Pediatric Rheumatology

REVIEW

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# Insights from the 2024 pediatric rheumatology basic/translational years in review

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## Abstract

**Background** Advances in Pediatric Rheumatology are driven by mechanistic insights from basic and translational science. We have selected and reviewed the most impactful basic/translational science from our "Year in Review (YIR)" presentations from the 2024 Pediatric Rheumatology European Society and American College of Rheumatology Convergence meetings (September and November 2024, respectively).

**Main body** We drew from fundamental immunology, human genetics, animal models, and computational & "omic" manuscripts published in the year preceding these meetings. Avoiding overlap with other topics presented in this "Perspectives" series, summarized herein are the major themes we gleaned from that process. These include (1) innovative concepts and tools to study immune health, (2) new mechanistic insights into pediatric rheumatic diseases and (3) novel therapeutic targets and treatment approaches in rheumatic disease.

**Conclusions** As part of a living relationship with the basic/translational literature that shapes our field and practice, we hope readers will be inspired to delve more deeply into the topics and manuscripts highlighted in this YIR summary.

**Keywords** Cytokines, Neuroimmunology, Multi-omic investigation, Immune effector cell therapy

## Background

In the modern era, the field of rheumatology is uniquely tied to advances in basic and translational immunology. New tests and targeted treatments are increasingly developed as a result of insights into specific molecular and cellular mechanisms. Pediatric rheumatologists have the added challenge of incorporating a steady stream of discoveries associating previously enigmatic phenotypes to single gene defects. We delivered the Pediatric Rheumatology (PedRheum) Basic/Translational "Year in Review (YIR)" lectures for the Pediatric Rheumatology European Society (PReS) meeting in September 2024 and the American College of Rheumatology (ACR) Convergence meeting in November 2024. We cannot overstate the challenge of this distillation process, but having

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previously benefited from the efforts of YIR presenters-past, we recognize the utility of attempting to do so. This "Perspectives" manuscript is an attempt to capture and disseminate our YIR preparations and findings more broadly. Our process, as demonstrated herein, included both broad-but-shallow and deep-dive approaches. It is worth noting that we are both busy and human with (far too) many competing obligations as well as both overt and implicit biases; we seek your forgiveness in advance for all the important work we have overlooked or underemphasized. In preparing the YIR presentations, and this editorial, we were left more inspired than overwhelmed, and hope to leave readers with the same optimism for the exciting future of our field.

## Methods

Relevant articles published in the calendar years prior to the PReS and ACR meetings were selected based on author preference, advice of colleagues (see Acknowledgements), and Pubmed & Google Scholar searches. The outcome of this process for the PReS search is collected in Supplemental Table 1.

## Main body

### Innovative concepts and tools to study immune health

*Striving toward a goal of immune health* Molecular and bioinformatic-based studies are often focused on identifying the presence of dysregulated biological processes and pathways in rheumatic disease. *Sparks et al.* reframed this question and instead asked what constitutes immune health [1]. Through integrating and analyzing whole blood transcriptome, serum proteome and immune cell frequency data across a cohort of 228 patients with various monogenic immune diseases and 42 healthy controls, a quantitative immune health metric (IHM) was developed. The IHM is composed of multiple features, including more traditional inflammatory and myeloid cell signaling proteins (MIP1a, IL18R1) as well as NK cell frequency, but also lesser considered contributors to immune health, such as transcription factors like eIF4A3. The IHM can potentially be used as a biomarker of disease activity and treatment response across multiple diseases. As related to the field of Pediatric Rheumatology, the IHM was discovered to be lower with higher disease activity in a cohort of pediatric systemic lupus erythematosus patients.

*A (mouse) cytokine response dictionary* Cytokines don't exist just to confuse medical students [2], they orchestrate and regulate immune responses in health and disease. Adding to an increasingly rich and important body of "omic" resources [3], *Cui et al.* performed single-cell RNAseq on lymph node cells following systemic administration of 86 cytokine combinations [4]. They curated responses of 17 immune cell types, and found that certain cytokines (IL-2, IL-12, IL-18, IL-15, IFNg) resulted in an overall similar pattern of responses. IL-1β uniquely executed a different transcriptional pattern in nearly every cell type examined. Rare immune cell types often demonstrated the most robust increases in cytokine gene expression. They built a computational tool, the Immune Response Enrichment Analysis (IREA), that can be used to assess for cytokine signatures or immune cell polarization in other investigators' datasets.

*Our massive immune systems* While all cells are immune cells, we tend to favor cells of hematopoietic (and sometimes yolk sac) origin as more relevant for the study of immune dysregulation. *Sender et al.* performed an estimation of the number and mass of immune cells in the typical adult human, with some unexpected insights [5]. Though the gastro-intestinal tract is often considered the largest "immune" organ, of our estimated $1.8 \times 10^{12}$ immune cells, 39% reside in lymphatic organs (including the spleen), and both gastrointestinal (GI) tract and lymphatic organs were dominated by T, B, and plasma cells. Another 39% reside in the bone marrow, dominated by a tremendous reservoir of neutrophils. Mast cells, often overlooked as esoteric "allergy" cells not present in blood, constituted up to 30% of the "immune" cells of the skin or lungs.

*Neuroimmunity (because immunology was getting too simple)* It is increasingly obvious that the central and peripheral nervous systems contribute to adaptive and innate immune host defense. Three manuscripts beautifully illustrate this concept and how understanding the specifics may foster new diagnostic and therapeutic strategies.

- In trying to understand how the brain contributes to controlling systemic inflammation, *Jin et al.*. demonstrated how both pro- and anti-inflammatory cytokines, via different types of vagal nerves (CALCA and TRPA1, respectively), acted via the central nervous system to coordinate an appropriately calm peripheral inflammatory response [6].
- Patients with pain sensitization disorders are often among the most disabled by their disorder to appear before a Pediatric Rheumatologist, making the complex interplay between inflammation and pain sensitization a pressing problem. *Jain et al.* found that macrophage responses to inflammatory signals could either promote (via prostaglandins) or inhibit (via thrombospondin) pain-sensing nerve hypersensitivity, providing a possible means of preventing the development of pathologic pain syndromes [7].
- The gut is a large immune organ, and critically regulated by the enteric nervous system, with

implications particularly for inflammatory bowel disease (IBD). *Zhu et al.* used a chemogenetic screen to show that signals from afferent Trpv1-expressing nociceptive nerves, acting through dorsal root (but not vagal) ganglia, inhibited a critical population of gut-resident CD4 + regulatory T-cells (Treg) [8]. Inhibition of this pathway may stabilize gut Treg and offer a novel IBD treatment approach.

*Promising new technologies* Amongst a plethora of advances, a few novel technologies promise to change how we study, understand, and possibly treat PedRheum diseases.

- Given the outsize importance of monogenic variants in PedRheum diseases, *Schmidt et al.*'s demonstration of base-editing (targeted changes in DNA sequence) in primary human T-cells may revolutionize how we study the effects of specific genetic variants [9].
- For years investigators have had the ability to identify clonal T-cell populations in cancer. In autoimmunity, clonal proliferations of CD4 T-cells could be autoreactive or regulatory, but their peptide specificity remained mysterious. *Dezfulian et al.* created a platform called TScan-II that enabled them to identify the peptides associated with CD4 T-cell clones. This enables investigators to ask a host of new questions relevant to the nature of maintaining and breaking tolerance.
- PedRheum owes a great debt to insights gleaned from animal models, but understanding these has been hampered by the challenge of tracking cell-cell interactions in vivo. *Nakandakari-Higa et al.* developed a universal version of their Labeling Immune Partnerships by SorTagging Intercellular Contacts (uLIPSTIC) to enable the temporal tracking of cells with whom your cell-of-interest has significantly interacted [10].
- Combining single-cell sequencing with sequential intravascular labeling of immune cells in a glioblastoma mouse model, *Kirschenbaum et al.*., have taken another step in integrating the variable of time to single-cell systems-immunology approaches to immune responses. [11].
- Spatial transcriptomics technology has also been rapidly evolving even over the last year. The ability to better understand cell-cell interactions and in particular tissue-resident-immune cell interactions at single-cell spatial resolution has the potential to pave the way toward precision medicine in PedRheum diseases. As an example toward insights spatial transcriptomics technology can provide within PedRheum diseases, *Danaher et al.*. utilized the CosMx platform to evaluate diagnostic kidney biopsies from 7 children with proliferative lupus nephritis (LN) and 4 non-inflammatory controls, identifying increased myeloid cell populations within LN glomeruli and variable macrophage gene expression based on spatial localization, perhaps suggesting emerging connections of macrophage tissue localization to function and disease pathogenesis [12]. Additional investigation into three serial kidney biopsies from a single treatment refractory pediatric LN patient revealed persistent tubulointerstitial B-cells despite aggressive immunosuppression with the B-cell depleting agent rituximab as well as cyclophosphamide and multiple other agents, highlighting the importance of understanding how to target tissue-based as well as circulating cells.

## New mechanistic insights into pedrheum diseases

*Linking infectious response to development of multi-system inflammatory syndrome in children (MIS-C)* A subset of children infected with SARS-CoV-2 develop a severe, post-infectious complication termed MIS-C; yet, the mechanistic link leading to MIS-C development in only some children is unclear. *Bodansky et al.* utilized a technique called phage immunoprecipitation sequencing (PhIP-seq) to identify autoreactivity of patient antibodies to the human and SARS-CoV-2 proteomes [13]. Notably, children previously infected with SARS-CoV-2 with development of MIS-C had enrichment for 107 autoantigens, including sorting nexin 8 (SNX8), as well as a specific epitope within the SARS-CoV-2 proteome, termed the MIS-C associated domain of SARS-CoV-2 (MADS). The immunoreactive regions of SNX8 and MADS were demonstrated to have high sequence similarity, and children with development of MIS-C also displayed cross-reactive CD8 + T-cells specific for SNX8. These identified T-cells were further able to cross-react with the SARS-CoV-2 MADS region, suggesting that cross-reactive CD8 + T-cells may drive MIS-C pathogenesis in a subset of children after SARS-CoV-2 infection.

*Was there MIS-C before COVID?* Interestingly, syndromes with a clinical phenotype similar to MIS-C have previously been described in children, such as Kawasaki's disease shock syndrome. *Benezech et al.* reported expansion of Vβ21.3 + T-cells in two separate cohorts of children pre-COVID-19 pandemic, including (1) children admitted to the ICU with a clinical phenotype resembling MIS-C, with later viral testing indicating positive antibodies for coronaviruses, including the seasonal human coronavirus 229E in one patient, and (2) children with a diagnosis of Kawasaki's disease shock syndrome [14]. These findings indicate that MIS-C may be a broader

pediatric syndrome that can be triggered by multiple infectious agents.

*Activated CD8 T-cells as biomarkers and pathogenic in MAS and HLH* Hemophagocytic Lymphohistiocytosis (HLH) refers to a physiotemporal cytokine storm syndrome of fever, cytopenias, coagulopathy, hepatosplenomegaly, hepatitis, CNS inflammation, and potential for multi-organ dysfunction and death. Macrophage Activation Syndrome (MAS) refers to this syndrome occurring in the context of a rheumatic disease, most specifically Still's Disease (a.k.a. either Systemic JIA (sJIA) or Adult-onset Still's disease (AOSD)) [15], but HLH occurs in infectious, malignant, iatrogenic, and monogenic contexts as well. These monogenic forms of HLH, specifically defects in Perforin or other proteins necessary for granule-mediated cytotoxicity, have long identified Cytotoxic T Lymphocyte (CTL) dysfunction as a potential driver of familial HLH. In this *Perspectives* series, Lam et al. [16] more closely overviews the many recent studies that implicate highly activated T-cells, specifically $CD38^{+}HLA\text{-}DR^{+}CD8$ T-cells, as a potential biomarker and unifying pathogenic mechanism in familial HLH [17, 18], MAS [19, 20], and HLH-like presentations of liver failure [21], [22], [23]. Such cells may also be part of typical immune responses to certain HLH-prone infections, like EBV [24, 25].

*Mitochondrial nucleic acids not only drive interferon response, but also IL-1β secretion in systemic lupus erythematosus (SLE)* The role of mitochondrial nucleic acids (mtNAs) in contributing to autoimmune disease pathogenesis is increasingly being recognized, but disease-specific mechanisms and relevant associated signaling pathways need to be further delineated [26, 27]. *Caielli et al.* noted that active SLE patients with presence of red blood cells with retained mitochondria (Mito + RBCs) also have an expansion of IL1β + MxA + monocytes [28]. To better understand the mechanism leading to interferon (IFN)-stimulated gene and IL1β expression on monocytes, Mito + RBCs were generated that were deficient in mitochondrial nucleic acids. Monocyte stimulation with Mito + RBCs deficient in mtNAs resulted in decreased IFN-stimulated protein and IL1β production, highlighting the critical role of mitochondrial nucleic acids for both IFN response and IL-1β production from monocytes. Monocyte-derived mtDNA was then identified as a trigger for IL-1β production, and MxA enabled IL1β translocation and secretion.

*Calprotectin-mediated thrombocytopenia in antiphospholipid syndrome (APS)* Pediatric APS often manifests with thrombocytopenia as an extra-criteria manifestation and can associate with higher risk of future thrombosis. *Sloan et al.* identified calprotectin, a heterodimer of S100A8 and S100A9, to be elevated in primary pediatric APS patients and to also negatively associate with platelet count [29]. Treatment of platelets with plasma from calprotectin-high vs. calprotectin-low APS patients was additionally found to decrease platelet viability. *Hoy et al.* further identified that there was a synergistic effect on platelet viability as well as platelet caspase-1 activity after concurrent treatment with both calprotectin and APS IgG [30]. Additionally, inhibition of TLR4 with Paquinimod and NLRP3-mediated inflammasome activity with MCC-950 rescued platelet viability. In conclusion, circulating calprotectin levels may indicate risk for thrombocytopenia and potentially subsequent risk for thrombosis in APS patients.

*UNC93B1 links TLR7 and TLR8 with Monogenic lupus* One of the unique contributions of the pediatric rheumatologist is our experience with so-called Inborn Errors of Immunity (IEI), which provide concrete links between specific genes and complex inflammatory phenotypes. Perhaps no phenotype is more complex than that of SLE, and the tableau of genes with high-penetrance associations with SLE includes classical complement components (e.g. C1Q), DNAses (e.g. TREX1 & DNASE1L3), signaling molecules (e.g. TNFAIP3, PTPN2), and the endosomal nucleic acid sensor TLR7. While TLR7 gain of function is known to cause a SLE-like IEI [31], the specificity for this link– especially relative to other endosomal PRRs like TLR9– remains unknown.

Over the past year, several groups identified variants in UNC93B1 leading to hyperactivity of TLR7 and/or TLR8 (Table 1) [32, 33, 34, 35, 36]. Though phenotypes were distinctly SLE-like, variants that led to hyperactivity of only TLR8 were conspicuously associated with Chilblain's-like cutaneous features, but not the systemic autoimmunity associated with variants that also affected TLR7 activation. UNC93B1 is a chaperone and scaffolding protein that assists in both TLR transport and proper TLR configuration in the endosome. *Wolf et al.* determined that a specific *UNC93B1* variant associated with early-onset SLE led to decreased stability of the UNC93B1 protein and subsequent destabilized interaction with TLR7, resulting in TLR7 hyperactivation [32]. Additional *UNC93B1* variants leading to TLR7 hyperactivation by other mechanisms were soon discovered, including an *UNC93B1* variant that results in endosomal TLR7 build-up as a result of reduced interaction with BORC (biogenesis of lysosomal organelles complex-1 related complex) [33]. BORC is needed for TLR7 receptor turnover and degradation; therefore, reduced interaction of TLR7 with BORC or BORC deficiency leads to accumulation of TLR7.

*PTPN2 haploinsufficiency also leads to development of SLE and Evan's syndrome* Previously associated with

**Table 1** UNC93B1 variants leading to hyperactivity of TLR7 and/or TLR8

| ***UNC93B1* variant** | **Mechanism** | **Symptoms** | **Ref** |
|---|---|---|---|
| D34A* het (mouse only) | ↑ TLR7 actvity | n/a | [53] |
| E92G hom | ↓ TLR7 interaction → ↑ Signaling | 4mo-2y: ITP, AIHA, rash, GN, arthritis | [32] |
| R336L het | | 18mo: rash, LAD, GN | |
| E49dup het | ↓ BORC, ↓ TLR7 turnover | 7y: Eczema, thyroid, SjS, LAD | [33] |
| T93I* het | Impaired regulatory domain | Rash (tumid, Chlb), Arthritis, CNS | [34] |
| R336C* het | | | |
| R525p het | ↑ TLR8 only | Chlb | [35] |
| L330R het | ↑ TLR8 only | Chlb | |
| I317M hom | ↑ TLR7 > 8 | SLE | |
| R466S het | ↑ TLR8 only | Chlb | |
| G325C het | ↑ TLR7 > 8 | SLE | |
| T314A het | Via IRAK1/4 | SLE | [36] |
| V117L* het | | 18x SLE risk | |

*includes mouse model with similar phenotype. ITP = Immune Thrombocytopenic Purpura; AIHA = autoimmune hemolytic anemia; GN = glomerulonephritis; LAD = lymphadenopathy; SjS = Sjogren's Syndrome; Chlb = Chilblain's

autoimmune enteropathy, combined immunodeficiency and multi-organ autoimmunity [37, 38], *JeanPierre et al.* described six novel variants in protein tyrosine phosphatase non-receptor type 2 (PTPN2) in children with lupus and Evan's syndrome [39]. PTPN2 plays a role as a negative regulator of JAK-STAT signaling, and loss of PTPN2 protein expression leads to JAK/STAT pathway hyperactivation and presentation of clinical autoimmune disease features. This highlights that it is equally as important to consider negative regulators of cytokine and immune pathways and their role in preventing hyperactivation in the development of autoimmune disease. We can also consider mimetics of negative regulators as possible alternate treatments to develop in PedRheum patients.

*Ubiquitinopathies and autoinflammatory disease* Ubiquitylation is a necessary post-translational modification to regulate protein stability, function, signaling and degradation. As ubiquitylation is also essential for innate immune response regulation, there have been autoinflammatory disorders described as ubiquitinopathies. *Davidson et al.* recently described a dominant negative mutation in OTU-

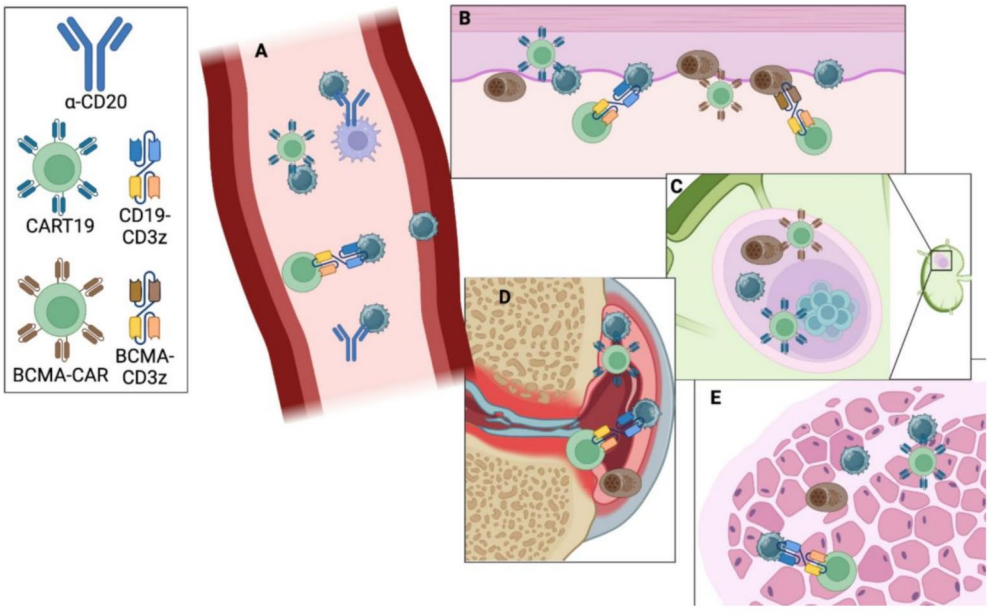


**Fig. 1** Antibody versus Immune Effector Cell (IEC) Strategies for B-cell Depletion: Antibodies like rituximab and obinutuzumab bind CD20 on B-cells and target them for death via phagocytosis by macrophages or antibody-dependent cellular cytotoxicity by NK cells. This is efficient in peripheral blood (**A**). By contrast, CART and bi-specific antibody strategies rely on T-cells and appear to be effective at depleting B- and plasma cells in blood as well as skin (**B**), lymph node (**C**), synovium (**D**), muscle (**E**), etc

LIN, a deubiquitinating enzyme, that led to OTULIN-related autoinflammatory syndrome (ORAS), manifested by fever, cutaneous inflammation and lung involvement in the setting of an elevated type I IFN signature and increased sensitivity to TNF-induced cell death [40]. A loss of function mutation in SHARPIN, a component of the linear ubiquitin assembly complex, was also identified as a new ubiquitinopathy, with clinical manifestations of recurrent fever, parotitis, arthritis and colitis [41].

## Novel therapeutic targets and treatment approaches in rheumatic disease

*Non-inflammatory pathways for therapeutic targeting in myositis* Non-immune mechanisms may contribute more to disease chronicity and immune activation in PedRheum than we currently account for. *Abad et al.* sought to evaluate mechanisms contributing to development of myositis in an inducible T cell co-stimulator (Icos) knock out (KO) Non-Obese Diabetic (NOD) mouse model. Myositis develops at about 25 weeks of age in this model, with muscle tissue displaying elevation of both IFNβ and IFNγ gene expression [42]. Muscle proteomic analysis in these mice revealed a theme of metabolic signaling pathway downregulation, and the majority of dysregulated proteins localized to mitochondria. Icos KO NOD mice with myositis also displayed increased expression of oxidative response genes in muscle, and muscle tissue homogenates produced more reactive oxygen species as compared to $Icos^{+/+}$ NOD mice. Treatment of mice with both N-acetyl cysteine (NAC) and anti-IFNγ treatment led to improved strength and decreased inflammatory infiltrate in muscle tissue. Based on this study and also other work describing oxidative stress and mitochondrial dysfunction in juvenile dermatomyositis [43, 44], it is possible that targeting reactive oxygen species or mitochondrial dysfunction may have a role in treatment of myositis.

*Glucocorticoids and macrophage mitochondrial metabolism* Despite the essential role played by glucocorticoids (GC) in the current management of inflammatory and immune-mediated disease, their mechanisms of action remain mysterious. *Auger et al.* identified an acute effect of glucocorticoids on the induction of itaconate, a TCA-cycle intermediate with potent anti-inflammatory effects in myeloid cells like macrophages [45]. This effect required the glucocorticoid receptor (GC-R), but not new transcription. Instead, the activated GC-R interacted with the mitochondrial pyruvate dehydrogenase complex, driving TCA flux and aconitate decarboxylase 1 (*ACOD*)-dependent itaconate production. This mechanism was crucial for GC's ability to restrain models of innate, autoimmune, and allergic inflammation.

*Deeper B-cell depletion with immune effector cells (IECs)* For the first time in decades, clinicians and investigators are beginning to entertain the notion of a cure for autoimmunity. The idea that B-cell depletion might treat autoimmune disease is as old as their connection to autoantibodies. Borrowing tools from oncology, the first experience with rituximab in Rheumatoid Arthritis is now more 20 years old [46]. The use of B-cell depleting antibodies has become widespread in autoimmune diseases, but despite rapid and robust elimination of peripheral B-cells, durable remissions have been rare. Borrowing again from oncology, the avalanche of case series reporting almost "too-good-to-be-true" efficacy of T-cell dependent B-cell depletion for patients with refractory autoimmunity may represent an inflection point in the history of our field. The clinical details of these reports are beyond the scope of this *Perspective*. They derive mostly from Chimeric Antigen Receptor T-cells (CART) directed against B-cell antigens like CD19 and BCMA in treatment refractory SLE, inflammatory myositis, and scleroderma [47]. In PedRheum, case reports in refractory Juvenile Dermatomyositis [48] and SLE nephritis [49] have been similarly positive. Autologous CART are difficult and costly to make, and patients must receive chemotherapeutic lymphodepletion to "make room" for the CART. It is therefore reassuring that early experience with engineered proteins that biochemically link B-cell antigens to T-cell signaling molecules termed bispecific T-cell engagers or BiTEs (namely CD3ζ, e.g. blinatumomab and teclistamab) have been similarly impressive [50, 51, 52].

IEC therapies result in rapid peripheral B-cell depletion, and like B-cell depleting antibodies, the B-cell compartment begins to repopulate about 3 months after IEC treatment. By contrast, the B cells that begin to emerge following IEC treatment are overwhelmingly naïve. When viewed alongside profound & durable clinical improvement and autoantibody normalization, this suggests that deeper B-cell depletion may provide the autoreactive B-cell "reset" that rheumatologists having been seeking for decades. The mechanism for this deeper depletion likely rests with T-cells' expertise in infiltrating tissues, expanding in response to TCR stimulation, and killing multiple targets. That IEC therapies target B-cell antigens expressed throughout the B-cell life cycle and/or in plasma cells (e.g. CD19 & BCMA, respectively) that may also contribute to their greater depth of depletion. It remains an open question whether IEC therapy is also a "reset" in terms of B-cell memory to pathogens, in part due to the widespread availability of immunoglobulin replacement. In short, it appears that B-cells are the "bad guys" in autoimmunity, but effectively depleting them requires recruiting expert killers (Fig. 1).

## Conclusions

Overall, the last year in Pediatric Rheumatology basic and translational research has led to development of bioinformatic and immunology tools that can be applied to PedRheum resesearch, advancement in knowledge of underlying genetic and mechanistic etiologies of PedRheum diseases and the beginnings of immune effector cell therapy for PedRheum. The importance of cross-disease comparative studies is increasingly being recognized to identify and characterize unifying themes of both immune health and dysregulation across PedRheum. The identification of less traditional inflammatory or non-immune pathways for treatment targeting is changing our perspective on potential initiating events for clinical onset of PedRheum diseases. New mechanistic insight contributing to pathogenesis of well recognized PedRheum diseases is leading to generation of novel cellular biomarkers to improve monitoring of disease activity and severity. We are moving toward clinical trials for new therapies, including cellular therapy, for children with PedRheum diseases. While we still need to optimize specificity of antigenic targets and thoroughly evaluate the safety of any new therapies, we are closer than ever before to the hope of sustained disease remission, and the possibility of a cure, for children with PedRheum diseases.

### Abbreviations

| | |
|---|---|
| PedRheum | Pediatric rheumatology |
| YIR | Year in review |

## Supplementary Information

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Supplementary Material 1

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### Author contributions

JLT and SWC both contributed equally to all aspects of article conception, literature review, interpretation, perspective, writing and revisions. JLT and SWC both reviewed and approved the final submitted manuscript draft.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable; As this was a review article and does not include report of new research, we ask that readers please refer to complete individual manuscripts for the referenced studies for ethics approval and consent to participate.

### Consent for publication

Not applicable.

### Competing interests

JLT has served on an advisory board for Cabaletta Bio. SC has been an ad hoc consultant for AB2Bio, Apollo, BMS, Johnson & Johnson, and SOBI; been on a speaker's bureau for SOBI & BMS; and has received in-kind support from Simcha.

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