Closer Look

Rachmiel Levine-Arthur Riggs Diabetes Research Symposium 2025

November 14-17, 2025; Pasadena, California; Day #1 Highlights – Draft

Executive Highlights

- **City of Hope's 2025 Rachmiel Levine-Riggs Diabetes Research Symposium began strong in Pasadena, California.** This annual meeting is named after the late Drs. Rachmiel Levine (1910-1998) and Arthur Riggs (1939-2022). Day #1 featured engaging presentations about basic science and clinical pearls in T1D care, including islet transplantations and immunosuppressive therapies. Check out our coverage from 2024, 2022, 2019, 2018, 2017, 2016, 2015, 2014, 2013, and 2012.
- **Dr. Piotr Witkowski (The University of Chicago) delivered an opening address highlighting the evolution of islet transplantation therapies.** He began by underscoring how the toxicity of standard immunosuppression regimens has limited who can benefit from islet allogenic transplantation. The treatment is largely reserved for people with T1D who: (i) have already had a solid organ transplant and are currently on immunosuppressive therapies; (ii) will undergo a solid organ transplant and can simultaneously undergo an islet allogenic transplant; or (iii) have severe hypoglycemia unawareness. While developing therapies not requiring immunosuppression is the goal, he said that incremental steps and alternative immunosuppressive agents still have value.
- **Dr. Witkowski highlighted the promising efficacy and safety profile of tegoprubart,** an anti-CDL40L monoclonal antibody. Tegoprubart aims to suppress immune response without systemic immunosuppression while eliminating the interactions responsible for increased thromboembolic risk. Clinical studies have shown promising results. In the phase 2b kidney transplant data (n=127), a tegoprubart-based regimen provided comparable islet graft function to tacrolimus while reducing rates of tremor, hypertension and hypertensive crisis, heart failure, delayed graft function, and sepsis. In Dr. Witkowski's single-center pilot (n=6), all participants with longstanding T1D achieved insulin independence after one or two islet transplants with tegoprubart. There were no reports of unexpected adverse events, severe hypoglycemic episodes, or evidence of nephrotoxicity or neurotoxicity.
- **On stem cell-based therapy, Prof. Shusen Wang (Nankai University, China) discussed the first international case** of transplanting CiPSC-derived insulin-producing islet cells into a person with T1D, achieving insulin independence, and what Prof. Wang termed as a "functional cure." CiPSC-derived islets aim to solve the "donor problem" that limits standard islet transplantation. Prof. Wang's group uses a patient's own somatic cells – typically adipose tissues – and applies a chemical reprogramming protocol to generate CiPSCs. Those CiPSCs are then differentiated into islets for autologous transplantation. Moreover, rather than infusing cells into the hepatic portal vein, researchers implanted CiPSC-derived islets beneath the anterior rectus sheath on the abdominal muscles, which offer substantial advantages for monitoring, biopsy, and further mechanistic research. The first patient achieved insulin independence, Time in Range (TIR) >98%, and an A1c ~5.0% after one year, with no transplant-related abnormalities observed.
- **Rounding out the night, Dr. Carmella Evans-Molina offered his "Christmas Wish List" for the future of T1D research during the evening dinner reception.** Given recent breakthroughs in the field – most notably with Sanofi's Tzield (teplizumab), which was accepted for expedited review in the US for stage 3 T1D through the new Commissioner's National Priority Voucher (CNPV) pilot program last month – Dr. Evans-Molina highlighted the need for: (i) running faster, smarter clinical trials, (ii) embracing heterogeneity in T1D, and (iii) building systems for better long-term follow-up.

See the conference website, register here, and read through the full agenda here. As well, check out our preview to see what sessions we look forward to in the coming days!

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1. Dr. Witkowski delivers an opening address highlighting the evolution of islet transplantation treatments

In the opening address, Dr. Piotr Witkowski (The University of Chicago). Dr. Witkowski kicked off the gathering by dubbing it "the best diabetes meeting in the world" and reminded the audience how far the field has come since its first islet allogenic transplant in 1974 and the first insulin-independent islet recipient in 1989.

- **Toxicity of standard immunosuppression regimens has limited the use of islet allotransplantation.** Dr. Witkowski underscored that current immunosuppressive regimens limit who can benefit from islet allogenic transplantation. Today, the treatment is largely reserved for people with T1D who: (i) have already had a solid organ transplant and are currently on immunosuppressive therapies; (ii) will undergo a solid organ transplant and can simultaneously undergo an islet allogenic transplant; or (iii) have severe hypoglycemia unawareness. For most others, current standard of care confers an unacceptable risk-benefit ratio of lifelong immunosuppression.
- **Avoiding immunosuppression is the ultimate goal, but incremental steps and alternative immunosuppressive agents are needed in the meantime.** Dr. Witkowski mentioned active work on immune-protective environments or devices, genetic modification of islet cells, and other tolerance-inducing strategies that might one day overcome the need for systemic immunosuppression. Yet, until such advancements gain regulatory approval in humans, using less toxic immunosuppressive, including tegoprubart (anti-CDL40L monoclonal antibody), in place of calcineurin inhibitors (e.g. tacrolimus) offers a potential path forward for islet transplantations which require immunosuppression.

2. Tegoprubart as a less toxic alternative for immunosuppression in islet allogenic transplantation

Dr. Witkowski highlighted the promising efficacy and safety profile of tegoprubart, an anti-CDL40L monoclonal antibody. Tegoprubart aims to suppress immune response without systemic immunosuppression. Dr. Witkowski noted that earlier anti-CD40L antibody therapies conferred significant thromboembolic event risk. Over two decades later, however, scientists have developed tegoprubart, eliminating the interactions responsible for increased thromboembolic risk and allowing targeted immunosuppressive approach for transplant protection.

- **In the phase 2b kidney transplant data (n=127),** a tegoprubart-based regimen provided comparable islet graft function to tacrolimus while reducing rates of tremor, hypertension and hypertensive crisis, heart failure, delayed graft function, and sepsis. There was a modest numerical increase in mostly mild, treatable rejection episodes, which was likely related to conservative dose-lowering in the setting of viral infections. Importantly, there was no signal for excess thromboembolic events.
- **In Dr. Witkowski's single-center pilot (n=6), every adult with longstanding T1D achieved insulin independence after one or two islet transplants.** Results were supported by robust stimulated C-peptide and stable graft function. Across the cohort, there have been no unexpected adverse events, severe hypoglycemic episodes, or evidence of nephrotoxicity or neurotoxicity, which Dr. Witkowski noted to be in contrast to historic tacrolimus-based controls. Such preliminary data suggests that tegoprubart may offer a more tolerable immunosuppressive platform for islet allogenic transplantation in T1D. Attesting to the strength of these findings, Breakthrough T1D has already funded an additional six participants, expanding the study to 12 patients and paving the way for larger trials of tegoprubart-based regimens in islet transplantation.

3. Chemically induced pluripotent stem cell-derived islet transplantation as the future of T1D cures

In a fascinating talk, Prof. Shusen Wang (Nankai University, China) discussed the clinical progress of chemically induced pluripotent stem cell (CiPSC) derived islet transplantation, and its potential to overcome the donor problem in islet transplant therapy. As background, alongside Prof. Zhognyang Shen (Nankai University, China) and collaborators, Prof. Wang published the first international case of transplanting CiPSC-derived insulin-producing islet cells into a person with T1D, achieving insulin independence, and what Prof. Wang termed as a "functional cure." See our coverage on this publication, as well as KOL commentary back then from Drs. Mark Atkinson and Holger Russ (University of Florida)!

- **CiPSC-derived islets aim to solve the "donor problem" that limits standard islet transplantation.** Prof. Wang opened by saying that there are not enough high-quality organ donors to make conventional islet transplantation a scalable cure for T1D. While donor islets or xenotransplantation are often used today, immune rejection remains difficult to control. To address both problems, his group uses a patient's own somatic cells – typically adipose tissues – and applies a chemical reprogramming protocol to generate CiPSCs. Those CiPSCs are then differentiated into islets for autologous transplantation.
- **A novel implant site under the anterior rectus abdominal sheath was essential to the first-in-human CiPSC-derived islet success.** Rather than infusing cells into the hepatic portal vein, researchers implanted CiPSC-derived islets beneath the anterior rectus sheath on the abdominal muscles in their first patient, who had lived with T1D for 11 years, exhibited complete islet failure, had received two liver transplants, one pancreas transplant, and an allograft pancreatectomy. After transplantation, Prof. Wang noted that the graft required several weeks to mature, with early C-peptide levels being low. Around Day 56, however, post-meal C-peptide levels rose, and by Day 75, the patient achieved complete insulin independence. Over two years later, that same patient remains insulin independent, with no evidence of tumor formation.
- **The rectus sheath implantation site offers substantial advantages for monitoring, biopsy, and further mechanistic research.** Using MRI scans, researchers continue to noninvasively confirm graft location, structure, and stability over time. Because the site is superficial and accessible, Prof. Wang described ultrasound-guided biopsy as straightforward. Such access allows for serial sampling for histology, proteomics, and protein transcriptomics to track cell fate, proportions of different cell types, spatial architecture, inflammation, and immunologic changes. This visibility into the graft's biology, he added, is a major advantage for the rectus sheath site over intraportal islet delivery.
- **Three patients have undergone the procedure to date, all on immunosuppression.** On immunosuppression, Prof. Wang acknowledged that many people prefer to live with T1D rather than accept chronic immunosuppression: "I prefer the devil I know over the devil I don't know," he said. Such a reality underscores the need to reduce or ultimately eliminate immune rejection responses. Given this challenge, he suggested gene-edited hypoimmune cells as the next logical step for CiPSC-derived islet therapy.
- **Cell therapy for T1D is coming, Prof. Wang concluded.** Current CiPSC-derived islet approaches are "first-generation" systems with relatively mature differentiation protocols. "Second-generation" advances include genetic editing or incorporating biomaterials into prior advancements. In the meantime, Prof. Wang said that clinical trials are underway across multiple centers, and China's Human Islet Resource Center has already supported more than 30 clinical islet cases. Looking ahead, Prof. Wang envisioned CiPSC-derived islets to be a simple, one-dose therapy that might offer a functional cure that scales to meet the international needs of the T1D population.

4. Dr. Michael Rickels on stem cell-derived islets and Vertex's VX-880 (zimisclecel)

In an engaging Friday morning address, Dr. Michael Rickels (University of Pennsylvania) discussed the current state of islet cell transplantation, highlighting Vertex's FORWARD-101 trial, which is the first registration trial for stem cell-derived islets in the US.

- **As highlighted throughout the day, while deceased-donor islet transplantation remains an effective therapy, limited donor availability and the need for immunosuppression limit its risk-benefit**

ratio. Access to deceased-donor islets access is currently hindered by a need for regional cGMP isolation facilities, and only one is currently available in the US. Further, immunosuppression, which typically involves a toxic panel of low-dose tacrolimus/sirolimus, T-cell depletion, and etanercept, is necessary for engraftment success according to clinical islet transplantation (CIT) protocols. Despite its risks, islet transplantation has been shown to provide durable metabolic benefits and improve clinical outcomes. CIT phase 3 trials have shown a sustained ~1.5 percentage point reduction in A1c over five years post islet transplantation. Similar results, notably, have been observed in islet transplantation after a prior kidney transplant.

- **Dr. Rickels noted stem cell-derived islets as a next step in T1D cures that builds on established delivery and immunosuppression frameworks.** Specifically, he tabbed Vertex's VX-880 (zimislecel) as an example of a fully differentiated, stem cell-derived islet transplant that is infused into the liver using the same immunosuppressive regimen for CIT phase 3 trials. Phase 1 and phase 2 results from FORWARD-101 (n=14), which investigated VX-880 in people with T1D and recurrent severe hypoglycemia, showed clinically meaningful endogenous insulin production, improved glucose tolerance by day 90, and successful engraftment in all participants. Further, in the 12-participant NEJM cohort, all maintained insulin secretion that was responsive to glucose through Day 365, achieved an A1c of less than 7% (all had A1c's greater than 7% at baseline), and experienced no severe hypoglycemic events after Day 90. All 12 patients also reduced exogenous insulin use. On safety, results remained consistent with expectations for immunosuppressive therapies and intraportal infusions.
    - **On CGM outcomes,** all patients showed a dramatic improvement in TIR and hypoglycemic event incidence. Before treatment, Dr. Rickels shared that participants struggled to achieve even 50% TIR. At Day 180, participants were nearing a 90% average TIR.

5. Dr. Carmella Evans-Molina's "Christmas Wish List" for the future of T1D research

On the first night of the Rachmiel Levine Diabetes Research Symposium, Dr. Carmella Evans-Molina (University of Indiana) shared her "Christmas Wish List" for the future of T1D research. In a packed dinner hall, she identified what the disease-modifying field urgently needs in order to build upon recent breakthroughs – most notably with Sanofi's Tzield (teplizumab), which was accepted for expedited review in the US for stage 3 T1D through the new Commissioner's National Priority Voucher (CNPV) pilot program last month.

Her three wishes were:

1. **Running faster, smarter clinical trials.** Now that an approved therapy exists for stage 2 T1D, enrolling participants in placebo-controlled studies is becoming increasingly difficult. Recent analyses have shown that historical datasets, alternative endpoints, and redesigned platform trials could shorten timelines and reduce reliance on placebo arms.
2. **Embracing heterogeneity in T1D.** Children and adults progress through T1D stages and respond to disease-modifying therapy differently. Age-related differences in pancreatic tissues, including gene expression and pathway regulation, may require tailoring disease-modifying approaches when developing therapies.
3. **Building systems for better long-term follow-up.** Linking early treatment effects, such as preserved C-peptide, to real-world outcomes, like glycemic stability and hypoglycemia risk, will be critical.

-- Elizabeth Rose, Elaine Young, Kat Moon, and Kelly Close