factor required for infection of mouse cells, *Nature*, 457: 882-6. PMCID**:** PMC2762424

b. Dorner, M., Horwitz, J.A., Robbins, J., Barry, W.T., Mu, K., Jones, C.T., Schoggins, Catanese, M.T., J.W., Burton, D.R., Law, M., Rice, C.M., **Ploss, A.** (2011) A genetically humanized mouse model for hepatitis C virus infection, *Nature*, 474: 209-211. PMCID**:** PMC3159410

c. Dorner M., Horwitz J.A.*, Donovan B.M.*, Labitt R.N., Budell W.C., Friling T., Vogt A., Catanese M.T., Satoh T., Kawai T., Akira S., Law M., Rice C.M., **Ploss A.** (2013) Completion of the entire hepatitis C virus life-cycle in genetically humanized mice, *Nature,* 501(7466):237-41, PMCID: PMC3858853

d. Gaska, J., Balev, M., Ding, Q., Heller, B., **Ploss, A.** (2019) Species-specific differences across cyclophilin A orthologs contribute to the host range restriction of hepatitis C virus, *eLIFE*, 8. pii: e44436. doi: 10.7554/eLife.44436. PMCID: PMC6510530

3. Mechanisms of hepatitis E virus infection: The enterically transmitted hepatitis E virus (HEV) is responsible for ~3 million symptomatic infections and ~70,000 deaths per year globally. The lifecycle of HEV, a small quasi-enveloped (+)-sense RNA belonging to the genus orthohepevirus remains incompletely understood. We have contributed to delineating the functions of the major gene products of HEV, open reading frames (ORF) 1, 2 and 3. ORF1 is a multifunctional polyprotein that contains the essential functions for viral genome replication. Recently, we have taken a combined computational, genetic and biochemical approach yielding a structural model of the ORF1 polyprotein. We further defined a novel function for HEV open reading frame ORF3 protein as a viroporin whose ion channel activity is critical for release of virions from infected cells. We have also demonstrated that heat shock protein 90 plays a critical role in the HEV replication cycle highlighting new ways for interfering with HEV infection.

a. Ding, Q., Nimgaonkar, I. Archer, N., Bram, Y., Heller, B., Schwartz, R.E., **Ploss, A.** (2018) Identification of the intragenomic promoter controlling hepatitis E virus subgenomic RNA transcription, *mBio*, 9(3). pii: e00769-18, PMCID: PMC5941075

b. Ding, Q, Heller, B., Capucino, J.M.V., Song, B., Nimgaonkar, I., Hrebikova, G., Contreras, J.E, **Ploss, A.** (2017) Hepatitis E virus ORF3 is a functional ion channel required for release of infectious particles, *Proc Natl Acad Sci U S A*, 114(5):1147-1152. PMCID: PMC5293053

c. Nimgaonkar, I., Archer, N.F., Becher, I., Shahrad, M., Savitski, M.M., Kim, H.K., **Ploss, A.** (2021) Inhibition of heat shock protein 90 suppresses hepatitis E virus replication, *Antiviral Research*, 185:104997. doi: 10.1016/j.antiviral.2020.104997. PMCID: PMC8649941

d. LeDesma, R.A., Biswas, A., Maya, S., Gili, S., Higgins, J.A., **Ploss, A.** (2023), Structural features stabilized by divalent cation coordination within hepatitis E virus ORF1 are critical for viral replication, 12:e80529. doi: 10.7554/eLife.80529. PMCID: PMC9977285

4. Analysis of flavivirus tropism and pathogenesis: Infections with arthropod-borne flaviviruses such as dengue virus (DENV), yellow fever virus (YFV) or Zika virus (ZIKV) remain major contributors to morbidity and mortality in the human population. With particular focus on yellow fever virus, the prototypic member of the flavivirus genus, we have analyzed host defense mechanisms interfering with viral infections in vivo. We previously determined that a combination of type I and III interferon (IFN) dependent pathways is responsible for attenuating the YFV vaccine strain in vivo. Likewise, we are able to show that cGAS-STING-dependent signaling restricts ZIKV propagation in murine cells. We further generated highly sensitive method for tracking flavivirus genomes in complex cell populations.
   a. Douam, F., Hrebikova, G., Soto Albrecht, Y.E., Sellau, J., Sharon, Y., Ding, Q., **Ploss, A.** (2017) Single-cell tracking of flavivirus RNA uncovers species-specific interactions with the immune system dictating disease outcome. *Nature Communications*, 8:14781. PMCID: PMC5424064
   b. Ding, Q., Gaska, J.M., Heller, B., **Ploss, A.** (2018) Species-specific disruption of the STING-dependent antiviral cellular defenses by the Zika virus NS2B3 protease, *Proc Natl Acad Sci U S A*. pii: 201803406. doi: 10.1073/pnas.1803406115. PMCID: PMC6142274
   c. Douam, F., Soto-Albrecht, Y.E., Hrebikova, G., Sadimin, E., Davidson, C., Kotenko, S., **Ploss, A**. (2017), Type III interferon mediated signaling is critical for controlling live-attenuated yellow fever virus in vivo, *mBio*, 8(4) pii: e00819-17, PMCID: PMC5559630
   d. Tamura, T., Zhang, J., Madan, V., Biswas, A., Schwoerer, M.P., Cafiero, T., Heller, B.L., Wang, W., **Ploss, A.** (2022) Generation and characterization of genetically and antigenically diverse infectious clones of dengue virus serotypes 1-4, *Emerging Microbes and Infections*, 11(1):227-239. PMCID: PMC8745371
5. Humanized mouse models for viral immunity and pathogenesis: Many pathogens causing disease in humans exhibit a very narrow host tropism. Complementary to our work aimed at defining the molecular basis of the limited host range of human-tropic viruses we have pioneered numerous humanized xeno-transplantation models. Humanized mice, are amenable small animal models transplanted with human cells or tissues (and/or equipped with human transgenes). We continuously refine methods for generating mice (co-)engrafted with a human(ized) liver and components of human immune system We have successfully employed such models to study human-tropic pathogens such as HBV, HCV, HIV, Epstein Barr virus, yellow fever and dengue viruses and most recently for SARS-CoV2. We have also created humanized mice in which the tissue compartments relevant to the mammalian stages of plasmodial parasites are humanized. Collaboratively, we demonstrated that these humanized mouse models have great utility for studying the mammalian stages of the parasitic life-cycle.
   a. Klein F., Halper-Stromberg A., Horwitz J.A., Gruell H., Scheid J.F., Bournazos S., Mouquet H.,… Bieniasz P.D., Seaman M.S., Bjorkman P.J., Ravetch J.V., **Ploss A.**, Nussenzweig M.C. (2012), HIV therapy by a combination of broadly neutralizing antibodies in humanized mice, *Nature*, 492: 118-22. PMCID: PMC3809838
   b. de Jong, Y.P., Dorner, M., Mommersteeg, M.C., Xiao, J.W., Balazs, A.B., Robbins, J.B., Vega, K., Labitt, R.N., Donovan, B.M., Giang, E., Krishnan, A., Chiriboga, L., Charlton, M.R., Burton, D.R., Baltimore, D., Law, M., Rice, C.M., **Ploss, A.** (2014) Broadly neutralizing antibodies abrogate established hepatitis C virus infection, *Science Translational Medicine*, 6(254):254ra129, PMCID: PMC4312107
   c. Douam, F., Ziegler, C.G.K, Hrebikova, G., Fant, B., Leach, R., Parson, L., Wang, W., Gaska, J.M., Winer, B.Y., Heller, B., Shalek, A.K., **Ploss, A.** (2018) Selective expansion of myeloid and NK cells in humanized mice yields human-like host responses to vaccination, *Nature Communications*, 28;9(1):5031. PMCID: PMC6262001
   d. Kenney, D.J.*, O'Connell, A.K.*, Turcinovic, J.*, Montanaro, P.*, Hekman, R.M.*, Tamura, T.*, Berneshawi, A., Cafiero, T., Al Abdualatif, S, Blum, B., Goldstein, S.I., Heller, B.L., Gertje, H.P., Bullitt, E., Trachtenberg, A., Chavez, E., Tuekam Nono, E., Morrison, C., Tseng, A., Sheikh, A., Kurnick, S., Grosz, K., Bosmann, M., Ericsson, M., Huber B.R., Saeed, M., Balazs, A.B., Francis, K.P., Klose, A., Paragas, N., Campbell, J.D., Connor, J.H., Emili, A., Crossland, N.**, **Ploss, A.****, Douam, F.** (2022) Humanized mice reveal a macrophage-enriched gene signature defining human lung tissue protection during SARS-CoV-2 infection, Cell Reports, 39(3):110714. doi: 10.1016/j.celrep.2022.110714. PMCID: PMC8977517

Link to publications in My NCBI bibliography: https://pubmed.ncbi.nlm.nih.gov/?term=Ploss%2C%20Alexander