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ThymUS approaching maturity

The thymus produces T cells, and an improved understanding of thymus biology is likely to have therapeutic potential. Here we summarize the 2025 ThymUS conference, focusing on fundamental insights and translational potential.

Fig. 1 | Keynote speakers at ThymUS 2025. The 2025 ThymUS conference in Kauai, Hawaii, featured three Keynote speakers: Hergen Spits, Alfred Singer and Ellen V. Rothenberg (shown from left to right). These scientists have discovered many of the concepts that anchor fundamental and translational work in the thymus field.

The thymus is essential for normal T cell development. Within the thymus, precursor T cells termed thymocytes undertake a stepwise developmental process linked to their migration between two major anatomical compartments, the cortex and medulla. These compartments are largely composed of thymic epithelial cells (TECs), together with other cell types including fibroblasts and endothelial cells. In the cortex, T cell precursors experience Notch signaling to commit to the T cell lineage, concomitantly rearranging and expressing their T cell receptor genes. Thymocytes in the major αβ T cell lineage then undergo positive selection on major histocompatibility complex (MHC)–peptide complexes expressed on cortical TECs (cTECs). Subsequently, these thymocytes commit to the CD4 or CD8 lineage, overlapping with their migration to the medulla, where negative selection and the generation of regulatory T cells together ensure a self-tolerant T cell repertoire. Medullary TECs (mTECs) control key aspects of T cell repertoire selection in collaboration with medullary dendritic cells and B cells. In addition to the abundant αβ T cell lineage, the thymus produces several innate-like and adaptive T cell types, which together constitute the T cell arm of the immune system.

Because of the importance of T cells for immune protection, autoimmunity and immunotherapy, the thymus has been intensely researched for many years. The 2025 ThymUS conference, part of the Global Thymus Network, was held in Lihue in Kauai, Hawaii, from 27 April to 1 May 2025, and was organized by Jarrod A. Dudakov, Nancy Manley, David L. Wiest, Marcel van den Brink and Juan Carlos Zúñiga-Pflücker. Apart from three Keynote lectures presented by leaders in the field, all talks were selected from submitted abstracts. Along with fundamental insights, there was a noticeable surge in patient-centric research applications, signifying that our knowledge of thymus biology is maturing.

T lineage commitment: nature versus nurture

ThymUS 2025 was kicked off by Ellen V. Rothenberg's Keynote plenary session (Fig. 1). Her research over many years has imposed structure on the plethora of transcriptional controllers that act in early T cell development, with a focus on the shifting gene regulatory landscape that underlies commitment to the T cell lineage. By tracking early development in an in vitro culture system in combination with gene perturbations, Rothenberg's laboratory had previously come to the realization that no single transcription factor can explain T cell development. They have been dissecting a 'tug-of-war' between transcription factors expressed before thymic entry, versus those whose expression is upregulated by the thymic environment. A new research question is whether developmental alterations in the kinetics between fetal and postnatal thymocytes are cell intrinsic. Indeed, direct comparison revealed markedly accelerated differentiation of fetal precursors. Rothenberg's group is currently investigating epigenetic differences that might underly these differences in developmental kinetics.

Continuing the theme of cell-intrinsic differences in fetal progenitors, Isabel Forlastro showed that the development of an early wave of fetal-derived innate CD8 T cells uses the RNA-binding protein Lin28b to upregulate EOMES and promote effector differentiation. Adult thymocytes that overexpress Lin28b were capable of forming innate CD8 T cells in adult thymi, similar to fetal progenitors, highlighting the influence of cell-intrinsic factors. A tour-de-force was presented by H. Leighton (Lee) Grimes, whose team molecularly and functionally characterized bone marrow progenitors including precursors of T cells. The work used CITE-seq and massively parallel profiling (InfinityFlow) together with measures of chromatin accessibility to provide high-resolution maps of developmental intermediates together with proposed gene regulatory networks that operate at successive stages of hematopoietic precursor differentiation. Yuichi Kama dissected RUNX1 protein–protein interactions by combining in vitro differentiation assays with gene perturbations and proteomics. The data showed that the primary interacting partner of RUNX1 switched from CTCF before Notch signaling to Notch-IC (intracellular) after Notch signaling. Hai-Hui (Howard) Xue used single-cell RNA sequencing (scRNA-seq) and single-cell

assay for transposase-accessible chromatin sequencing (scATAC-seq) to demonstrate that perturbation of transcription factors TCF-1 and LEF-1 impaired the formation of early thymic progenitors and T lineage commitment.

Thus, progress has been made in assembling the detailed molecular networks that underlie hematopoiesis and early T cell development.

TCR-dependent selection and CD4/CD8 fate

After T lineage commitment, αβ-lineage thymocytes undergo TCRβ-selection and positive selection in the cortex. Ève Mallet Gauthier studied the effect of MHC expression on TCRβ selection, which assesses the success of the initial step of TCRβ rearrangement. She found that absence of MHC class I (MHC-I) or MHC-II significantly inhibited developmental progression and altered the T cell receptor (TCR) repertoire, which indicates that the pre-TCR containing TCRβ but not TCRα may interact productively with MHC molecules. Arpita Prusty presented work describing a system that enables in vivo monitoring of Id3 transcriptional bursting in immature thymocytes. She observed that differing TCR signal intensity produced distinct Id3 bursting codes in αβ versus γδ T cell progenitors.

Successful αβ TCR rearrangements are followed by positive selection, in which some $CD4^+CD8^+$ (double-positive) thymocytes successfully interact with cTECs via TCR–peptide–MHC interactions. Continuing previous discoveries on MHC-II-mediated selection of CD4 T cells, Nuno Alves used tissue-specific LAMP2-knockout mice and LC3-dual mice co-expressing red fluorescent protein (RFP), enhanced green fluorescent protein (eGFP) and autophagy protein LC3 in a single protein, which reports pH-dependent loss of eGFP when LC3 is incorporated into different lytic vacuoles[1]. This enabled the tracking of autophagosome maturation in TECs in context of positive selection. In LAMP2-knockout cTECs, autophagic flux was impaired and positive selection was altered, reducing CD4 TCR diversity. Yousuke Takahama presented work on CCL25, a CCR9 ligand implicated in trafficking to the thymus but whose subsequent functions within the thymus have been unclear. He established a role for CCL25 in positive selection, in which CCL25-conditional knockout (cKO) mice had reduced $CD69^+$ double-positive thymocytes that had been positively selected. Mami Lennikov from the same group reported on experiments using isolated cTECs from mice that lack or express the thymus-specific β5t proteasomal subunit. Remarkably, they identified β5t-proteasome dependent and independent peptides presented on MHC-I using mass spectrometry. The identification of cTEC-restricted peptides provides clear evidence for the long-standing idea that such peptides exist, and can support positive selection of developing CD8 T cells while allowing them to avoid subsequent negative selection in the thymic medulla[2].

Over the years, the Alfred Singer lab has established our current understanding of CD4 helper and CD8 cytotoxic αβ T cell lineage bifurcation, encapsulated in the kinetic signaling model[3]. In brief, TCR signaling results in attenuation of CD8, but not CD4, transcription, leading to two signaling outcomes: persistent signaling resulting in CD4-lineage commitment, and interrupted signaling resulting in CD8-lineage commitment. This model explains how TCR specificity for MHC-II or MHC-I is matched to lineage choice and appropriate coreceptor expression. More recently, the Singer lab established the concept of clonal eviction in which immature CD8 lineage thymocytes leave the thymus before medullary residence, to be tolerized in the periphery[4]. During his Keynote lecture, Singer extended this concept to γδ T cells (Fig. 1). He presented data indicating that strong γδ TCR signaling resulted in clonal eviction, meaning that immature γδ T cells could be detected in the periphery. Miho Shinzawa presented results from CD8Dual mice, in which CD8 is expressed from both the CD8 and CD4 loci, resulting in production of both helper and cytotoxic lineage T cells restricted by MHC-I. In collaboration with the Takahama lab, they showed that β5t-independent peptides select helper lineage cells, whereas β5t-dependent peptides (only present in the cortex) select cytotoxic lineage cells. Thus, in addition to downregulation of the CD8 coreceptor, the distribution of anatomically restricted peptides within the thymus likely also attenuates TCR signaling in MHC-I restricted T cell precursors, resulting in CD8 lineage commitment.

The field thus provided insights into TCRβ selection and αβ T cell lineage choice during intrathymic T cell differentiation.

Negative selection

After positive selection, thymocytes migrate to the medulla for negative selection, in which self-reactive clones are either deleted by apoptosis or differentiated into regulatory T (T_{reg}) cells[5]. Xuguang Tai assessed T_{reg} cell generation after agonist signaling by preventing clonal deletion of high-affinity TCR-bearing thymocytes using BCL2 overexpression. These rescued cells can develop into T effector cells or T_{reg} cells depending on the duration of TCR signaling, which is regulated by TGFβ. Isabel Baldwin used TCR-transgenic mouse models with ex vivo thymic slices and antigen-loaded dendritic cells (DCs) to study the development of thymic T_{reg} cells. She found that thymocytes experiencing either weak positive selection signals in the cortex or weak agonist signals in the medulla favor the alternative pathway ($CD25^-FOXP3^+$) of T_{reg} cell generation. Hailyn Nielsen found that NR4A1 and NR4A3 are essential mediators of late thymic clonal deletion by transcriptional induction of BCL2L11 (also known as BIM). Thymocytes that lack both NR4A1 and NR4A3 escape deletion (and T_{reg} cell diversion) and instead adopt an anergy-like transcriptional program. Ichiro Taniuchi studied CD4 and CD8 fate by characterizing the intracellular protein interactome using proximity-dependent labelling. His laboratory established interactions between RUNX1, LCK and ZAP70 and RUNX1 phosphorylation in MHC-I-signaled thymocytes. Ilinca Patrascan discussed the temporal dynamics of CD4 versus CD8 lineage choice. Her approach combines single-molecule RNA fluorescence in situ hybridization (smRNA-FISH) and imaging flow cytometry and is based on differences in the turnover rates of primary transcripts, mature mRNA and proteins. A role for the transcription factor ETS1 in linking clonal deletion and development of innate-like $CD8\alpha\alpha^+$ lymphocytes was discovered by Mary Attaway, as thymocytes in ETS1-deficient mice had reduced clonal deletion with decreased BCL2L11 induction and a dramatic increase in thymic $CD8\alpha\alpha^+$ intraepithelial lymphocyte precursors.

Negative selection is mediated by a variety of cells including mTECs, B cells and DCs. $AIRE^+$ mTEC express tissue-restricted antigens, and have a central role in negative selection; however, a recently discovered, diverse class of mTEC called mimetic TECs can develop from AIRE-expressing TECs. Mimetics transcriptionally resemble peripheral cell types, and have been suggested to be involved in negative selection and self-tolerance[6]. Brooke Huisman performed scRNA-seq on both human and zebrafish TECs and established that mimetics, although broadly conserved in vertebrates, display species-specific subtypes and population abundances. The development of mTECs and mimetic TECs was addressed in several subsequent presentations. Joe Germino explored the role of the transcription factor FEZF2 in mTEC development using cKO mice, and observed

a reduction in AIRE-expressing mTECs and mimetics. Jun Hyung Sin used IKZF1-cKO mice to establish that transcription factor IKZF1 is important for mimetic heterogeneity and expression of tissue specific antigen (TSA), with deficient mice affected by autoimmunity. Michael Waterfield presented his lab's work on the roles of the transcription factors RUNX1 and RUNX3 in mTEC development and negative selection. Mice with RUNX1-deficient TECs were characterized by decreased AIRE$^+$ mTECs and a new mimetic population resembling AT2 alveolar cells, whereas mice with RUNX3-deficient TEC had decreased frequencies of AIRE$^+$ mTEC and tissue-specific antigen gene expression, with RUNX3-deficient mice developing autoimmunity. Gonçalo Nogueira showed that embryonic manipulations can affect the adult thymus, as injecting pregnant mice with anti-IL-7Rα led to a permanently altered thymic architecture in the progeny, and resulted in autoimmunity. Takeshi Nitta knocked out the RANKL decoy receptor OPG in TECs and observed an increase in medullary size and in negative selection, resulting in fewer auto-reactive T cells and fewer foreign antigen-reactive T cells.

Besides TECs, hematopoietic antigen-presenting cells (APCs) contribute to the establishment of central tolerance. Ryan Martinez showed that class-switched B cells colocalize with GP2-expressing mTECs and type III interferon (IFN)-producing mTECs, which suggests novel cellular interactions involved in establishing tolerance. The composition of thymic DCs was assessed in depth by Matouš Vobořil, who used scRNA-seq to describe nine populations of thymic DCs, including a population of transitional DCs that are localized close to the endothelium and can present circulating antigens. Miguel Ganuza developed a mouse model to study cell–cell interactions — that is, YinYang mice that are an in vivo, conditional, Cre-inducible, Notch receptor-based system that label interacting cells. The Ganuza lab is assessing the interactions of mature CD4$^+$ thymocytes.

Hergen Spits, a seminal member of the Thymus Global Network, delivered the Founder's Talk (Fig. 1). Early in his career, he discovered CD3-mediated redirected killing by T cells, now generalized in 'engager' bispecific antibodies. He determined mechanisms of T cell selection in human patients transplanted with allogeneic hematopoietic stem cells (HSCs), and the roles of IL-4 and IL-10 in T cells. He described transcriptional mechanisms involved in T cell, natural killer (NK) cell and DC development, and started a company that developed high-affinity antibodies to treat respiratory syncytial virus. Later, he discovered subsets of innate lymphoid cells (ILCs), and his findings have had an essential role in our current understanding of ILCs as innate counterparts of T helper cells. Spits reflected on the seminal contributions he made on ILCs, which together have established the concepts and nomenclature used in this field. Recently, his lab identified the human equivalent of extrathymic AIRE-expressing cells (eTACs), which are thought to be a subset of newly described and essential tolerogenic APCs[7–9]. These eTACs were identified in human tonsils, shared immunophenotypic characteristics with DCs, and were able to stimulate T cells. In addition, these cells expressed AIRE but did not express TSA, unlike AIRE$^+$ mTEC.

ThymUS 2025 revealed insights into TEC diversity, human counterparts of newly discovered tolerogenic APCs, and how tolerance is established — paving the way for new therapeutic approaches.

Tolerance gone wrong

Identifying the thymus-derived and peripheral sources of breakdowns in tolerance has been a central goal of research into the causes of autoimmunity. Because of the link between thymoma and autoimmunity, Nobuko Akiyama studied mTECs from individuals with thymoma and observed that they express lower levels of the transcription factor ASCL1. She also demonstrated that ASCL1 expression affects expression of TSA. Irina Proekt used AIRE-knockout mice to establish a causal role for anti-PLIN1 autoantibodies in the development of acquired generalized lipodystrophy. Adrianna M. Rivera-León reported the development of a type I IFN-neutralizing assay, which they used to detect autoantibodies against type I IFN in older AIRE-deficient mice. Motoko Kimura presented her work indicating that tumors can exploit thymus homing DCs to establish tolerance to tumor-derived antigens.

Tolerance can be broken outside of the thymus. Hisashi Arase presented evidence on how reactivation of Epstein–Barr virus (EBV) decreases expression of the MHC-II invariant chain, and enables abnormal, unfolded or misfolded self-antigens to be presented, leading to CD4 T cell activation and the breakdown of self-tolerance, resulting in lupus. Daniel Gray presented insights into intestinal T_{reg} cell subsets that are especially sensitive to necroptosis, opening avenues for new therapeutic approaches to treat gastrointestinal and metabolic diseases. Ulus Atasoy discussed the role of RNA-binding protein HuR in peripheral T_{reg} cells, showing that HuR is required for *Foxp3* mRNA expression and stability, with cKO mice displaying a scurfy-like phenotype.

The presented work provides insight into how autoimmunity develops and paves the way to new treatments to ameliorate or cure these conditions.

TEC organogenesis

T cells, and the thymus, fail to develop in the absence of functional TEC. For this reason, TEC development has been a core area of research. FOXN1 is an essential transcription factor for TEC development and function, but how FOXN1 expression is controlled is unclear. Laura Sousa crossed FOXN1-deficient mice to FOXN1 reporter mice to show that TEC can initiate *Foxn1* gene expression in the absence of functional FOXN1, but require functional FOXN1 to sustain *Foxn1* expression, as predicted by earlier work[10]. Using a new inducible lineage-tracing mouse in combination with flow cytometry, scRNA-seq, and 3D confocal microscopy, Marieke Lavaert showed that adult TEC progenitors express FOXN1 and that mTEC progenitors can give rise to both CCL21A-expressing mTECs and AIRE-expressing mTECs in vivo. Dinah Singer reported that the transcription factor BRD4 is required for the maturation of bipotent TECs to mTECs. Finally, Pedro Rodrigues characterized the developmental defect in KLF15-cKO mice that resulted in a smaller thymus and diminished mTEC cellularity, largely due to changes in the proportions of CCL21A-expressing mTECs and certain mimetic TEC subpopulations.

These talks focused on understanding the cellular and molecular mechanisms that underlie TEC development and maintenance, supporting T cell development.

The thymus in youth and old age

The thymus rapidly increases in size after birth, then shrinks during aging. By profiling transcriptional changes during the perinatal window, Lauren Ehrlich showed that APCs, TECs and stromal cells start downregulating E2F target genes and upregulating type I IFN response genes as the thymus transitions from neonatal growth to juvenile homeostasis, coinciding with higher expression of CD5 on developing thymocytes. CD5 expression increases with the strength of TCR signaling, which suggests that changes to TECs and APCs in the perinatal window could contribute to increased TCR signaling and the concomitant selection of agonist-signaled innate-like and T_{reg} cells in this developmental window. Shiyun Xiao

also noted dynamic changes in *Igf1r* expression in perinatal TECs. Using IGF1R-cKO and overexpression models, they demonstrated that IGF1R signaling is required for fetal thymic growth and has a sustained role in maintaining thymic size throughout life. The Dixit and Griffith labs highlighted the importance of FGF21 as a pro-longevity hormone that reduces fat accumulation and thymic involution in an mTOR-dependent manner. Izumi Ohigashi demonstrated that the *Calcoco1* gene restrains involution, with CALCOCO1-cKO mice displaying early onset involution. Carmela Cela disrupted Notch signaling in TECs, which resulted in a progressive decline in mTEC numbers owing to apoptosis associated with increased FAS expression and the accumulation of mitochondrial reactive oxygen species (ROS). The effects of protein misfolding in TEC during aging was examined by Emma Lederer, who observed marked changes in thymic cellularity with altered translational fidelity.

Endothelial cells, mesenchymal cells and adipocytes are also present in the thymus. Stephanie de Barros used lineage-tracing mice to study the abundances of lymphatic and blood vessel endothelial cells, observing lymphatic endothelial cells to be more abundant at birth, whereas blood vessel endothelial cells increased in abundance from the first week after birth. Anastasia Kousa profiled aging human thymi using spatial transcriptomics, enabling the assessment of all cells within the thymus. She observed a decrease in interactions between developing thymocytes and their microenvironment with age and a unique transcriptional signature in aged adipocytes. The heterogeneity of adipocytes in mice was explored using single-nucleus RNA sequencing by Dean Tantin, who identified several adipocyte subsets consisting of white fat, beige or brown fat, and a unique population characterized by open chromatin in the *Foxn1* locus, which suggests that TECs can differentiate into this population. Wanjun Chen presented work on thymic mesenchymal cells, highlighting the role of the *Mrap* gene in the differentiation of mesenchymal cells into thymic adipocytes that accumulate in the aging thymus.

Aging also affects the development and function of T cell hematopoietic progenitors. Using artificial thymic organoids, Julia Gensheimer provided insights into how aging affects lymphoid output from HSCs, describing young and old lymphoid-biased HSCs to have similar capability of generating T cells in vitro. Nicole La Gruta used scATAC-seq on young and old peripheral CD8 T cells to observe age-associated alterations in chromatin accessibility and a new CD8 T_{reg} cell population characterized by expression of CD32b. The Janko Nikolich lab tied age-associated lymph node dysfunction to metabolic dysfunction in fibroblastic reticular cells and demonstrated that antioxidant treatment rejuvenated aging lymph nodes.

These presentations provided insight into the mechanisms that contribute to thymic involution, and will facilitate therapies aimed at improving thymic function in aging.

Thymic regeneration

Another active area of investigation with clinical applications is thymus regeneration, which is a desirable therapeutic goal after HSC transplantation or chemotherapy. Jennifer Tsai presented an optimized feeder-free DLL4-Fc culturing system that generates immature thymocyte precursor cells that enhance thymic reconstitution when co-administered with allogeneic HSC transplantation, generating mature T cells and enhancing antitumor responses. Using single-cell multiomics to profile immature thymocytes at steady state and after irradiation in young and aged mice, Preet Kaur identified distinct transcriptional and epigenetic changes that potentially underlie decreased thymopoiesis and delayed recovery after thymus injury in aged individuals. Jonah Pierce demonstrated that T_{reg} cell-derived TFF1 is important for TEC homeostasis and recovery after irradiation. Dante Dennis Acenas II characterized TECs after injury by irradiation and found that mainly cTECs and CCL21A$^+$ mTEC persist after irradiation, potentially implicating them in thymic recovery. Thymic recovery was incomplete after three rounds of irradiation, suggesting that irradiation may affect TEC progenitors. Andri Lemarquis presented a role for TLR4-mediated phagocytosis of apoptotic thymocytes by thymic macrophages in controlling thymus size. Continuing previous work, Christian Burns presented his two-photon microscopy method for intravital imaging of the thymus, enabling recurrent timelapse imaging and assessment of cell motility and hemodynamics after irradiation and with age.

Understanding the molecular mechanisms that underlie thymic injury and how to improve thymic recovery was a translational focus of the meeting.

Organoid systems

Organoid systems grow organs in vitro, overcoming limits of patient derived biopsies and avoiding the use of animal models. Clevers and colleagues[11] previously established a culturing system for the long-term expansion of adult mouse TEC and the generation of functional TEC organoids. Sam Willemsen adapted this system to expand human TECs and generate human TEC organoids, overcoming limitations of patient-derived biopsies. Paola Bonfanti previously identified human multipotent epithelial stem cells (polyKRT TECs) that are clonogenic in vitro and reconstitute human thymopoiesis in athymic NSG-nude mice[12,13]. Building on this work, polyKRT TECs were used to generate, within decellularized human scaffolds, a functional microenvironment de novo, that enables TCR rearrangement and development of both CD4 and CD8 mature T cells ex vivo. Although these approaches used ex vivo isolated TEC progenitors, organoids can be derived from induced pluripotent stem cells (iPSCs). The Yoko Hamazaki lab presented an iPSC-based multilineage TEC induction system that enables in vitro human naive T cell development with diverse TCR repertoires. Meanwhile, Katja Weinacht's lab differentiated iPSCs into a TEC organoid system that gave rise to mature TECs upon implantation under the kidney capsule of humanized athymic mice. iPSC-derived TECs led to human T cell reconstruction in the athymic mice, including αβ T cells and T_{reg} cells with a diverse TCR repertoire. The novel organoid systems presented here hold both fundamental and clinical promise as these approaches mature.

Organoids are also used to produce and study T cells. Zandstra and colleagues[14] previously established a feeder-free culturing system that allows the generation of T cells from iPSCs. Now, Mona Siu used this system to dissect T lineage gene regulation using CRISPR screens, which will enable improved understanding of T cell development. Yangmin Qiu presented an improved protocol to generate immature T cell precursors (pro-T cells) from iPSCs that enabled the engraftment of these pro-T cells in mice, resulting in the development of functional T cells and establishing a potential avenue for cell therapies. Whereas most Vγ9Vδ2 T cell therapies focus on expanding these cells through their TCRs, Louis Perriman presented work on the generation of functional Vγ9Vδ2 T cells for iPSCs, which phenotypically and functionally resemble ex vivo-isolated Vγ9Vδ2 T cells for therapeutic use.

Considerable progress in the development of T cells and TECs from iPSCs was presented at this year's meeting, providing both fundamental insights and future clinical opportunities.

Understanding primary immunodeficiency

Inborn errors of the immune system result in primary immunodeficiency (PID). Identifying the mutation and which cells are directly and indirectly impacted is a key step in planning treatment. Although our understanding of mutations impacting immune cells has been developed over many years, our knowledge of mutations impacting TEC is still in its infancy. Consequently, Marita Bosticardo together with Luigi Notarangelo used an organoid system to differentiate iPSC lines from patients with PID with mutations in *HOXA3*, *FOXI3* or *TP63* into TECs and identify where development is interrupted. This work will facilitate the diagnosis of new mutations that affect TEC, and provide fundamental insights into these PID syndromes. A potential gain-of-function mutation in the human *FOXN1* gene was presented by Xian Liu. Using a mouse model containing this mutation, they demonstrated that it primarily affects cTEC differentiation and the transition to double-positive thymocytes, leading to T cell lymphopenia. Using spatial transcriptomics on thymi from individuals with 22q11.2 deletion syndrome, Viktoria Hennings described unique gene signatures that affect collagen production in these thymi, potentially contributing to their hypoplasia. Cynthia Turnbull presented a new *DECTIN-1* (also known as *CLEC7A*) variant that functions as a modifier gene in combination with CTLA-4 haploinsufficiency, exacerbating the T_{reg} cell defect caused by damaged *CTLA4* alleles. By assessing hypomorphic RAG1 mice that modeled patient mutations, Francesca Pala observed a non-cell-intrinsic reduction in mTEC compartments. Although this phenotype was reversible upon HSC transplantation, incomplete reconstitution limited recovery of the mTEC compartment, highlighting the clinical importance of adequate conditioning prior to HSC transplantation in patients with PID.

Studies on PID offered fundamental and translational insights and emphasized how alterations to TEC development and differentiation that result from gene mutations and altered thymic crosstalk can affect T cell production.

T cells in disease

Understanding T cell function in disease may enable treatments that boost their efficacy or facilitate their removal. Fotini Gounari presented a model of spontaneous T cell acute lymphoblastic leukemia (T-ALL) that recapitulates features of human disease, including *MYC* enhancer duplications and overexpression. This model is a valuable tool to study T-ALL etiology and develop therapeutic strategies. The role of Notch signaling in T cell exhaustion during chronic infection was addressed by Nathalie Labrecque, who established that a lack of Notch signaling increases CD8 exhaustion. The Nicholas Gascoigne lab presented evidence that Themis promotes PD1 phosphorylation during chronic infection, driving T cell exhaustion. B7-H3 is a candidate checkpoint inhibitor that is upregulated in many human cancers. Virginia Smith Shapiro's group showed that B7-H3 binds to the inhibitory receptor SIGLEC-9 and developed antibodies against human B7-H3 to block its interaction with SIGLEC-9 on NK cells and T cells and improve anti-tumor immunity. The clinical relevance of γδ T cells was further highlighted by Yingying Geng and colleagues, who presented their work on anti-CD30 chimeric antigen receptor (CAR)-T cells derived from isolated Vγ9Vδ2 T cells. These CAR-T cells were shown to functionally outperform CAR-T cells derived from αβ T cells.

In summary, ongoing efforts to understand T cell function in disease were presented, including new approaches to CAR-T cell therapy and checkpoint inhibitors.

Conclusion

The quality of research at the 2025 ThymUS meeting rivaled the location. Fundamental research into T lineage development has continued to provide insights that hold clinical potential. This year, we started to see some clinical applications come into focus, as befits a maturing field. On the T cell front, research with clinical applications continued to flourish including T cells derived from iPSCs, feeder-free culturing systems to enhance thymic recovery after hematopoietic stem cell transplantation, γδ CAR T cells and a new immune checkpoint inhibitor. There was increased focus on TECs, which have been difficult to study owing to technical limitations in their isolation. Many groups presented new systems that have enabled insights into their development, diversity and function. There was an emphasis on factors that contribute to age-related thymic involution as well as regeneration after damage. Advancements in the generation of TEC organoids were presented and applied in the diagnosis of PIDs that affect the thymus.

Following the virtual edition of the meeting during the global pandemic, this year's 2025 ThymUS meeting was a success. Many scientists from around the world showed up in Kauai for the new and exciting science presented here. The field's continued dedication to the thymus results in a commitment to deliver on the medical promises this organ holds, which is increasingly becoming clear. We eagerly await the scientific advances presented as part of the Global Thymus Network during next year's KTCC conference in Kyoto, Japan.

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Competing interests

The authors declare no competing interests.