Going Viral: Exploring Viral Triggers of Autoimmune Diseases

OADR-ORWH ScienceTALKS

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Event Webpage
Event Recording

Welcome and Opening Remarks

Victoria Shanmugam, MBBS, MRCP, FACR, CCD, Director, NIH Office of Autoimmune Disease Research in the Office of Research on Women's Health (OADR-ORWH)

Dr. Shanmugam opened the OADR-ORWH ScienceTALKS webinar, introduced the moderators and speakers, and outlined the meeting's agenda.

Viral Exposures as a Driver of Autoimmune Diseases

Judith A. James, M.D., Ph.D., Executive Vice President and Chief Medical Officer, Professor and Program Chair Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation

Autoimmune diseases encompass a wide range of conditions, with systemic lupus erythematosus (SLE) being one of the most intricate and varied. SLE disproportionately affects women, with a prevalence of nine women to every man. This condition particularly poses a significant health concern for U.S. females aged 15–45 and women of color, highlighting the urgent need for focused research to address these disparities.

Among infectious agents, particularly viruses, Epstein-Barr virus (EBV) is strongly linked to SLE. This large, enveloped, double-stranded DNA herpesvirus primarily targets epithelial and B cells. EBV has a biphasic lifecycle that begins with a lytic phase, where the virus actively replicates within infected cells, leading to the production and release of new viral particles. Following the lytic phase, EBV transitions into a latent phase, during which the virus remains dormant as an episome within memory B cells. In this dormant state, EBV can persist in the host for life without engaging in continuous active replication.

Greater than 95% of adults are infected with EBV, which is primarily transmitted through saliva. While infections in early childhood are often asymptomatic, EBV can cause infectious mononucleosis in adolescence or later. This virus is associated with several conditions, including lymphomas, nasopharyngeal carcinoma, and autoimmune diseases. The immune response to EBV predominantly involves cytotoxic T cells, with humoral responses indicating viral reactivation. In patients with SLE, EBV infection is more prevalent and associated with stronger immune responses compared to those without SLE. These immune responses are marked by elevated levels of antibodies against the EBV early antigen (anti-EA antibodies) and the EBV capsid antigen (anti-VCA antibodies), along with increased detection of EBV DNA.

Dr. James and her research team have been investigating the initial autoantibody responses in patients with SLE. The team conducted a longitudinal study on a patient from Oklahoma, monitoring the development of autoantibodies over several years. The patient initially exhibited minimal reactivity but, over time, developed anti-Smith (anti-Sm) antibodies. These autoantibodies target the Smith antigen, a

key component of small nuclear ribonucleoproteins (snRNPs) involved in RNA processing. As the disease progressed, the patient produced antibodies against various regions of the Sm B' protein, part of the snRNP complex. Notably, these antibodies targeted the carboxyl terminus sequence PPPGMRPP, a dominant epitope in the Sm B' protein and a major target for anti-Sm sera, representing 30-65% of the total anti-Sm antibody response. These findings underscore the progression and specificity of autoantibody development in SLE, offering insights into the immunological mechanisms underlying the disease and potential targets for diagnostic and therapeutic strategies.

The team also investigated early autoantibodies targeting the 60 kDa Ro/SSA protein, a common autoantigen in SLE and other autoimmune diseases such as Sjögren's syndrome. The team discovered that the initial epitope targeted was the Ro 169 peptide, a 12-amino acid sequence beginning at residue 169 of the Ro/SSA protein. Over time, this initial response led to epitope spreading, with antibodies recognizing additional regions of the protein. Notably, antibodies against the Ro 169 peptide were found to cross-react with Epstein-Barr Nuclear Antigen 1 (EBNA-1). Immunization with the Ro 169 peptide in animal models not only induced antibodies against EBNA-1 but also produced features similar to those observed in SLE, suggesting a potential link between EBV infection and the development of autoimmunity.

The team's studies also revealed that the nature of the immune response elicited by EBV might be crucial in understanding how EBV contributes to the development of autoimmune diseases. Specifically, the team found that pediatric patients with SLE develop antibodies against a broader range of epitopes across the EBNA-1 protein compared to healthy controls, who mainly target the glycine-alanine repeat region of EBNA-1. These findings suggest that SLE patients experience a more extensive and potentially pathogenic immune response, resulting in antibodies that cross-react with self-antigens.

Additionally, the team investigated whether EBV reactivation is associated with the onset of clinical SLE. Using the Lupus Family Registry and Repository, which includes more than 3,660 patients with SLE and many unaffected family members, the team re-enrolled 436 previously healthy relatives of SLE patients to monitor the development of SLE over time. The study revealed that 56 of these individuals transitioned to SLE over an average follow-up period of 6 years. Individuals who developed SLE were found to have higher levels of anti-VCA antibodies, with particularly elevated levels of anti-EA antibodies, which are indicative of frequent EBV reactivation. This finding suggests that EBV reactivation, particularly in individuals with specific genetic risk factors, may increase the likelihood of developing SLE.

Furthermore, the team examined the relationship between EBV reactivation and SLE disease activity or inflammatory cytokine production. By analyzing more than 200 patients with SLE from the Oklahoma Rheumatic Disease Cohort, categorized by varying levels of disease activity (measured using the SLE Disease Activity Index, or SLEDAI scores), the team compared these patients to healthy controls. The study found that patients with SLE, especially those with higher disease activity (SLEDAI ≥ 6), were more likely to have elevated levels of anti-EA and anti-VCA antibodies. Notably, only anti-EA antibodies were significantly elevated in patients with high disease activity, suggesting a potential link between EBV reactivation and increased disease activity in SLE patients.

Dr. James and her research team have further explored the relationship between EBV reactivation and autoimmune disease activity in SLE. They investigated whether frequent viral reactivation correlates with elevated levels of interferon-associated molecules. Their findings revealed that individuals who tested positive for anti-EA antibodies had elevated levels of interleukin-10 (IL-10), including both human

IL-10 and viral IL-10 (vIL-10). These individuals also exhibited increased levels of interferon gamma-induced protein 10 (IP-10), also known as CXCL10, a cytokine associated with interferon responses, as well as elevated B lymphocyte stimulator (BLyS) levels, which are linked to B cell activity. These results suggest a significant correlation between frequent EBV reactivation and elevated levels of interferon-associated molecules in patients with SLE.

In addition, the team analyzed gene expression profiles from patients with SLE and identified seven distinct clusters with different gene expression patterns. Cluster 4 was characterized by high inflammation and interferon activity, while clusters 3, 6, and 7 showed various immune and inflammatory signatures. Notably, anti-EA positivity was significantly high in clusters 4 and 3, suggesting a link between viral reactivation and specific patterns of disease activity in SLE, with certain clusters showing a stronger association with EBV-related immune responses.

The research team also explored functional molecular mimicry, focusing on vIL-10. They observed that vIL-10, which closely resembles human IL-10, was present at higher levels in SLE patients compared to healthy controls. However, vIL-10 did not correlate perfectly with human IL-10 levels. Specifically, vIL-10 was less effective at inhibiting pro-inflammatory mediators and induced lower levels of STAT-3 phosphorylation compared to human IL-10. This differential effect on monocyte activation and apoptotic cell clearance suggests that vIL-10 may contribute to immune dysregulation in SLE.

Additionally, the team investigated the role of EBV latent membrane protein 1 (LMP1), which mimics human CD40, a critical cell surface protein in the immune system. Their studies, involving both animal models and human samples, demonstrated that LMP1 could drive autoantibody production and immune dysregulation, potentially accelerating the disease process in SLE.

Overall, these studies highlight the complex interplay between EBV, immune dysregulation, and autoimmunity. The findings suggest that viral reactivation, molecular mimicry, and functional mimicry may all contribute to the pathogenesis of SLE. This research underscores the potential for deeper insights and novel approaches to managing autoimmune diseases linked to viral infections.

Epstein-Barr Virus and Multiple Sclerosis

William H. Robinson, M.D., Ph.D., James W. Raitt Professor of Medicine Chief, Division of Immunology and Rheumatology, Stanford University

Research has highlighted a significant role for EBV in the development of multiple sclerosis (MS), with nearly 100% of MS patients having a history of EBV infection. However, while this association is robust, EBV infects the vast majority of the general population, including many healthy individuals, complicating the establishment of a direct causal link between EBV and MS. This complexity reflects the ongoing nature of research in this area. Additionally, EBV has been linked to other autoimmune diseases, including SLE, rheumatoid arthritis (RA), and Sjögren's syndrome, suggesting that EBV may contribute causally to these conditions rather than merely being associated with them.

The intricate lifecycle of EBV, which involves various latency phases and the low frequency of EBV+ B cells in autoimmune diseases, adds complexity to understanding the virus's role in autoimmunity. Despite these challenges, EBV reactivation has been associated with disease progression and clinical flares in conditions such as SLE and RA.

T-cell therapy targeting EBV-positive B cells has demonstrated efficacy in treating post-transplant lymphoproliferative disease, an EBV-associated malignancy. However, this approach has not been successful in clinical trials for primary progressive MS, highlighting the difficulties of targeting EBV in autoimmune diseases, where the underlying mechanisms may differ significantly from those in EBV-related cancers.

Dr. Robinson's team conducted research to explore the role of B cells in MS by sequencing B cell repertoires in the spinal fluids of patients with the disease. The team collected spinal fluid samples, isolated B cells, and sequenced their antibody repertoires. The results revealed clonal expansions of B cells in the spinal fluid of patients with relapsing-remitting MS, indicating a highly oligoclonal response, where a few B cell clones dominate the immune response. In contrast, blood samples from these patients showed predominantly single B cell families, reflecting a more diverse B cell population.

The team then investigated the targets of these clonally expanded B cells by expressing representative antibodies and testing them against a viral proteome array, which included EBV and other viruses. Notably, one antibody, named MS39, specifically bound to a region of the EBV EBNA-1 protein. This region, rich in proline and arginine, had previously been identified as cross-reacting with human myelin proteins, suggesting a potential mechanism for autoimmune targeting in MS.

Further experiments showed that the MS39 antibody also bound to GlialCAM, a human protein expressed in the brain that is crucial for maintaining the myelin sheath—a protective layer around nerve fibers. The binding affinity of MS39 to GlialCAM increased when GlialCAM was phosphorylated, indicating that this cross-reactivity might contribute to the demyelination observed in MS. Additionally, immunizing mice with EBNA-1 led to the development of antibodies against GlialCAM, resulting in a more severe form of experimental autoimmune encephalomyelitis (EAE), an animal model of MS.

Dr. Robinson's research has also demonstrated a coordinated T cell response against both EBNA-1 and GlialCAM, suggesting that EBV-induced B cells may activate T cells that contribute to the autoimmune response in MS. This study emphasized a specific region within the EBNA-1 protein where molecular mimicry with human myelin proteins occurs, potentially explaining the association between EBV infection and the development of MS and other autoimmune diseases.

The research concludes that EBV could play a critical role in autoimmune disease development through mechanisms such as molecular mimicry, B cell transformation, and possibly lytic reactivation of the virus. However, uncertainty persists regarding whether EBV directly triggers autoimmunity or whether specific viral strains are more likely to promote autoimmune responses. Further studies are needed to clarify the exact relationship between EBV and the onset of autoimmune diseases such as MS.

Several important questions remain regarding the role of EBV in autoimmune diseases such as MS, SLE, and RA. First, the high heterogeneity of these diseases, both within individual conditions and across different conditions, complicates the understanding of how a single virus such as EBV might be involved in the development of such diverse and distinct diseases.

Second, despite EBV infecting approximately 95% of the global population, MS shows a highly localized geographic distribution, with higher prevalence in specific regions. This discrepancy raises the question of why MS is not uniformly distributed if EBV is a primary cause. Furthermore, EBV appears to influence MS development even in individuals without classic autoimmune susceptibility genes, such as specific

major histocompatibility complex (MHC) alleles, suggesting that EBV may play a more significant role in predisposing individuals to autoimmunity than previously recognized genetic factors.

Another key question concerns the molecular mimics identified in MS, such as GlialCAM, CRYAB, and Anoctamin-2. These mimics are present in only certain subsets of MS patients, and clarity is lacking on whether these subsets overlap or encompass all cases of the disease. The widespread nature of EBV and the selective development of autoimmune diseases in some individuals but not others suggest that specific EBV strains or additional mechanisms may predispose certain individuals to autoimmunity.

Finally, the concept of a "second hit" is crucial for understanding autoimmunity. Because many individuals are infected with EBV long before autoimmune diseases develop, additional triggers—such as environmental factors, further infections, or other immune system stressors—are likely necessary for the clinical manifestation of the disease in predisposed individuals. Identifying and understanding these additional factors and their interactions with EBV in the development of autoimmune diseases underscores the need for further research.

Exploring Viral Triggers of Type 1 Diabetes and Celiac Disease
Marian Rewers, M.D., Ph.D., Professor of Pediatrics and Medicine, Executive Director of Barbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus

Several studies, including the Environmental Determinants of Diabetes in the Young (TEDDY) study, have investigated the potential connections between viral infections and the development of type 1 diabetes (T1D) and celiac disease. The increasing global incidence of T1D has driven research into various environmental factors, such as viral infections such as rubella, enteroviruses, and more recently, SARS-CoV-2. Although the potential link between viral infections and T1D was first suggested decades ago following local outbreaks of aseptic meningitis, the exact role of viruses remains an active area of research.

Enteroviruses, particularly coxsackievirus, have been closely associated with the progression of T1D. These viruses can infect pancreatic beta cells, essential for insulin production, because of the presence of the coxsackievirus and adenovirus receptor (CAR) on these cells' surface. In individuals with a genetic predisposition, persistent enteroviral infections can stimulate immune responses that may lead to T1D.

The TEDDY study, a major multi-center initiative focused on identifying environmental triggers for T1D, has found a link between prolonged infections with enterovirus B and the development of islet autoimmunity. This finding supports the hypothesis that chronic viral infections could play a significant role in the onset of T1D, particularly in individuals with a genetic predisposition.

Autoimmunity in T1D can manifest through various autoantibodies. In young children, particularly those with the human leukocyte antigen (HLA)-DR4 genotype, insulin autoantibodies (IAA) are often the first to appear. This phenotype is strongly associated with persistent enterovirus B detected in stool samples. In contrast, individuals who develop antibodies against glutamic acid decarboxylase (GADA) often have a history of gastroenteritis and the presence of Norwalk virus in their stool.

The TEDDY study's extensive analysis of DNA and RNA viruses in children's stool samples found that prolonged fecal shedding of enterovirus B is linked with both types of autoimmunity observed in T1D. Specifically, IAA-first autoimmunity is characterized by the presence of IAAs as the initial marker, while

GADA-first autoimmunity is distinguished by the early appearance of GADAs. Additionally, infections with mastadenovirus C might offer protection against developing autoimmunity. Research has also highlighted the role of gene–environment interactions involving the coxsackievirus and adenovirus receptor (CAR) in influencing autoimmune risk.

T1D is a heterogeneous disease with diverse phenotypes and endotypes. Generally, IAA-first disease manifests earlier in life, while GADA-first disease appears later. Recent transcriptomics data from the TEDDY study reveal that both autoimmunity phenotypes are linked to deficient antiviral immune responses. Children with GADA-first autoimmunity often exhibit high eosinophil levels, whereas IAA-first autoimmunity is typically characterized by a predominance of monocytes. Further research is needed to fully understand these immune cell profiles and their implications.

The COVID-19 pandemic has led to speculation about a potential increase in T1D cases. However, current data suggest that any observed increase is more likely attributed to changes in clinical care and earlier diagnosis rather than a direct impact of SARS-CoV-2 on autoimmunity. A large study involving more than 50,000 children found no significant association between SARS-CoV-2 infection and the development of islet autoimmunity, aligning with findings from TEDDY.

In terms of prevention, developing an enteroviral vaccine for high-risk individuals remains a promising research area. Although an inactivated vaccine tested in adults has shown safety and immune response, the vaccine remains in the early stages and is not yet available for broader use.

Among environmental factors linked to T1D, enteroviruses consistently show strong evidence. Other viruses, such as rotaviruses and SARS-CoV-2, demonstrate less consistent associations with T1D. Notably, recurrent rotavirus infections have been linked to the development of celiac autoantibodies in children at high risk for celiac disease, especially those on a high-gluten diet. The TEDDY study continues to explore the role of viruses in both T1D and celiac disease using advanced methodologies, such as Phage ImmunoPrecipitation Sequencing (PhIP-Seq) and multiplex virus antibody detection systems, to enhance understanding of these associations.

Panel Question and Answer

Moderators:
Beena Akolkar, Ph.D., Senior Advisor, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive Kidney Diseases
Mireia Guerau, Ph.D., Program Officer, Autoimmunity and Mucosal Immunology Branch, Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases

Question 1: What factors contribute to viral reactivation?
Dr. James emphasized the complex role of co-infections in EBV reactivation. Some co-infections may actively drive viral reactivation, while others may merely exist within the broader pathological environment, such as latent viruses. Oxidative stress and inflammation, commonly observed in autoimmune diseases, are also significant contributors. Identifying direct causes of reactivation remains challenging, and developing a humanized mouse model with productive EBV infection could aid in studying these co-factors. Additionally, more research is needed to establish criteria for safely discontinuing immunosuppressive medications, utilizing biomarkers to identify patients at high risk of reactivation, and enabling safer treatment breaks.

Dr. Robinson noted that certain immune activation events, including B cell activation and specific drugs, are known to induce EBV reactivation. Immunosuppression and inadequate T cell responses against EBV also constitute strong risk factors. Additionally, the relationship between lytic reactivation and autoimmune flare-ups is unclear—whether lytic reactivation drives autoimmune flares or whether B cell activation during a flare triggers reactivation. Because B cell activation induces transcription factors that promote EBV reactivation, lytic reactivation may potentially occur as a secondary effect of autoimmune flare-ups.

Dr. Rewers discussed a Norwegian study aimed at treating T1D by targeting a presumed persistent enteroviral infection at clinical diagnosis. Researchers used pleconaril, a drug originally designed to prevent viral invasion in nasal cells, although not specifically intended for viral eradication. The study showed a modest effect in preserving C-peptide, a marker of insulin secretion, and some improvement in immune biomarkers, although the impact was limited. Once autoimmunity progresses and multiple autoreactive cells are activated, reversing the condition becomes challenging. This challenge has led to the belief that future efforts should focus on vaccination studies to prevent T1D by building early immunity. Although EBV is widespread and may have evolutionary significance, targeting enteroviruses—offering no known benefits—appears to be a safer approach. This strategy parallels efforts against rotavirus and rubella, the latter of which has been linked to a diabetes-like condition in adults with congenital rubella syndrome, potentially providing a model for preventing certain forms of T1D.

Question 2: What are the current research strategies and technological advancements needed to improve our understanding of viral triggers of autoimmune diseases?

Dr. James noted that advancing research on EBV and its role in autoimmune diseases and malignancies requires a multifaceted approach. Recent progress in RNA-based vaccines holds promise, with an EBV vaccine potentially benefiting both cancer prevention and autoimmune disease management. However, more precise viral serology testing is crucial to better understand active EBV infections and their effects on the immune system. Integrating this approach with genetic and therapeutic data could provide deeper insights into disease mechanisms. Additionally, natural history studies, which follow diseases over time, and the incorporation of epigenetic data will be essential for unraveling the complex interplay between genetics, viral infections, and immune responses.

Dr. Robinson added that advancing EBV research will necessitate a combination of longitudinal cohort studies, cutting-edge single-cell technologies, and the development of reliable animal models for EBV infection. Although significant progress has been made, these areas require further development to fully understand the virus and its broader implications for human health.

Dr. Rewers highlighted the substantial technological advances over the past decade in detecting viruses across various tissues. The TEDDY study, for instance, is now focused on tracking the development of viral antibodies throughout the human lifespan, particularly examining maternal antibody protection in infants. Generally, maternal antibodies are assumed to last for 6 to 9 months; however, this duration can vary based on environmental exposures. This variability raises the possibility that vaccinating mothers might be more effective than vaccinating infants.

Dr. Rewers also emphasized strategies that enhance overall population immunity, rather than focusing solely on the most vulnerable, such as infants. Changes in hygiene practices have reduced infection rates for viruses such as enteroviruses and EBV, which mirrors the historical shift in polio infections from infancy to older ages. However, the rise in certain diseases may be attributed to altered herd immunity,

particularly because women of reproductive age may lack immunity to viruses that pose significant risks during pregnancy, potentially endangering their offspring.

Question 3: Considering the widespread nature of viral exposures and the known genetic predisposition to autoimmune diseases, what insights can we gain from individuals who encounter these viruses without developing autoimmunity?
Dr. James discussed the significance of studying first-degree relatives who, despite sharing genetic predispositions, may develop autoantibodies without showing disease symptoms. These studies can reveal potential protective factors. Additionally, discordant monozygotic twins, who share identical genetics but exhibit different health outcomes, provide valuable insights into the role of genetic and environmental interactions. Advances in omics technologies and computational methods are being developed to integrate multi-omic data with environmental exposure information. These tools could significantly enhance our understanding of how genetic and environmental factors interact to influence autoimmunity and help identify mechanisms that protect certain individuals from autoimmune diseases.

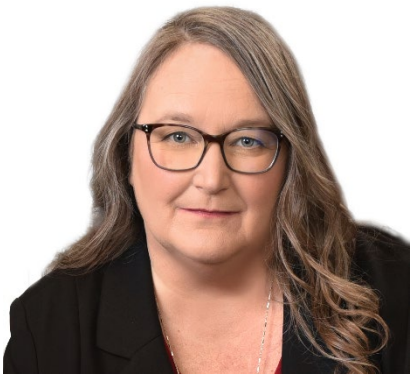
Dr. Rewers emphasized the crucial role of genetics in understanding autoimmunity. Family members often have varying genetic variants, which are further influenced by epigenetic modifications. Identifying genetic variants associated with protection or risk can inform the development of new prevention strategies. Rather than relying solely on current immunomodulation approaches, future strategies might focus on early interventions, such as blocking viral entry in at-risk individuals. The complex relationship between genetic factors and protection against infections underscores the need for continued research in this area.

Closing Remarks

Dr. Shanmugam thanked the speakers and moderators for their insightful presentations and valuable time. She also encouraged audience members to stay engaged with OADR-ORWH via email subscription.

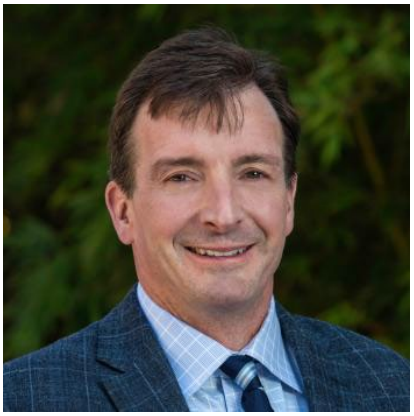
Speaker Biographies

Judith A. James, M.D., Ph.D.



Dr. James is a fifth-generation Oklahoman who has dedicated her career to understanding autoimmune diseases and improving the health of Oklahomans. As chief medical officer, Dr. James oversees all clinical activities at the Oklahoma Medical Research Foundation (OMRF), which treats and conducts clinical research involving thousands of patients suffering from lupus, rheumatoid arthritis, multiple sclerosis, and other autoimmune diseases. A board-certified rheumatologist and internationally acclaimed researcher, she is best known for her work in the prediction and prevention of the autoimmune disease, lupus. Her research has resulted in OMRF being named a National Institutes of Health Autoimmunity Center of Excellence, one of only eight nationwide. Dr. James has published more than 330 articles and is the principal investigator for numerous National Institutes of Health–funded grants. She leads national consortia focused on finding better directed therapies for patients with autoimmune diseases.

William H. Robinson, M.D., Ph.D.



Dr. Robinson serves as chief of the Division of Immunology and Rheumatology at Stanford University. Dr. Robinson's laboratory aims to elucidate the molecular and cellular mechanisms underlying autoimmune diseases and to leverage these insights to develop next-generation diagnostics and therapeutics. One major line of research in his laboratory focuses on autoimmunity, including defining the role of the Epstein-Barr virus in the initiation and progression of multiple sclerosis and systemic lupus erythematosus, investigating the role of B cells in autoimmune disease, and defining the role of mucosal breaks of bacteria in rheumatoid arthritis and anti-neutrophil cytoplasmic autoantibody vasculitis. Another research focus area in his laboratory investigates innate immune mechanisms that mediate osteoarthritis. Dr. Robinson draws on his experiences as a researcher, clinician, and entrepreneur to lead researchers and clinicians to decipher the mechanisms underlying pathogenic and protective immune responses and to turn scientific discoveries into tomorrow's transformative solutions.

Marian Rewers, M.D., Ph.D.

Dr. Rewers joined the faculty of the Barbara Davis Center for Diabetes in 2000 as clinical director and has served as executive director of the Center since 2012. His primary research is in the etiology/epidemiology of type 1 diabetes (T1D), as well as in insulin resistance and cardiovascular complications of both type 1 and 2 diabetes. Dr. Rewers has been the principal investigator of several large National Institutes of Health–funded projects: The Environmental Determinants of Diabetes in the Young (TEDDY), the Diabetes Autoimmunity Study in the Young (DAISY), and the Celiac Disease Autoimmunity Research (CEDAR). These prospective cohort studies expanded knowledge of the causes and risks of autoimmunity. To translate these results to public health and prevention, Dr. Rewers initiated Autoimmunity Screening for Kids (ASK), which is supported by the Breakthrough T1D and Helmsley Charitable Trust. ASK screens general population children aged 1–17 for presymptomatic T1D and celiac disease, provides education to prevent delayed diagnosis and complications, and facilitates access to prevention trials. Dr. Rewers has also studied the development of cardiovascular disease in T1D in a large longitudinal study, the Coronary Artery Calcification in Type 1 (CACTI). This study had basic research omics components that evaluated the underlying pathophysiology of T1D and its complications as well as clinical translational and epidemiology components that provided opportunities for investigation across the spectrum of T1D research.