BIOGRAPHICAL SKETCH

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NAME: Lothar Hennighausen, PhD

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

POSITION TITLE: Chief, Section of Genetics and Physiology

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	Year(s)	FIELD OF STUDY
University of Marburg, Germany	B.S.	1977	Biology
University of Köln, Germany	Diploma	1979	Biology
University of Köln, Germany	Doctorate	1982	Genetics
Harvard Medical School	Postdoctoral	1985	Genetics

A. Personal Statement

Over the last few decades, our laboratory has studied the biology of the Janus Kinase / Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathway, with a particular emphasis on the STAT5a/b transcription factors, in response to cytokines across a spectrum of tissues. These studies provided in depth mechanistic understanding of the vital role of STAT5 and other transcription factors in the establishment of enhancers and super-enhancers controlling genetic programs in the immune system, the mammary gland during pregnancy and lactation and sexual dimorphism of the liver. With the advent of the COVID-19 pandemic, we brought our understanding of JAK-STAT-mediated immune response to studies investigating the range of homeostatic responses to infection and vaccination across community and hospital-based populations. This led us to become interested in the possible role of SNPs within the JAK-STAT pathway that induce amino acid changes and structural alterations and have the capacity to disrupt immune homeostasis.

I have extensive experience working in community-based genetic research with clinicians and Institutional Review Boards (IRBs). I have mentored and trained scientists at all levels to design and execute scientific studies and break new ground. This proposed project represents a collaboration between an Associate Scientist and three post-doctoral fellows in the laboratory, community physicians and physicians Board Certified in Rheumatology, Laboratory Medicine and Infectious Diseases, with the goal to advance our knowledge of any role of JAK-STAT missense mutations in contributing to the female predominance of multiple autoimmune syndromes. My laboratory has embedded bioinformatics platforms in our work as they have become available and relevant to our studies. This was particularly significant for our COVID-19 based studies. To expand our laboratory's capacity in investigative bioinformatics and AI in 2023 we recruited two post-doctoral fellows with PhDs in computational science and bioinformatics to our team to expand our coding skills for approaching questions using big data.

a. Shin HY, Willi M, Yoo HK, Zeng X, Wang C, Metser G, **Hennighausen L** (2016) Hierarchy within the mammary STAT5-driven Wap super-enhancer. Nature Genetics 48: 904-911 PMCID: PMC4963296
b. Lee KH, Hoechstetter MA, Buchner M, Pham TT, Huh JW, Müller K, Zange S, von Buttlar H, Girl P, Wölfel R, Brandmeier L, Pfeuffer L, Furth PA, Wendtner CM, **Hennighausen L** (2023) Robust transcriptional response to COVID-19 immunization despite ineffective humoral immune responses in CLL patients. Blood Advances 7: 2214–2227 PMCID: PMC9906673
c. Lee HK, Knabl L, Moliva JI, Knabl Sr. L, Werner AP, Boyoglu-Barnum S, Kapferer S, Pateter B, Walter M, Sullivan N, Furth PA, **Hennighausen L** (2022) mRNA vaccination in octogenarian nuns 15 and 20 months after recovery from COVID-19 elicits robust immune and antibody responses that include Omicron. Cell Reports 39:110680 PMCID: PMC8947943

d. Lee HK, Knabl L, Pipperger L, Volland A, Furth PA, Smith HE, Knabl L, Bellmann R, Bernhard C, Kaiser N, Ganzer H, Strohle M, Walser A, von Laer D, **Hennighausen** L (2021) Immune transcriptomes of highly exposed SARS-CoV-2 asymptomatic seropositive versus seronegative individuals from the Ischgl community. Scientific Reports 11:4243 PMCID: PMC7895922

B. Positions and Honors

Positions and Employment

1985 – 1991 National Institute of Diabetes and Digestive and Kidney Diseases
Principal Investigator and Group Leader
1992 – 1993 Max-Planck-Institute for Biophysical Chemistry, Göttingen, Germany
Visiting Scientist and Humboldt Fellow
1991 – 1997 National Institute of Diabetes and Digestive and Kidney Diseases
Chief, Developmental Biology Section
2002 – 2003 Max-Planck-Institute for Biochemistry, Martinsried - München, Germany
Humboldt Scholar and Visiting Professor
2007 – 2009 Technical University of Munich, München, Germany
Mercator Visiting Professor
1997 – 2021 National Institute of Diabetes and Digestive and Kidney Diseases
Chief, Laboratory of Genetics and Physiology
2021 - National Institute of Diabetes and Digestive and Kidney Diseases
Chief, Section of Genetics and Physiology

Other Experience and Professional Memberships

- Organizer, Conference on Bioinformatics and Clinical Research, Technical University Munich (2023)
- Organizer, Symposium on CRISPR Genome Engineering, NIH Research Festival (2018)
- Visiting Professor, Chonnam National University Medical School, Gwangju, Republic of Korea (2009 -
- Visiting Professor, Dankook University, Cheonan, Republic of Korea, Visiting Professor (2011 – 2013)
- Chairman, Scientific Advisory Board, Georg-Speyer Institute, University of Frankfurt, Germany (2007-2016)
- Organizer, International Cytokine Conference, Frankfurt, Germany (2011)
- Organizer, International JAK-STAT Conference, Bethesda (2011)
- Organizer, several conferences and workshops at the NIH and the Jackson Laboratory
- Member, Mouse Model Consortium for Human Cancer

Selected Honors

- Hans-Fischer Senior Fellow, Institute for Advanced Study (IAS), Technical University Munich (TUM), Germany (2020)
- Global Visiting Professor, Technical University Munich, Germany (2019)
- NIH Director's award for outstanding accomplishments (2019)
- Director's Award, NIDDK/NIH (2017)
- Orloff Award, NHLBI/NIH (2017)
- World Class Scholar, Korea Science and Engineering Foundation (2009)
- Mercator Professorship, Deutsche Forschungsgemeinschaft (2007)
- Equal Employment Opportunity Special Achievement Award, NIH (2004)
- Alexander von Humboldt Research Award (2001)
- Washington Press Club, presentation on the use of transgenic animals as bioreactors (1987)

Selected Lectures

- International Graduate School in Molecular Medicine, Ulm, Germany, Invited speaker (2024)
- International Lupus Conference, invited plenary lecture, Seoul, South Korea (2023)
- Student invited Seminar Series, Case Western Reserve University, Speaker (2018)
- Keynote lecture, FASEB Conference, Growth Hormone / Prolactin Family (2019)
- Keynote lecture, Mammary Gland Biology Gordon Conference (2016)
- Distinguished Lecture Series, McGill University, Montreal, Canada (2012)

- Distinguished Professor, St. John's, Canada (2011)
- Plenary Speaker, Endocrine Society Annual Meeting, San Diego (2010)
- Plenary Speaker, Korean Society of Molecular and Cellular Biology, Seoul, Republic of Korea (2009)
- Seminars in Oncology, Dana-Farber Cancer Center (2005)
- Distinguished Lecture Series, Center for Cancer Immunology, MD Anderson (2005)
- Olof Pearson Memorial Lecture, Case Western Reserve University (2003)
- Presidential Lecture, Society for the Study of Reproduction (2002)
- Keynote Address, Mouse Models for Prostate Cancer, The Jackson Laboratory (2001)
- Keynote Address, American Society for Urology, Houston (2000)
- Keynote Address, Massachusetts Breast Cancer Coalition, Boston Univ. School of Medicine (1996)

C. Contributions to Science

A. In the Spring of 2020, responding to the COVID-19 pandemic, we contributed our expertise and logistics and partnered with community-based physicians in a quest to understand the immune response in COVID-19 patients infected with SARS-CoV-2 variants and the impact of prior vaccination. Although a large percentage of infected individuals are asymptomatic, the response of their immune systems and prevalence of unrecognized ongoing inflammation to SARS-CoV-2 was not understood at the time the pandemic started. We addressed this question and initially investigated immune transcriptomes in individuals from one of the original super spreading events in Europe. Whole blood transcriptomes identified individual immune profiles within a community population and showed that asymptomatic infection within a super-spreading event was not associated with enduring immunological activation. As the pandemic progressed, we investigated the innate immune response of patients infected with emerging variants carrying specific mutations thought to enhance viral fitness.

   Our studies also demonstrated a more intensive immune response in BNT162b2 vaccinated hospitalized elderly patients infected with the Beta variant as compared to unvaccinated ones. Transcription factors linked to the JAK-STAT pathway, interferon stimulated genes, and genes associated with innate antiviral immunity and COVID-19 were highly enriched in vaccinated patients. Our studies demonstrate that transcriptomes provide a deep understanding of immune responses elicited by viral infections and the impact of prior vaccination. **Our cumulative work demonstrates how variations in the JAK-STAT signaling network and related immune pathways could be associated with the response to different viral variants and different vaccine platforms.**

   a. Lee HK, Knabl L, Walter M, Knabl Sr L, Dai Y, Füßl M, Caf Y, Jeller C, Knabl P, Obermoser M, Baurecht C, Kaiser N, Zabernigg A, Wurdinger GM, Furth PA, **Hennighausen** L (2022) Prior vaccination exceeds prior infection in eliciting innate and humoral immune responses in Omicron infected outpatients. Frontiers in Immunology 13:916686 PMCID: PMC9240221
   b. Lee HK, Knabl L, Pipperger L, Volland A, Furth PA, Smith HE, Knabl L, Bellmann R, Bernhard C, Kaiser N, Ganzer H, Strohle M, Walser A, von Laer D, **Hennighausen** L (2021) Immune transcriptomes of highly exposed SARS-CoV-2 asymptomatic seropositive versus seronegative individuals from the Ischgl community. Scientific Reports 11:4243. PMCID: PMC7895922
   c. Knabl L, Lee HK, Wieser M, Mur A, Zabernigg A, Knabl Sr. L, Rauch S, Bock M, Schumacher J, Kaiser N, Furth PA, **Hennighausen** L (2022) BNT162b vaccination enhances interferon-JAK-STAT-regulated antiviral programs in COVID-19 patients infected with the SARS-CoV-2 Beta variant. Communications Medicine 2:17 PMCID: PMC9029844
   d. Lee SG, Furth PA, **Hennighausen** L, Lee HK (2024) Variant- and Vaccination-Specific Alternative Splicing Profiles in SARS-CoV-2 Infections. iScience 27: 109177 PMCID: PMC10897911

B. In December 2020, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19. **There was an urgent need to understand the immune response mounted in different population groups.** Among those are the response of young versus old and the response of individuals that had been previously infected. Equally, and maybe even more critical, is an understanding of the immune response in immunocompromised individuals, such as cancer patients as well as those with organ transplants.

We partnered with community-based physicians and conducted four studies. First, we investigated the impact of prior SARS-CoV-2 infection of the elderly (octogenarians) on mRNA vaccination response and found a stronger innate immune response compared to a naïve population. In a second study we investigated the impact of heterologous ChAdOx1-BNT162b2 vaccination and found that it induces a stronger innate and adaptive immune response that exceeds homologous BNT162b2 vaccination. In a third study we investigated the immune response to COVID-19 vaccination in patients with chronic lymphocytic leukemia (CLL), which are considered high-risk for severe COVID-19 infection, mainly due to their complex underlying immunodeficiency and inadequate immune response to infections. Key transcriptional findings were that interferon-mediated signaling activation including activation of the JAK-STAT pathway generally occurred within days of vaccination but was independent from the magnitude of the antibody response. Importantly a normal T cell response was observed. In a fourth study we examined the immune response to vaccination in an Adult-Onset Still's Disease (AOSD) patient with a history of vaccine-induced disease flare. He was found to carry a novel JAK2 mutation and have an exacerbated innate immune response after receiving the BNT162b vaccine. **Our studies demonstrated the value of vaccination even after infection and contribute to the management of future pandemics. Specifically, we demonstrated that the elderly manifested a very vigorous response to vaccination.**

a. Lee HK, Knabl L, Moliva JI, Knabl Sr. L, Werner AP, Boyoglu-Barnum S, Kapferer S, Pateter B, Walter M, Sullivan N, Furth PA, **Hennighausen** L (2022) mRNA vaccination in octogenarian nuns 15 and 20 months after recovery from COVID-19 elicits robust immune and antibody responses that include Omicron. Cell Reports 39:110680 PMCID: PMC8947943
b. Lee HK, Go JY, Sung HS, Kim SW, Walter M, Knabl L, Furth PA, **Hennighausen** L, Huh JW (2022) Heterologous ChAdOx1-BNT162b2 vaccination in Korean cohort induces robust immune and antibody responses that includes Omicron. iScience 25:104473 PMCID: PMC9132682
c. Lee KH, Hoechstetter MA, Buchner M, Pham TT, Huh JW, Müller K, Zange S, von Buttlar H, Girl P, Wölfel R, Brandmeier L, Pfeuffer L, Furth PA, Wendtner CM, **Hennighausen** L (2023) Robust transcriptional response to COVID-19 immunization despite ineffective humoral immune responses in CLL patients. Blood Advances 7: 2214–2227 PMCID: PMC9906673
d. Knabl L, Lee HK, Walter M, Furth PA, **Hennighausen** L (2022) Immune transcriptome in adult-onset Still's disease with mild flare following administration of mRNA vaccine BNT162b2. Rheumatology, 61, e305-e307 PMCID: PMC9536777

C. Starting in March 2020, we initiated COVID-19 research in mice and human primary cells to understand the impact of cytokine storms on lung and kidney with an emphasis on the SARS-CoV-2 receptor ACE2. This study also permitted us to investigate molecular mechanisms of Janus kinase (JAK) inhibitors, which suppress immune activation and inflammation and are used therapeutically in COVID-19 patients. Through integrating RNA-seq and ChIP-seq data we provided an in-depth understanding of genetic programs activated by interferons and highlight JAK inhibitors as suitable tools to suppress these in bronchial and renal cells. We also discovered a new intronic enhancer within the ACE2 gene that leads to the expression of a short form of ACE2. In a study following up on our community based COVID-19 studies, we utilized computational deconvolution approaches to define changes in individual white blood cell compartments associated with different viral variants.

a. **Hennighausen** L, Lee HK (2020) Activation of the SARS-CoV-2 receptor Ace2 through JAK/STAT-dependent enhancers during pregnancy. Cell Reports 32:108199 PMCID: PMC7474886
b. Lee HK, Jung O, **Hennighausen** L (2021) JAK inhibitors dampen activation of interferon-stimulated transcription of ACE2 isoforms in human airway epithelial cells. Commun. Biology 4:654 PMCID: PMC8172581
c. Jankowski J, Lee HK, Wilflingseder J, **Hennighausen** L (2021) JAK inhibitors dampen activation of interferon-activated transcriptomes and the SARS-CoV-2 receptor ACE2 in human renal proximal tubules. iScience 24:102928 PMCID: PMC8321697
d. Hoffmann M, Willruth LL, Dietrich A, Lee HK, Knabl L, Trummer N, Baumbach J, Furth PA, **Hennighausen** L, List M (2024) Blood transcriptomics analysis offers insights into variant-specific immune response to SARS-CoV-2. Scientific Reports, 14:2808 PMCID: PMC10837437

D. Our laboratory has contributed significantly to the understanding of female-based JAK-STAT cytokine signaling in the mammary gland and liver. We discovered and cloned relevant genes in the pathway, including STAT5b and LGP2 (DHX58), and investigated JAK-STAT controlled genetic programs using experimental mouse genetics. These studies demonstrated the pivotal role of enhancers and super-enhancers in the execution of genetic programs controlling mammary gland development during pregnancy and cellular differentiation enabling lactation. It also provided evidence that the transcription factor STAT5 controls sexual dimorphic programs in liver metabolism.

   a. Shin HY, Willi M, Yoo HK, Zeng X, Wang C, Metser G, **Hennighausen L** (2016) Hierarchy within the mammary STAT5-driven Wap super-enhancer. Nature Genetics 48: 904-911 PMCID: PMC4963296
   b. Holloway MG, Cui Y, Laz EV, Hosui A, **Hennighausen** L, Waxman DJ (2007) Loss of sexually dimorphic liver gene expression upon hepatocyte-specific deletion of Stat5a-Stat5b locus. Endocrinology 148: 1977-86 PMCID: PMC3282149
   c. Liu X, Robinson GW, Wagner KU, Garrett L, Wynshaw-Boris A, **Hennighausen** L (1997) Stat5a is mandatory for adult mammary gland development and lactogenesis. Genes Dev 11: 179-86 PMID: 9009201
   d. Liu X, Robinson GW, Gouilleux F, Groner B, **Hennighausen L**. (1995) Cloning and expression of Stat5 and an additional homologue (Stat5b) involved in prolactin signal transduction in mouse mammary tissue. Proc Natl Acad Sci USA. 92:8831-8835 PMCID: PMC41061

E. Our laboratory has extensive experience with genome engineering dating back to 1987 when we introduced transgenes into the mouse germline. We have used CRISP-Cas9 technologies extensively to interrogate STAT5-dependent transcription enhancers and other regulatory elements in the mouse genome. More recently we have used deaminase base editing to introduce point mutations (SNPs) into the mouse genome and investigated the role of super-enhancers in controlling genetic programs in the mammary gland. As part of these studies, we defined the strength and weaknesses of gene editing technologies, including different deaminase base editors. Recently (yet unpublished) we have introduced human missense mutations in the transcription factors STAT3 and STAT5B into the male and female mouse genome. These mutations had been linked to leukemia and autoimmune disease.

   a. Lee HK, Willi M, Liu C, **Hennighausen** L (2023) Cell-specific and shared enhancers control a multi-gene locus active in mammary and salivary glands. Nature Communications 14:4992 PMCID: PMC10435465
   b. Lee HK, Smith HE, Liu C, Willi M, **Hennighausen** L (2020) Cytosine base editor 4 but not adenine base editor generates off-target mutations in mouse embryos. Communications Biology 3:19 PMCID: PMC6952419
   c. Willi M, Smith HE, Wang C, Liu C, **Hennighausen** L (2018) Mutation frequency is not increased in CRISPR-Cas9-edited mice. Nature Methods 10:756-758. PMID: 30275594
   d. Lee HK, Willi M, Miller SM, Kim S, Liu C, Liu DR, **Hennighausen** L (2018) Targeting fidelity of adenine and cytosine base editors in mice. Nature Communications 9:4804 PMCID: PMC6238002

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PubMed

D. Research Support

Ongoing Research Support
NIH NIDDK
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"Genetic approaches to understanding organ development and function"